PREŽIVETJE BOLNIKOV Z RAKOM, ZBOLELIH V LETIH 1991–2005 V SLOVENIJI

SURVIVAL OF CANCER PATIENTS, DIAGNOSED IN 1991–2005 IN SLOVENIA

Maja Primic-Žakelj
Vesna Zadnik
Tina Žagar
Branko Zakotnik

PREŽIVETJE BOLNIKOV Z RAKOM, ZBOLELIH V LETIH 1991–2005 V SLOVENIJI

SURVIVAL OF CANCER PATIENTS, DIAGNOSED IN 1991–2005 IN SLOVENIA

Maja Primic-Žakelj
Vesna Zadnik
Tina Žagar
Branko Zakotnik

Onkološki inštitut Ljubljana
Epidemiologija in register raka
Register raka Republike Slovenije
2009

Institute of Oncology Ljubljana
Epidemiology and Cancer Registry
Cancer Registry of Republic of Slovenia
2009

CIP – Kataložni zapis o publikaciji
Narodna in univerzitetna knjižnica, Ljubljana

616-006-036.8(497.4)

PREŽIVETJE bolnikov z rakom, zbolelih v letih 1991–2005 v Sloveniji = Survival of cancer patients, diagnosed in 1991–2005 in Slovenia / Maja Primic-Žakelj … [et al.] ; [prevod Olga Schrestha]. – Ljubljana : Onkološki inštitut, 2009

ISBN 978-961-6071-53-6
1. Vzp. stv. nasl. 2. Primic-Žakelj, Maja
245077248

Avtorji:
Authors: Maja Primic-Žakelj, Vesna Zadnik, Tina Žagar, Branko Zakotnik

Sodelavci:
Co-workers: Franc Anderluh, Nikola Bešić, Peter Černelč, Tanja Čufer, Andrej Debeljak, Ibrahim Edhemović, Janez Eržen, Albert Peter Fras, Eldar M. Gadžijev, Marko Hočevar, Janez Jazbec, Barbara Jezeršek-Novaković, Andrej Kmetec, Elga Majdič, Uroš Mlakar, Mojca Modic, Irena Oblak, Janja Ocvirk, Mirko Omejc, Stane Repše, Boris Sedmak, Uroš Smrdel, Miha Sok, Primož Strojan, Breda Škrbinc, Lojze Šmid, Marjetka Uršič-Vrščaj, Vaneja Velenik, Samo Zver, Matjaž Zwitter, Janez Žgajnar, Mirjana Žumer-Pregelj

Analiza slovenskih podatkov:
Analysis of Slovenian data: Tina Žagar

Analiza podatkov EUROCARE-4 in SEER:
Analysis of EUROCARE-4 and SEER data: Silvia Francisci

Recenzenta:
Reviewers: Vera Pompe-Kirn, Matjaž Zwitter

Lektor za slovenščino:
Reader for Slovenian language: Jože Faganel

Prevod:
Translation: Olga Schrestha

Oblikovanje:
Design: Monika Fink-Serša, Samo Rovan / NAVA arhitektura in oblikovanje

Fotografija:
Photo: Andrej Korenč

Priprava za tisk:
Typesetting: SYNCOMP d. o. o.

Tiskarna:
Printed by: Birografika Bori d. o. o.

Izdajatelj: Onkološki inštitut Ljubljana
Published by: Institute of Oncology Ljubljana

Naklada: 800 izvodov
Published in: 800 copies

Strokovni in akademski nazivi ter ustanove zaposlitve vseh sodelujočih so na zadnji strani.
Professional and academic titles with affiliations of all contributors are published at the end.

VSEBINA

CONTENTS

SEZNAM OKRAJŠAV

5-FU	5-fluoruracil
ABVD	Doksorubicin, bleomicin, vinblastin, dakarbazin
AP	Melfalan, prednizolon
BEACOPP	Cikolfosfamid, doksorubicin, etoposid, vinkristin, bleomicin, prokarbazin, prednizon
BFM	Shema Berlin-Frankfurt-Münster
CT	Računalniška tomografija
ECF	Epidoksorubicin, cisplatin, fluoruracil
ERC	Endoskopska retrogradna holangiografija
EUZ	Endoskopska ultrazvočna preiskava
HPV	Humani papilomski virus
MKB 10	Mednarodna klasifikacija bolezni in sorodnih zdravstvenih problemov za statistične namene, 10. revizija
MRI	Magnetnoresonančno slikanje
NHL	Ne-Hodgkinov limfom
OI	Onkološki inštitut
PET	Pozitronska izsevna tomografija
PKMC	Presaditev krvotvornih matičnih celic
PSA	Za prostato specifični antigen
RFA	Radiofrekvenčna ablacija
RRS	Register raka Republike Slovenije
rhTSH	Rekombinantni humani TSH
RTG	Rentgenska preiskava
SB	Splošna bolnišnica
SEER	Nadzor, epidemiologija in končni rezultati
TACE	Transhepatična arterijska kemoembolizacija
TUR	Transuretralna resekcija
UKC	Univerzitetni klinični center
UZ	Ultrazvočna preiskava
VAD	Vinkristin, doksorubicin, deksametazon
VATS	Z videom podprta torakoskopska kirurgija

LIST OF ABBREVIATIONS

5-FU	5-fluoruracil
ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
AP	Melphalan, prednisolone
BEACOPP	Cyclophosphamide, doxorubicin, etoposide, vincristine, bleomycin, procarbazine, prednisone
BFM	Berlin-Frankfurt-Münster scheme
CRS	Cancer Registry of Republic of Slovenia
CT	Computer tomography
ECF	Epidoxorubicin, cisplatin, fluoruracil
ERC	Endoscopic retrograde cholangiography
EUS	Endoscopic ultrasound examination
GH	General hospital
HPV	Human papiloma virus
ICD 10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IO	Institute of Oncology
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin's lymphoma
PET	Positron emission tomography
PKMC	Hematopoietic stem cell transplantation (HSCT)
PSA	Prostate-specific antigen
RFA	Radiofrequent ablation
rhTSH	Recombinant human TSH
RTG	X-ray, radiography
SEER	Surveillance, Epidemiology and End Results
TACE	Transhepatic arterial chemoembolization
TUR	Transuretral resection
UMC	University medical center
US	Ultrasound examination
VAD	Vincristine, doxorubicin, dexamethasone
VATS	Video-assisted thoracoscopic surgery

PREDGOVOR

Mnogo več kot le statistika. To bi lahko bil najkrajši opis knjige, ki predstavi breme raka v Sloveniji v zadnjih dveh desetletjih. Knjiga o preživetju bolnikov z rakom v Sloveniji je izjemen dosežek celotne posadke RRS in še nekaj stotin sodelavcev v skoraj vseh zdravstvenih ustanovah v Sloveniji, ki RRS vestno pošiljajo podatke. Pred nami je nepogrešljiv temelj in vodnik za vse bodoče razprave o preventivi, diagnostiki in zdravljenju raka.

Knjiga je kot otrok. V nosečnosti si le megleno predstavljaš, kaj prihaja na svet, in šele pozneje spoznaš vse njegove odlike, a tudi pomanjkljivosti. Kakor otrok ni nikoli po okusu prav vseh tet, stricev in sosedov, tako bodo tudi v tej knjigi nekateri pogrešali to in ono. Delo, ki so ga opravili uredniki, je res obsežno, a obseg knjige je omejen, zato vsega, kar bi morda koga zanimalo, preprosto ni bilo mogoče zajeti. Osebno bi pri pogostejših rakih rad videl prikaz uspešnosti zdravljenja po posameznih regijah Slovenije, saj bi nam bilo to v dragoceno pomoč pri odpravljanju slabosti zdravstvene oskrbe. Nekateri se bodo morda ustavili pri velikih skokih in nenavadno žagastih krivuljah incidence, ki lahko kažejo na nedoslednosti pri prijavljanju. Naj se ta kritika usmeri v še skrbnejši popis vseh, ki so zboleli za rakom. Tako se bomo izognili možnosti, da si zaradi nepopolnega prijavljanja rišemo slabšo podobo o uspešnosti zdravljenja, kot je v resnici.

Rak sodi med bolezni z močno socialno razsežnostjo: ljudje iz nižjih socialnih slojev zbolevajo pogosteje, kasneje pridejo do prave diagnoze in si težje izborijo optimalno zdravljenje. Pogosteje zbolijo zaradi nezdravih življenjskih navad in zaradi zdravju škodljivega delovnega in bivalnega okolja. Nizka splošna raven izobrazbe in nizko socialno okolje predstavljata oviro pri pravočasni diagnostiki in pri dostopnosti do optimalnega zdravljenja. Zakaj ob knjigi o preživetju bolnikov z rakom omenjam te razumljive, pa vendar pogosto spregledane okoliščine? Zato, ker bodo mnogi v tej knjigi gledali le eno: primerjavo med odstotki ozdravljenih pri nas, v Evropi in v ZDA. Ta primerjava je seveda dragocena, pa vendar jo moramo jemati z veliko rezervo. Vedeti moramo, da naš register pokriva celotno populacijo Slovenije, torej tudi njene najbolj revne odročne predele. Primerjava med takšnim populacijskim registrom in med zbirko podatkov, kakršno predstavljata evropska raziskava EUROCARE, ali pa med oceno programa SEER ameriškega Državnega inštituta za raka je v najboljšem primeru le orientacijska. Za evropsko raziskavo, ki temelji na poročilih izbranih regij izbranih držav, zanesljivo lahko napovemo, da slabo pokriva revne, socialno zapostavljene predele Evrope. Dvom v reprezentativnost podatkov je še toliko večji pri ZDA, kjer so vsi statistični podatki zgolj ocena in kjer znaten del populacije ostaja brez osnovne zdravstvene oskrbe, pa seveda tudi zunaj vseh analiz.

Najpomembnejše sporočilo te knjige ni nezanesljiva primerjava z Evropo in z ZDA, pač pa zelo očiten napredek pri nas. V 15 letih se je petletno preživetje odraslih bolnikov z rakom zvečalo z 39,6 % na 51,8 %, otrok pa s 70,6 % na 82,7 %. Rak, ki je bil nekoč kot trdna stena, se počasi ruši. Ne bo padel v enem zamahu kot berlinski zid, toda vsi vidimo, da ni nepremagljiv. Ni ga, ki bi ob misli na rakavo bolezen ostal neprizadet – pa naj gre za bolnika, sorodnika, prijatelja, zdravnika, medicinsko sestro. V imenu vseh naj zato končam z zahvalo vsem imenovanim in neimenovanim sodelavcem te knjige, da so nam ponudili to dragoceno spodbudo.

Matjaž Zwitter

FOREWORD

Much more than just a statistics. This could be the briefest description of the book that presents cancer burden in Slovenia in the last two decades. The book on cancer patient survival in Slovenia is an outstanding achievement of the whole staff of the CRS, as well as of a few hundred co-workers from almost all Slovenian health institutions, who have been accurately sending their data to the CRS. Thus we have obtained an indispensable foundation and a guidebook for all further discussions about the prevention, diagnosis and therapy of cancer.

A book is like a child. During pregnancy, you have but a vague idea what is about to be born, and later only you come to know all the advantages as well as drawbacks of the »newborn«. Likewise a child that can never meet the expectations of all his aunts, uncles and neighbors, also in this book some readers may miss one thing or the other. The work performed by the editors is really huge, and given the limited volume of the book, not everything that might be of interest to various readers could be included into it. As regards frequent cancers, personally I would appreciate a presentation of treatment success by individual regions of Slovenia, since this would be a valuable help in eliminating the shortcomings of healthcare. Some may wonder about the underlying causes of rapid changes and unusually fluctuating incidence curves, which may be indicative of inconsistency in reporting. May this criticism lead to an even more conscientious recording of all persons diagnosed with cancer. Thus, it may not happen that owing to incomplete reports the treatment success would appear worse than it actually is.

Cancer belongs to the diseases with a strong social dimension: people from lower social class get cancer more frequently, are diagnosed at a later stage and have more problems in obtaining an optimum therapy. They fall ill more frequently because of unhealthy lifestyle as well as working and living conditions that are detrimental to their health. A low general education level and low social environment represent an obstacle to timely diagnosis and accessibility of optimal treatment. Referring to the book on cancer patient survival, why to mention these self-evident though often neglected circumstances? Hence, because many will see in this book but one thing: the percentages of the cured patients in Slovenia as compared to the relevant percentages in other European countries and in the USA. Although this comparison is valuable, it should be interpreted with considerable degree of caution. It should be kept in mind that our registry covers the whole territory of Slovenia, thus also its most remote and neglected regions. A comparison between such a population registry and databases provided by the EUROCARE study or the SEER Program of the National Cancer Institute can in the best case be only of an indicative value. As for a European study based on reports from selected regions of selected countries, it can be said with great certainty that its coverage of poor and socially deprived territories of Europe is insufficient. The representativeness of data for the USA is even more doubtful, since all their statistics are mere presumption, considering that a large segment of their population is left without basic healthcare and thus also lost to any analyses.

Therefore, the most important message of this book is not the unreliable comparison with Europe and the USA, but the obvious advances made in Slovenia. In 15 years, 5-year survival of adult cancer patients has increased from 39.6% to 51.8%, and of children from 70.6% to 82.7%. Cancer, which appeared to be an impenetrable wall in the past, is slowly falling down. It will not collapse at once like the Berlin Wall, but we can see that it is not invincible. A thought of cancer leaves no one indifferent, may it be a patient, a relative, a friend, a physician or a nurse. Let me therefore end this foreword with thanks to all the named and anonymous co-workers of this book for offering us such a valuable enticement.

Matjaž Zwitter

UVOD

Rak ni ena sama bolezen, pač pa več sto različnih, ki lahko vzniknejo v vseh tkivih in organih človeškega organizma. Razlikujejo se po pogostosti, imajo pa tudi različne, bolj ali manj znane nevarnostne dejavnike, med katerimi so javnozdravstveno najpomembnejši tisti, ki so bodisi posledica življenjskih navad in razvad bodisi naravnega procesa staranja. Politične in ekonomske spremembe, ki smo jim bili priča v zadnjem desetletju prejšnjega stoletja, so vplivale na življenjski slog pa tudi na organizacijo zdravstvenega varstva. Ker je latenčna doba pri raku večinoma daljša od 20 let, lahko pričakujemo, da se bo mnogo posledic teh sprememb pokazalo šele v prihodnosti. Tudi življenjska doba prebivalstva se daljša, poleg tega pa je številčnejša povojna generacija že v letih, v katerih je pojavljanje rakave bolezni pogostejše, zato je pričakovati, da bo breme te bolezni pri nas vse večje. Rak je zato pomemben javnozdravstveni, socialni in ekonomski problem sodobne družbe in obvladovanju te bolezni bo treba posvečati vse več pozornosti.

Uspešnost in učinkovitost prizadevanja zdravstvene politike in služb zdravstvenega varstva za obvladovanje raka je mogoče objektivno ovrednotiti le z ustreznimi podatki o bremenu te bolezni in njegovem spreminjanju v času. Samo podatki o tem, koliko sredstev je namenjenih raznim programom, namreč še ne potrjujejo, da so ta sredstva učinkovito porabljena in da imajo za posledico boljše zdravje prebivalstva.

Breme raka opisujejo osnovni kazalci, kot so incidenca, umrljivost, prevalenca in preživetje. Zbiranje podatkov o bolnikih z rakom ima v Sloveniji dolgoletno tradicijo, saj imamo na Onkološkem inštitutu Ljubljana enega najstarejših populacijskih registrov raka v Evropi, ki zagotavlja podatke o incidenci, prevalenci in preživetju. Podatke o umrljivosti za rakom zbira Inštitut za varovanje zdravja in jih redno pošilja banki podatkov Svetovne zdravstvene organizacije. Vsi ti podatki pa ne prikazujejo le bremena rakavih bolezni v državi, ampak so tudi izhodišče za ocenjevanje uspešnosti onkološke primarne in sekundarne preventive, diagnostike, zdravljenja, rehabilitacije in paliativne oskrbe ter za načrtovanje zmogljivosti in sredstev (osebja, medicinske opreme, posteljnih zmogljivosti …), ki so potrebni za obvladovanje rakavih bolezni na vseh omenjenih področjih.

Osnovni kazalec bremena raka po svetu, ki je na voljo za največje število držav, je umrljivost za rakom. Ta je po eni strani odvisna od števila novih bolnikov, incidence, po drugi strani pa od preživetja bolnikov. Samo preživetje ni odvisno od incidence, saj upošteva samo tiste, ki so že zboleli, zato posredno kaže na uspešnost zdravljenja. Populacijsko preživetje bolnikov z rakom, kot ga prikazujejo registri raka, je sestavljen kazalec, v katerem se zrcalijo tako značilnosti bolnikov kot tudi organizacija, dostopnost, kakovost in učinkovitost sistema zdravstvenega varstva; večinoma se precej razlikuje od preživetja skupin bolnikov z določeno boleznijo, zdravljenih v posameznih bolnišnicah, kakor običajno svoje rezultate prikazujejo kliniki. Na populacijsko preživetje vpliva npr. stadij bolezni ob diagnozi, ki je odvisen od časa od prvih sumljivih znakov do postavitve diagnoze; ta čas pa je tem krajši, čim bolj je prebivalstvo zdravstveno ozaveščeno, kdaj naj se ob težavi z zdravjem odloči za pregled pri zdravniku, čim bolj je zdravnik prvega stika usposobljen, da sploh pomisli na možnost resne bolezni, čim večja je dostopnost diagnostičnih preiskav in čim krajše so zanje čakalne vrste. Razpoložljivost presejalnih programov za tiste rakave bolezni, pri katerih je dobrobit programov neizpodbitno dokazana, dodatno veča možnost ozdravitve ali vsaj boljšega preživetja. Ko je diagnoza postavljena, pa je uspeh zdravljenja odvisen od vrste rakave bolezni, bolnikovih značilnosti (starosti, spremljajočih bolezni, splošne telesne zmogljivosti), in tudi od usposobljenosti zdravstvenega tima, to je izkušenosti

INTRODUCTION

Cancer is not a single disease but rather a few hundreds of different disorders that may originate from in all tissues and organs of the human body. They differ with respect to their frequency as well as to more or less known risk factors, among which those resulting from unhealthy lifestyles or natural ageing are most relevant in terms of public health. Political and economic changes witnessed in the last decade of the previous century have influenced the population's lifestyle as well as the organization of the healthcare. The latency period in cancer being generally longer than 20 years, it may be expected that many consequences of these changes will become apparent only in the future. Moreover, the population's life expectancy is increasing and the more numerous after-war generation has reached an age when the occurrence of cancer is more frequent, and therefore it may be expected that the burden of this disease in our country will further increase. This renders cancer an important public-health, social and economic problem of the modern society, and ever more attention should be devoted to the control of this disease.

The effectiveness and efficiency of the endeavours of health policy and healthcare services as regards cancer control can be objectively evaluated only by means of relevant data on cancer burden and its changes with time. Bare information on the amount of funds intended for different programs alone does not prove that these resources were used effectively, thus resulting in better health of the population.

Cancer burden can be described with basic indicators such as incidence, mortality, prevalence and survival. The collection of data on cancer patients has a long-standing tradition in Slovenia, as the IO Ljubljana manages one of the oldest population-based cancer registries in Europe, which provides data on incidence, prevalence and survival. Cancer mortality data are collected by the Institute of Public Health and regularly sent to the data bank of the World Health Organization. These data not only show the cancer burden in the country, but also serve as a basis for evaluation of the effectiveness of oncological primary and secondary prevention, diagnosis, treatment, rehabilitation and palliative care, as well as for planning the capacities and resources (personnel, medical equipment, bed fond …), needed for cancer control in the mentioned areas of activity.

Cancer mortality is the basic indicator of cancer burden in the world, which is available for most countries. This depends on the one hand on the number of new patients, i. e. incidence, and on patients' survival on the other. Survival alone does not depend on incidence, since it refers only to those who have already been diagnosed, thus indirectly reflecting the success of treatment. Population-based survival of cancer patients, as shown by cancer registries, is a complex indicator, which reflects patients' characteristics as well as the organization, accessibility, quality and efficiency of healthcare system; generally, it greatly differs from the survival of patient groups with a particular disease, treated in individual hospitals, as commonly presented by clinicians. The population survival is influenced e. g. by stage of the disease at diagnosis, which depends on the time from first suspicious symptoms to diagnosis, this time being the shorter, the better is public awareness about which health problems require medical attention, the more skilled is the physician who first sees the patient and considers the possibility of a severe illness, the greater the accessibility of diagnostic procedures and the shorter the waiting time. The availability of screening programs for those cancers in which the benefit of such programs is clearly demonstrated, further improves the chances of cure or at least better survival. After the diagnosis has been established, treatment success depends on the type of cancer, patient's characteristics (age, comorbidity, general performance status), as well as on the competence

in kakovosti kirurga onkologa ter vseh, ki sodelujejo v multidisciplinarni obravnavi; tam, kjer se zdravljenje začne, včasih takega tima sploh ni. Z javnozdravstvenega vidika k populacijskemu preživetju prispeva manj dostopnost najnovejših in najdražjih zdravil. Vse te dejavnike, ki odločajo o populacijskem preživetju, mora upoštevati, kdor interpretira rezultate raziskav o preživetju v kakšni državi, še bolj pa, kdor primerja preživetje po državah.

Sedanja publikacija je že tretje obsežnejše poročilo RRS o preživetju slovenskih bolnikov z rakom. Obravnava tiste, ki so zboleli in bili zdravljeni v samostojni državi Sloveniji. Kaže napredek, ki so ga zagotovili slovenska onkologija in slovensko zdravstveno varstvo skupaj s celotno družbo v 15 letih; o doseženem in možnostih za še boljše rezultate pišejo kolegice in kolegi, ki se dnevno ukvarjajo s specifičnim zdravljenjem bolnikov z rakom na OI Ljubljana in klinikah UKC Ljubljana.

Največja evropska raziskava o preživetju bolnikov z rakom v Evropi se kratko imenuje EUROCARE. Podatke dobiva iz evropskih registrov raka. Doslej je objavila štiri poročila in drugo že vsebuje tudi podatke RRS. Prvo je obravnavalo 800.000 bolnikov, ki so v letih 1978–1985 zboleli v 12 evropskih državah in o katerih je prispevalo podatke 30 populacijskih registrov raka, za četrto pa je podatke o 2.699.086 bolnikih, ki jim je bila diagnoza postavljena v letih 1995–1999, dalo 83 registrov raka iz 23 evropskih držav; za dodatne analize obdobnega preživetja bolnikov, zbolelih v letih 2000–2002, pa je prispevalo podatke 47 oz. 31 registrov, med njimi tudi slovenski.

Vsi, ki sodelujemo v raziskavah o preživetju bolnikov z rakom v Evropi, se zavedamo, da ima naše sodelovanje več metodoloških pomanjkljivosti: registracija in sledenje bolnikov nista povsod enako popolna in kakovostna, definicije vseh rakavih bolezni pri registraciji bolnikov niso enotne, pa tudi nekateri rezultati niso reprezentativni za vse države, saj nekateri registri pokrivajo področja celih držav, nekateri pa le posamezne regije. Ne glede na to pa so izsledki raziskave EUROCARE pomembni predvsem zato, ker vsem sodelujočim kažejo, ali so na pravi poti; marsikje so jih že izkoristili za to, da so izboljšali sistem organizacije zdravstvenega varstva, saj je slabo preživetje zastavilo številna, ne le strokovna, pač pa tudi ostra politična vprašanja.

REGISTRIRANJE RAKA V SLOVENIJI IN SPREMLJANJE BOLNIKOV

RRS je eden najstarejših populacijskih registrov raka v Evropi. Leta 1950 ga je ustanovila in do leta 1975 vodila pokojna profesorica dr. Božena Ravnihar. Njeno delo je prevzela profesorica dr. Vera Pompe Kirn, ki je do upokojitve leta 2003 skrbela za nadaljnjo uveljavljanje RRS v domačem in mednarodnem merilu. Od leta 2003 je RRS skupaj z Enoto za epidemiologijo v enotni službi Epidemiologija in register raka. V njej so poleg RRS še bolnišnični register OI Ljubljana, ki posreduje RRS velik del podatkov in omogoča podrobnejši pregled nad bolniki, zdravljenimi v naši ustanovi ne glede na to, kje imajo stalno prebivališče. V zadnjem desetletju smo vzpostavili še nov državni register za vodenje in spremljanje organiziranega presejalnega programa za raka materničnega vratu (ZORA), od leta 2007 pa izgrajujemo informacijski sistem DORA, ki bo informacijska podpora organiziranemu presejalnemu programu za raka dojk. Tudi obstoj teh novih registrov prispeva k popolnosti in kakovosti podatkov RRS, po drugi strani pa podatki RRS prispevajo k vrednotenju učinkovitosti presejalnih programov.

Prijavljanje raka je v Republiki Sloveniji obvezno in z zakonom predpisano že od ustanovitve RRS (Ur. l. SRS, št. 10/50, št. 29/50, št. 14/65, št. 1/80, št. 45/82, št. 42/85; Ur. l. RS, št. 9/92 in št. 65/00). Osnovni vir podatkov so prijavnice rakave bolezni, ki jih pošiljajo iz vseh bolnišnic in diagnostičnih centrov v Sloveniji, iz ordinacij osnovnega zdravstvenega varstva pa le izjemoma, če bolnik ni napoten na nadaljnje preiskave in/ali zdravljenje. Dodatni vir podatkov so zdravniška poročila o vzroku smrti in obdukcijski zapisniki z diagnozo maligne bolezni.

of health team, i. e. on the experience and skills of the oncological surgeon and all those involved in the multidisciplinary treatment approach; sometimes, in the institutions where first treatment is started, no such team is available at all. From the public health point of view, population-based survival is less influenced by the availability of the latest and most expensive drugs. When interpreting the results of survival studies for a particular country, and particularly when comparing survival by countries, all these factors influencing the population-based survival should be taken into account.

The current publication is already the third extensive report by the CRS on the survival of Slovenian cancer patients, who were diagnosed and treated in the independent State of Slovenia. Presented are advances made by the Slovenian oncology and health care along with the whole society in fifteen years; the results achieved and the possibilities for further improvement are discussed by colleagues, daily involved in the specific treatment of cancer patients at the IO Ljubljana and in the departments of the UMC Ljubljana.

The largest European study of the survival of cancer patients in Europe has a short name EUROCARE. Data are obtained from the European cancer registries. So far, four EUROCARE reports have been published, and the second one already includes the CRS's data. The first report covered 800,000 patients diagnosed in the period 1978–1985 in 12 European countries; the data were contributed by 30 population-based cancer registries. For the fourth report, the data on 2,699,086 patients diagnosed in the period 1995–1999 were obtained from 83 cancer registries from 23 European countries; additional data for further survival period analyses of patients diagnosed in the years 2002–2002 were contributed by 47 or 31 registries respectively, among them also by CRS.

All of us taking part in the research of cancer patient survival in Europe are aware that our studies have a few methodological deficiencies: everywhere, registration and follow-up are not equally complete and of the same quality; in patient registration, the definitions of all cancer diseases are not uniform, and certain results are not representative for all countries since some registries cover the whole country while others present only individual regions. Nevertheless, the results of EUROCARE study are important primarily because they help the participants check whether they are on the right track; many have already used them to improve their organization of healthcare after the poor survival posed a number of not only professional but also political questions.

CANCER REGISTRATION AND FOLLOW UP OF PATIENTS IN SLOVENIA

CRS is one of the oldest population based cancer registries in Europe. It was founded in 1950 by the late Professor Božena Ravnihar, MD, PhD, who headed it till 1975. She was succeeded by Professor Vera Pompe-Kirn, who contributed a lot to the further development of the Registry as well as its recognition at the national and international level all until her retirement in 2003. Since 2003, the CRS together with the Unit of Epidemiology is merged in a single Epidemiology and Cancer Registry service. Besides the CRS, the new service also comprises the hospital-based Cancer Registry of the OI Ljubljana, which contributes a considerable part of information to the CRS and facilitates a more detailed overview of patients treated at the IO Ljubljana, irrespective of their permanent residence. In the last decade, we have established a new national registry in charge of coordinating and monitoring the organised cervical cancer screening programme (ZORA), while an information system DORA to support organized breast screening program has been underway since 2007.While the existence of these two new registries contributes to a higher quality and completeness of CRS's data, the latter contribute to the evaluation of the effectiveness of screening programs.

Notification of cancer has been compulsory in Slovenia since the foundation of the CRS and prescribed by law (Official Gazette of SRS, No 10/50, 29/50, 14/65, 1/80, 45/82 and 42/85;

Podatki, ki se zbirajo o novih primerih rakave bolezni, so naslednji:

- *identifikacijski podatki*: enotna matična številka občana (EMŠO), ime in priimek, dekliški priimek, rojstni kraj in naslov stalnega prebivališča;
- *podatki o bolezni*: anatomsko mesto raka, histološka oz. citološka diagnoza, stadij po TNM ali drugi ustrezni klasifikaciji, opredelitev stadija po vseh preiskavah, način postavitve diagnoze;
- *podatki o zdravljenju*: bolnišnica, oddelek, številka popisa, vzrok sprejema, datum sprejema, datum ugotovitve sedanjega raka, predhodno zdravljenje sedanjega raka, način zdravljenja med sedanjo hospitalizacijo, datum pričetega zdravljenja, zaporedna številka sedanjega raka, predhodno ugotovljen kakšen drug rak;
- *podatki ob odpustu oz. smrti*: datum odpusta oz. smrti, stanje ob odpustu, morebitna obdukcija, ali je predvidena kontrola oz. je bil bolnik premeščen.

Za izračun preživetja bolnikov, kar je ena izmed osnovnih nalog RRS, potrebujemo vitalno stanje bolnikov. Ta podatek štirikrat letno dobimo iz Centralnega registra prebivalstva za vse osebe iz RRS, za katere imamo podatek, da so še žive. Oseba je lahko živa, mrtva ali izgubljena. Pri izgubljenih osebah upoštevamo kot datum izgube datum zadnje prijave oz. datum izgube, ki nam ga posreduje Centralni register prebivalstva, odvisno od tega, kateri datum je kasnejši. Od leta 1983, odkar se v Sloveniji uporablja enotna matična številka občana, je v RRS odstotek izgubljenih manjši od 1 %; pri bolnikih, registriranih v desetletju 1996–2005, pa je bil 0,1 %.

PRIPRAVA PODATKOV ZA RAČUNALNIŠKO OBDELAVO

V RRS posebej usposobljene medicinske sestre kodirajo podatke, prispele na prijavnicah, v skladu z mednarodnimi in v RRS dogovorjenimi pravili.

Za razvrščanje neoplazem po umestitvi RRS od leta 1997 uporablja deseto revizijo Mednarodne klasifikacije bolezni in sorodnih zdravstvenih problemov za statistične namene, do takrat pa je uporabljal osmo. Prav pri uvrščanju med maligne bolezni je treba opozoriti še na klasifikacijo za morfologijo neoplazem, za katero uporabljamo morfološki del Mednarodne klasifikacije bolezni za onkologijo, od poročila za leto 2001 njeno tretjo izdajo. V tej izdaji je spet nekaj sprememb, tudi, katere histološke vrste sodijo med maligne. Po tretji reviziji so med maligne uvrščene kronične mieloproliferativne bolezni in mielodisplastični sindromi (sedaj v topografski šifri C96.7). V skladu z novimi pravili tudi mejno malignih ovarijskih tumorjev ne uvrščamo več v kategorijo C56, pač pa v D39.1.

Za opredelitev stadija v registrih večinoma uporabljamo poenostavljeno opredelitev stadijev, ki upošteva vse preiskovalne metode, vključno z operacijo; če bolnik ni bil poprej zdravljen, tudi obdukcijo. Uporabljamo in navajamo jo zato, ker so podatki o stadiju bolezni po klasifikaciji TNM na prijavnicah pogosto pomanjkljivi. Poenostavljena opredelitev stadijev pri solidnih tumorjih praviloma sledi klasifikaciji TNM. V omejeni stadij je razvrščena bolezen, kjer je tumor označen kot T1 in T2 (razen pri dojki, malignem melanomu in ščitnici, pri katerih so vključeni tudi tumorji T3, in maternicnem vratu, telesu in sarkomih, pri katerih so vključeni le tumorji T1) in pri kateri niso prizadete področne bezgavke in ni zasevkov v oddaljenih organih (N0, M0). V stadiju regionalne razširitve je bolezen, pri kateri je tumor opredeljen kot T3 in T4 (razen v omenjenih izjemah) in/ali so prizadete tudi področne bezgavke (N1), zasevkov v oddaljenih bezgavkah in organih pa ni (M0). V stadiju oddaljene razširitve pa je tista bolezen, pri kateri so zasevki že v oddaljenih bezgavkah ali organih (M1). Maligni limfomi so opredeljeni po klasifikaciji Ann-Arbor.

Official Gazette of RS, No 9/92 and 65/00). The main sources of data are notifications gathered from all hospitals and diagnostic centres in Slovenia, exceptionally also from primary health care centres in case the patient has not been referred for further diagnostic investigations and/or treatment. Additional sources of information are death certificates and autopsy protocols stating cancer diagnosis.

The following data are collect on new cancer cases:

- *Identity data:* a uniform personal ID number, name and surname, maiden name, place of birth and address of permanent residence;
- *Particulars of disease*: anatomic cancer site, histological or cytological diagnosis, stage by TNM or other suitable classification, staging after all examinations performed, method of establishing diagnosis;
- *Treatment information:* hospital, department, patient record number, reason for admission, date of admission, date of present cancer diagnosis, any former treatment of the present cancer, method of treatment during present admission, date of the beginning of treatment, sequential number of present cancer, previous evidence of any other cancer;
- *Information on discharge or death:* date of discharge or death, status on discharge, possible autopsy, any foreseen follow up or patient's transfer.

Calculation of patient survival, this being one of the primary tasks of CRS, requires the patient's vital status. This data is obtained quarterly from the Central Population Registry for all parsons registered in the CRS data base as alive. A person may be alive, dead or lost to follow-up. In lost persons, the date of last notification or the date of loss obtained from the Central Population Registry, whichever first, is considered as date of loss. From 1983, since the uniform personal ID number has been used in Slovenia, in CRS the percentage of the lost to follow-up is below 1%, in patients registered in the decade between 1996–2005 being 0.1%.

PREPARATION OF DATA FOR COMPUTER PROCESSING

In CRS specially trained nurses code the data retrieved from notifications in accordance with the internationally and internally agreed rules.

Since 1997, cancer sites are coded according to the 10th revision of the International Statistical Classification of Diseases and Related health Problems (ICD-10); before, the 8th revision was used (ICD-8). When classifying tumours as malignant, the behaviour digit of the morphology code of the third edition of International Classification of Diseases for Oncology has been used since the report for 2001 on. In this edition, some changes were introduced in terms of morphology and behaviour code. According to this classification, chronic myeloproliferative disorders and myelodisplastic syndromes are classified as malignant (currently C96.7 topography code), while ovarian tumours of borderline malignancy are currently coded as D39.1 (and not C56).

A simplified definition of stages is generally used for stage classification by registries, taking into account all investigation methods, including surgery; in case the patient was not treated before death, the autopsy record is considered as well. The simplified stage definition is used because the data on stage according to TNM Classification System are often lacking, in cancer notification forms. In solid tumors, the simplified stage definition generally follows the TNM classification. Localised stage includes all cancers where the tumour has been classified as T1 and T2 (except in breast, malignant melanoma and thyroid cancer, where T3 is also included, and uterine cervix, uterine corpus and sarcomas, where T1 only is included), where neither regional node involvement nor distant metastases are found (N0, M0). The regional stage includes tumours classified as T3 and T4 (exceptions already mentioned) and/or regional node metastases (N1),

KAKOVOST PODATKOV REGISTRA IN POPOLNOST REGISTRACIJE

Kakovost podatkov registrov raka osvetljujejo naslednji kazalci: odstotni delež mikroskopsko (histološko ali citološko) potrjenih primerov in odstotni delež primerov, registriranih samo iz zdravniških poročil o vzroku smrti. Vrednosti teh kazalcev v treh opazovanih obdobjih so prikazane v Tabeli 1.

Popolnost registracije kaže delež vseh novih primerov raka na področju, ki ga pokriva register in ki so vključeni v podatkovno zbirko registra. Neposredno jo je mogoče meriti samo s posebnimi raziskavami, namenjenimi oceni popolnosti, npr. s ponovnim pregledom odpustnih diagnoz in popisov bolezni v bolnišnicah ali ambulantah na določenem območju. V Sloveniji takih raziskav zaenkrat še nismo opravili, veliko pa nam k popolnosti zajema pomagajo kolegi kliniki, ki jih zanima preživetje pri njih zdravljenih bolnikov in nam pošljejo podatke o svoji skupini bolnikov, med katerimi velikokrat najdemo take, ki jih v podatkovni zbirki RRS še ni.

Popolnost je večja tam, kjer imamo registri dostop do zdravniških poročil o vzroku smrti. Tako v Sloveniji za umrle za rakom, ki jih še nismo registrirali, dodatno poizvedujemo. S tem se izboljša popolnost registracije rakov s slabo napovedjo izida, ne pa manj usodnih. V Sloveniji predvidevamo, da je registracija manj popolna pri nemelanomskem kožnem raku in pri tistih malignomih, ki se zdravijo samo ambulantno. Podoben problem imajo tudi drugi populacijski registri raka v Evropi.

Popolnost registracije merimo z razmerjem med umrljivostjo in incidenco ter s stabilnostjo incidence v času. To pomeni, da med posameznimi leti ni velikih nihanj incidence in da ni velikih razlik v odstotnem deležu primerov, ki jih register zabeleži po tem, ko že zaključi obdelavo podatkov za določeno leto. Razmerja med umrljivostjo in incidenco za posamezno petletno obdobje so prikazana v Tabeli 2, število naknadno prijavljenih primerov za vsa leta registracije pa je objavljeno v letnih poročilih RRS.

Tabela 1: *Incidenca raka v treh opazovanih petletnih obdobjih glede na način postavitve diagnoze.*

Table 1: *Cancer incidence in three 5-year observation periods by method for establishing diagnosis.*

Obdobje / Period	Vsi registrirani / All registered	Delež mikroskopsko potrjenih (%) / % of microscopically confirmed	Delež ugotovljenih z drugimi preiskavami (%) / % of diagnosed by other investigations	Delež registriranih samo iz zdravniških poročil o vzroku smrti (%) / % registred from death certificats only
1991–1995	35.166	92,4	4,0	3,6
1996–2000	42.425	93,1	5,1	1,9
2001–2005	50.815	93,6	5,2	1,2

IZBOR BOLNIKOV, VKLJUČENIH V ANALIZO PREŽIVETJA

V analizo smo vključili bolnike s stalnim prebivališčem v Sloveniji, ki jim je bil rak ugotovljen v letih 1991 do 2005. Za boljše spremljanje trendov incidenčnih in umrljivostnih stopenj in za oceno desetletnega relativnega preživetja so v slikah dodani še podatki o bolnicah in bolnikih, ki jim je bila diagnoza postavljena v letih 1986–1990. Bolniki, ki jih obravnavamo, so lahko imeli eno ali več primarnih rakavih bolezni. Če je imel bolnik več kot eno rakavo bolezen, je vsak primer rakave bolezni obravnavan v tistem poglavju, ki prikazuje preživetje po organskem sistemu, ki ga je rak prizadel.

Pri vseh analizah smo upoštevali stanje baze RRS na dan 1. junija 2008, zato se lahko incidenca iz naše analize po posameznih letih razlikuje od podatkov, kot jo objavlja RRS v letnih poročilih, saj okrog 4 % bolnikov registriramo šele po izdaji letnih poročil. Bolnike smo spremljali do 31. marca 2008. Iz analize preživetja smo izločili 2675 oseb, ki smo jih v RRS registrirali samo na podlagi zdravniških poročil o vzrokih smrti, saj za te ne poznamo datuma ugotovitve

without presence of metastases in distant lymph nodes or organs (M0). The disease with metastases in distant lymph nodes or organs is classified as the remote stage (M1). Malignant lymphomas are classified according to Ann-Arbor System.

DATA QUALITY AND COMPLETENESS OF REGISTRATION

The quality of information can be assessed by the following parameters: the percentage of microscopically (histologically or cytologically) confirmed cases and the percentage of cancer cases registered on the basis of death certificates only. The values of these parameters in the three observation periods are presented in Table 1.

The completeness of registration shows the proportion of all new cancer cases in the region covered by the registry, which are included in the registry's data base. It can be measured directly only by means of special surveys for the evaluation of completeness, e. g. by reviewing patient record in the hospitals or outpatient clinics in a particular region. In Slovenia, no such surveys have been carried out so far. However, a considerable contribution towards the completeness of registration is made by our colleagues – clinicians, who send us the data on their groups of patients in order to get information about their survival and among them we often find cases that have not been entered in the CRS database yet.

The registration is more complete where the registries have access to death certificates, and can send out additional inquiries about disease for the deceased that have not been entered into the database yet. This improves the completeness of registration of cancers with poor prognosis, but not also of less fatal ones. It is presumed that in Slovenia registration is less complete in non-melanoma skin cancer and in malignomas that are treated on the out-patient basis only.

The completeness of registration is measured by the ratio between mortality and incidence, and by stability of incidence in time, which means that there are no major fluctuations in the incidence between individual years, and neither great differences in the percentage of cases registered only after the data for a particular year have already been processed. The ratios between the mortality and incidence for individual 5-year periods are presented in Table 2; the numbers of subsequently reported cases for all registration years are published in the annual reports of the CRS.

Tabela 2: *Število umrlih in zbolelih za rakom ter razmerje med umrljivostjo in incidenco v treh opazovanih petletnih obdobjih.*

Table 2: *The number of the deceased and diagnosed with cancer and the ratio between the mortality and incidence in three 5-year observation periods.*

Obdobje / Period	Število umrlih / Number of deceased	Število novih primerov / Number of new cases	Umrljivost/incidenca / Mortality/incidence
1991–1995	17.690	35.166	0,50
1996–2000	23.572	42.425	0,56
2001–2005	25.054	50.815	0,49

SELECTION OF PATIENTS INCLUDED IN THE SURVIVAL ANALYSIS

The analysis includes patients with permanent residence in Slovenia diagnosed with cancer in the years 1991–2005. In figures, data on patients diagnosed in the period 1986–1990 were added for better presentation of trends in the incidence and mortality rates as well as for the evaluation of 10-year relative survival. The analysed patients might have had one or more primary cancers. If the patient had more than one cancer, each of them is dealt with in the chapter presenting the survival by organ system affected.

bolezni. Praviloma se iz analiz preživetja izključijo tudi primeri raka, pri katerih je datum ugotovitve enak datumu smrti, torej je čas preživetja enak nič. Izmed 1793 takšnih primerov so v 1553 z obdukcijo ugotovili, da so imeli raka. Prav tako nismo vključili podatkov o 117 bolnikih, za katere ne poznamo vitalnega stanja (oz. so bili izgubljeni iz evidence) (Tabela 3).

Tabela 3: *Število oseb, ki smo jih izločili iz analize preživetja.*
Table 3: *The number of persons excluded from the survival analysis.*

Obdobje / Period	Registrirani samo iz zdravniških poročil o vzrokih smrti / Registered from death certificates only	Ugotovljeni na obdukciji / Diagnosed at autopsy	Ugotovljeni na dan smrti / Diagnosed on the date of death	Izgubljeni / Lost
1991–1995	1263	492	95	59
1996–2000	792	548	59	35
2001–2005	620	513	86	23

V posameznih poglavjih obravnavamo odrasle bolnike s 30 izbranimi primarnimi mesti raka in z vsemi mesti raka skupaj. Po starosti smo jih razvrstili v tri večje skupine: 20–49, 50–74 in 75 let in več. Pri vseh primerih raka skupaj nismo upoštevali kožnega (C44), saj gre za bolezen, ki je praktično popolnoma ozdravljiva in zaradi nje v zadnjih desetletjih skoraj nihče več ne umre. Ker je prijavljanje kožnega raka povsod po Evropi pomanjkljivo, delež neregistriranega pa je zelo različen, tudi v mednarodnih primerjavah kožnega raka ne upoštevajo pri izračunu preživetja vseh bolnikov z rakom.

IZRAČUN PREŽIVETJA

V biostatistiki definiramo preživetje kot čas med dvema dogodkoma, najpogosteje med datumom diagnoze in datumom smrti. Pri skupinah bolnikov je preživetje delež bolnikov, ki so po izbranem obdobju od postavitve diagnoze še živi. Preživetje bolnikov z rakom običajno opazujemo po enem, treh, petih in desetih letih po diagnozi.

Možnosti in metod za izračun preživetja je več. Praviloma pa se v vsaki analizi preživetja pojavijo bolniki, pri katerih trajanja življenja po diagnozi ni mogoče izmeriti, saj za njih vemo le, da so živeli določen čas po diagnozi, podatka o času smrti pa ne poznamo. Takšnim podatkom pravimo krnjeni podatki. Razlogov za krnjenje je več: najpogosteje je posledica tega, da so ob koncu študije nekateri bolniki še živi, včasih pa posameznika tudi predčasno izgubimo iz evidence, na primer zaradi selitve v tujino. V vsakem primeru je zaradi krnjenih opazovanj potreben poseben pristop pri ocenjevanju deleža preživelih.

Osnovna in hkrati najpreprostejša mera preživetja je tako imenovano opazovano preživetje. Med različnimi metodami, ki so na voljo za izračun opazovanega preživetja, se danes največkrat uporablja Kaplan-Meierjeva metoda. Ta metoda je zaradi svoje natančnosti posebej primerna za analize z majhnim številom podatkov, vendar pa jo v času zmogljivih računalnikov uporabljamo tudi pri večjih vzorcih, saj je natančnost še vedno velika, metoda je uveljavljena, računanje pa enostavno. Za oceno opazovanega preživetja smo jo uporabili tudi v tej knjigi.

V kliničnih raziskavah, v katerih nas običajno zanimajo samo smrti, ki so posledica natančno določene bolezni, vse umrle zaradi drugih vzrokov v analizi obravnavamo kot krnjene (t. i. vzročno specifično preživetje). Tak pristop bi bil smiseln tudi v populacijskih raziskavah, vendar pa se v praksi izkaže, da je v njih vključeno število bolnikov praviloma preveliko, da bi za vsakega preverjali natančen vzrok smrti; uradni vzroki smrti, ki jih v Sloveniji zbira Inštitut za varovanje zdravja RS, so za take posebne namene pogosto premalo natančni. Zaradi tega in zaradi neprimerljivosti opazovanih preživetij med različnimi populacijami se danes v populacijskih raziskavah

In all the analyses, the status of CRS database on 1 June 2008 was taken into account, and therefore the incidence in our analysis by individual years may differ from the data published in CRS annual reports, as some 4% of patients were registered only after the annual reports had already been published. The patients were followed up until 31 March 2008. 2675 persons, registered only on the basis of autopsy reports, were excluded from the analysis because of the unknown date of diagnosis. Generally, the cases where the date of diagnosis is the same as the date of death are also excluded from analyses since the duration of survival in these cases is equal to zero. In 1553 out of 1793 such cases autopsy revealed cancer. The data of 117 patients with unknown vital status (or the lost ones) were not included either.

Individual chapters are dedicated to 30 selected primary cancer sites in adult patients and cumulatively to all cancers. They were distributed into three major categories by age: 20–49, 50–74 and 75 years plus older. Skin cancer (C44) was not considered among all cancers together, since this is a disease that is practically fully curable and of which hardly anyone has died in the last decades. As everywhere in Europe, the reporting of skin cancer is incomplete and the proportion of unregistered cases is greatly varying, in comparative international studies too skin cancer is not considered in the survival statistics of all cancer patients.

CALCULATION OF SURVIVAL

In biostatistics, survival is defined as the time between two events, mostly between the date of diagnosis and the date of death. In groups of patients, the survival represents the proportion of patients still alive after a selected period of time from diagnosis. Survival of cancer patients is generally observed after one, three, five and ten years from diagnosis.

There are more possibilities and methods for the calculation of survival available. In every survival analysis, however, there are patients in whom the duration of survival after diagnosis cannot be determined, since it is only known that they lived a certain period of time from diagnosis while the time of their death is unknown. Such data are referred to as censored data. The reasons for their occurrence are multifold: most frequently they are attributable to the fact that by the end of the study, some patients are still alive while others may be prematurely lost from evidence, e. g. because of moving abroad. In any case, such incomplete observations require a special approach to the evaluation of survival rates.

A basic and at the same time most simple measure of survival is the so-called observed survival. Among various methods available for calculating the observed survival, currently the most frequently used is Kaplan-Meier's method. High accuracy renders this method particularly suitable for analyses with a limited number of data; however, thanks to powerful computers available nowadays, it is also used in larger samples, since its accuracy is still high while the method is well established and calculation simple. For the needs of this publication too, observed survival was calculated according to this method.

In clinical studies, where our interest is generally focused on deaths due to a particular disease, in the analysis all deaths due to other causes are treated as censored (the so-called cause-specific survival). Such approach would seem reasonable also in population studies, however, in practice it turns out that the number of patients entered into such studies is too large to allow the exact cause of death to be established for each individual patient; the data on official causes of death that are collected by the Institute of Public Health of the Republic of Slovenia, are often insufficiently accurate for such purposes. Therefore, and because of the incomparability of the observed survival between different populations, currently relative survival rather than observed one is used in population studies. The calculation of relative survival does not require information on the cause of death, but nevertheless, the method yields a result that is

namesto opazovanega uporablja relativno preživetje. Za izračun relativnega preživetja ne potrebujemo vzrokov smrti, kljub temu pa je metoda zastavljena tako, da je rezultat dober približek preživetja bolnikov kot v primeru, da bi upoštevali kot vzrok smrti samo proučevanega raka.

Relativno preživetje je razmerje med opazovanim in pričakovanim preživetjem, t. j. preživetjem, ki ga glede na spol in starost v določenem obdobju pričakujemo v celotni populaciji, iz katere prihajajo bolniki. Pričakovano preživetje se izračuna na podlagi podatkov o splošni umrljivosti, ki se v obliki tablic umrljivosti za posamezno državo rutinsko objavljajo v okviru demografske statistike. Za izračun relativnega preživetja v tej knjigi smo uporabili slovenske letne popolne momentne tablice umrljivosti.

V praksi je relativno preživetje bolnikov z rakom praviloma manjše od 100 %. V redkih primerih, ko je relativno preživetje enako 100 %, pa lahko zaključimo, da je preživetje skupine bolnikov z rakom enako preživetju splošne populacije in torej bolezen sama ni skrajšala pričakovane življenjske dobe. Teoretično je izračunano relativno preživetje lahko tudi večje od 100 %, kar pomeni, da imajo bolniki boljše preživetje kot celotno prebivalstvo. To se lahko zgodi v primeru, če bolni privzamejo bolj zdrave življenjske navade, ali pa če njihove pridružene bolezni temeljiteje obravnavajo kot v povprečju v splošni populaciji. Takšnega, teoretično možnega primera, med slovenskih bolniki z rakom nismo zasledili.

Za izračun relativnega preživetja poznamo več metod. Pri kohortni metodi sledimo skupini bolnikov določen čas, običajno pet let. Vsaka oseba, vključena v analizo, mora imeti torej možnost preživeti pet let. Preživetje izračunamo kot delež bolnikov, živih po določenih obdobjih, običajno po enem, treh in petih letih po diagnozi. Pri popolni metodi vključimo v izračun tudi bolnike, ki so zboleli kasneje in smo jih ob koncu študije sledili manj kot pet let. Bolniki, ki smo jih sledili krajši čas, prispevajo v izračun popolnega relativnega preživetja samo toliko časa, kot smo jih dejansko lahko sledili. Tako skupina zbolelih tri leta pred zaključkom študije prispeva k eno- in triletnemu popolnemu relativnemu preživetju, k petletnemu pa ne.

Posebna oblika popolnega relativnega preživetja je obdobno relativno preživetje. Pri metodi obdobnega preživetja vključimo v izračun enoletnega preživetja samo tiste bolnike, ki so zboleli v zadnjem letu, v izračun dveletnega preživetja samo tiste bolnike, ki so zboleli dve leti nazaj in so preživeli prvo leto ter ustrezno v izračun petletnega preživetja samo tiste bolnike, ki so zboleli pred petimi leti in so po diagnozi živeli vsaj štiri leta.

Za nazornejši prikaz razlike med kohortnim, popolnim in obdobnim relativnim preživetjem si poglejmo primer analize relativnega preživetja, ki jo želimo narediti za bolnike z rakom, za katere imamo podatke o vitalnem stanju na dan 31. 12. 2008. Kohortno petletno relativno preživetje lahko izračunamo le za bolnike, ki so zboleli do konca leta 2003, saj je samo to skupino mogoče slediti vsaj pet let. V analizo popolnega petletnega relativnega preživetja lahko vključimo tudi vse bolnike, ki so zboleli do konca leta 2007 in jih spremljamo do 31. 12. 2008; na ta dan je njihov čas opazovanja krnjen, razen seveda pri tistih, ki so do takrat že umrli. Tako bolniki, zboleli leta 2007, prispevajo le k izračunu enoletnega preživetja, samo bolniki, ki so zboleli do konca leta 2003, pa imajo možnost prispevati k izračunu popolnega petletnega relativnega preživetja.

V analizo obdobnega petletnega relativnega preživetja ravno tako vključimo bolnike, zbolele v obdobju 2003–2007. Vendar se metoda bistveno razlikuje od prejšnje v tem, da bolniki, ki so zboleli leta 2003, prispevajo le k izračunu petletnega preživetja, medtem ko teh podatkov (za razliko od popolnega preživetja) ne upoštevamo pri izračunu enoletnega preživetja. Obdobno enoletno relativno preživetje tako izračunamo iz skupine bolnikov, zbolelih v letu 2007, dveletno preživetje iz skupine zbolelih leta 2006 itd. Zaradi vsakoletnega napredka medicine in s tem boljše napovedi izida bolezni pri bolnikih, ki so zboleli zadnja leta, so obdobna petletna relativna preživetja običajno večja od popolnih preživetij, ta pa boljša od kohortnih preživetij.

a good approximation of patients' survival in the case that the observed cancer would be considered as the only cause of death.

Relative survival is a ratio between the observed and the expected survival, i. e. the survival expected with respect to gender and age in certain time period in the whole population the patients come from. The expected survival is calculated from general mortality data, published routinely in the form of mortality tables for an individual country within the framework of its vital statistics The relative survival for the needs of this publication was calculated using the Slovenian annual complete yearly period life tables.

In practice, the relative survival of cancer patients is generally less than 100%. In rare cases, when the relative survival is equal to 100%, it can be concluded that the survival in cancer patient group is comparable with survival in general population, which means that the disease itself has not shortened the expected lifespan. Theoretically, the calculated relative survival may even exceed 100%, meaning that patients have better survival than the whole population. This may happen if the sick adopt a healthier lifestyle, or if their concomitant diseases are treated more consistently than in general population on average. No such theoretically possible case has been noted in the Slovenian cancer patient population.

Relative survival can be calculated by different methods. In the cohort method, a group of patients is followed up for a certain period of time, generally for five years. Thus, every person included in the analysis should have the possibility to survive five years. Survival is calculated as the proportion of patients alive after certain periods of time, generally after one, three and five years from diagnosis. In complete method, patients diagnosed later on and followed up for less than five years by the end of the observation period are also included. The patients followed up for a shorter period of time are considered in the calculation of complete relative survival only for the time when they were actually followed. Thus, a group diagnosed three years before the completion of study, contributes to one- and three-year complete relative survival but not also to five-year survival.

A special form of complete relative survival is period relative survival. In the method of period survival, only the patients diagnosed in the last year are included in the calculation of one-year survival, while the calculation of two-year survival includes only the patients diagnosed two years before and have survived the first year; accordingly, the calculation of five-year survival includes only the patients diagnosed five years ago and still alive at least four years from diagnosis.

For better demonstrating the differences between cohort, complete and period relative survival, a case of relative survival analysis carried out in cancer patients with data on their vital status on 31 December 2008 is presented. Cohort 5-year survival can only be calculated for patients diagnosed by the end of 2003, since only that group can be followed up at least five years. An analysis of complete 5-year relative survival can also include all patients diagnosed by the end of 2007 and followed up until 31 December 2008, their follow-up period being censored by that date, except in the patients that have already died. Thus, patients diagnosed in 2007 are considered only in the calculation of one-year survival, while only the patients diagnosed by the end of 2003 have the chance to be considered in the calculation of complete 5-year relative survival.

Likewise, an analysis of period 5-year relative survival includes patients diagnosed in the period 2003–2007. However, this method significantly differs from the former in that the patients diagnosed in 2003 are considered only in the calculation of 5-year survival, but (for the difference from complete survival) not in the calculation of one-year survival. Thus, period one-year relative survival is calculated from the group of patients diagnosed in 2007, two-year survival from the group of those diagnosed in 2006, etc. Because of the continuous advances in medicine, and associated with that better prognosis of the outcome of disease in patients

Pri prikazu in razlagi rezultatov obdobnega relativnega preživetja je določena zadržanost vseeno na mestu, saj gre, kot je razvidno iz opisanega postopka, v tem primeru zgolj za napoved preživetja bolnikov – bolniki, zboleli leta 2007, so konec leta 2008 lahko preživeli le leto dni. Tako z obdobnim relativnim preživetjem na opisan način le ocenimo, kakšno bi bilo njihovo petletno relativno preživetje.

V naši knjigi smo za izračun vseh relativnih preživetij uporabili metodo popolnega relativnega preživetja. Bolniki, vključeni v analize, so zboleli do konca leta 2005, sledili pa smo jih do 31. 3. 2008. Za izračun smo uporabili programsko kodo *relsurv* za okolje R. V študiji EUROCARE-4, ki jo povzemamo za primerjavo povprečnih slovenskih, evropskih in ameriških bolnikov, zbolelih v obdobju 2000–2002, ki so jim sledili do konca leta 2003, pa so uporabili metodo obdobnega preživetja tudi pri naših, slovenskih podatkih.

PRIKAZ REZULTATOV

Vsako poglavje obravnava eno od rakavih bolezni pri odraslih glede na organ, v katerem je nastala. Na koncu so prikazani vsi raki skupaj, razen kožnega, pri odraslih, nazadnje pa še rak pri otrocih in mladostnikih.

V začetku vsakega poglavja je navedeno število vseh zbolelih v 15-letnem obdobju, na Sliki 1 pa prikazujemo najosnovnejša kazalca bremena bolezni, incidenčne in umrljivostne stopnje določene rakave bolezni pri obeh spolih skupaj in njihove časovne trende v 20 letih, 1986–2005. Poleg grobih prikazujemo tudi starostno standardizirane stopnje. Za standardizacijo smo uporabili neposredno metodo, za standard pa starostno strukturo prebivalcev Slovenije sredi leta 1986. Iz razlike med grobimi in standardiziranimi incidenčnimi stopnjami lahko ocenimo, kolikšen delež sprememb gre pripisati staranju slovenskega prebivalstva, koliko pa gre na račun vseh drugih nevarnostnih dejavnikov. Spremembe umrljivostnih stopenj zrcalijo spremembe incidence in učinkovitosti zdravljenja. Povprečne letne odstotne spremembe smo ocenili z matematičnimi modeli segmentne linijske regresije. Za modeliranje smo uporabili statistični program Joinpoint, ki zaporedne večletne točkovne podatke o incidenci ali umrljivosti opiše z eno ali več regresijskimi premicami; iz regresijskega koeficienta vsake od premic pa lahko izračunamo povprečno letno spremembo za obdobje, ki ga posamezna premica (segment) predstavlja.

Trend incidenčnih in umrljivostnih stopenj, ki ga prikazujemo na začetku vsakega poglavja, se nanaša na vse bolnike z obravnavanim rakom vseh starosti, vključno s tistimi, ki jim je bila diagnoza postavljena šele ob smrti. Vse nadaljnje analize pa smo omejili samo na bolnike, ki jim diagnoza ni bila postavljena šele ob smrti, saj ti ne prispevajo ničesar k oceni preživetja, ker sta datum diagnoze in smrti enaka; bolnike smo razdelili na odrasle (stare 20 let in več) in na otroke in mladostnike (stare 0–19 let).

Prikazu trendov sledi opis števila v analizo vključenih in izključenih bolnikov. Kjer je bilo smiselno, navajamo odstotke bolnikov z natančneje opredeljenim mestom vznika raka v posameznem organu, pa delež mikroskopsko potrjenih primerov in najpogostejše histološke vrste malignoma.

Starost bolnikov ob diagnozi in stadij bolezni v treh obdobjih, 1991–1995, 1996–2000 in 2001–2005, sta prikazana v Tabeli 1 in Tabeli 2. Pri vsaki rakavi bolezni v besedilu navajamo tudi odstotek bolnikov, ki so bili po podatkih RRS specifično zdravljeni, kakšno je bilo prvo zdravljenje in v katerih slovenskih bolnišnicah se je začelo.

Relativno eno-, tri-, pet- in desetletno preživetje bolnikov obeh spolov skupaj, ki jim je bila diagnoza postavljena v štirih petletnih obdobjih, prikazuje Slika 2. V Tabeli 3 pa je prikazano opazovano in relativno eno-, tri- in petletno preživetje, ločeno po spolu. Slika 3 kaže petletno relativno preživetje po stadiju, Slika 4 pa po starosti. V obeh slikah je za primerjavo dodano še preživetje vseh bolnikov skupaj.

diagnosed in recent years, the period 5-year survivals generally turn out to be better than complete survivals, and the latter better than cohort survivals. But, the results of period relative survival should nevertheless be presented and interpreted with a certain degree of caution, since it is evident from the procedure described, that in this case the anticipated survival is but estimated; by the end of 2008, patients diagnosed in 2007 might have survived one year only. Using the described period relative survival method, we can assess what would be their 5-year survival.

In our publication, all relative survivals were calculated by means of the complete relative survival method. Patients included in the analyses were diagnosed until the end of 2005 and followed up till 31 March 2008. For calculation, the *relsurv* program code for R environment was used. In EUROCARE-4 study, which was used as a reference to compare the survival of average Slovenian, European and American patients diagnosed in the period 2000–2002 and followed up until the end of 2003, the method of period survival was also applied to the Slovenian data.

THE PRESENTATION OF RESULTS

Every chapter is devoted to one of the cancer diseases in adults, with respect to the organ of origin. In the end, all cancers (except cutaneous) in adults are presented together, and finally also cancers in children and adolescents.

Every chapter starts with the number of patients diagnosed in the 15-year period studied, while Figure 1 presents the basic indicators of disease burden, the incidence and mortality rates of a particular cancer disease in both genders together and their time trends in the course of 20 years, from 1986 to 2005. Besides the crude rates also the age-standardized rates are presented. Standardization was done by means of the direct method, using the age structure of Slovenia's population in the middle of 1986 as standard. From the difference between the crude and standardized incidence rates we can assess the proportion of changes that should be ascribed to population ageing and the proportion due to other risk factors. The changes in mortality rates reflect the changes in incidence and treatment success. Average annual percentage changes were calculated using the mathematical model of segmental linear regression. Statistical programme Joinpoint was used as a modelling tool presenting sequential long-term data on incidence or mortality as one or more regression lines; from the regression coefficient of each line we can calculate an average annual change for the period represented by an individual line (segment).

The trend in incidence and mortality rates, presented in the beginning of every chapter, refers to all patients of all ages, who have that particular cancer, including those diagnosed only after death. All further analyses were limited to patients diagnosed during their lifetime, as those diagnosed only after death do not contribute anything to the evaluation of survival, because their dates of diagnosis and death are the same.

After trend presentation, the numbers of patients included and excluded from the analysis are given. The percentages of patients with precisely defined cancer site in a particular organ, the proportion of microscopically confirmed cases and the most common histological types of malignomas are stated when appropriate.

Age of patients at diagnosis and stage of the disease in three time periods, i. e. 1991–1995, 1996–2000 and 2001–2005 are presented in Table 1 and Table 2. Each description of cancer disease also contains the data on the percentage of patients receiving specific treatment, the type of their primary treatment and the hospital where it was started.

Relative 1-, 3-, 5- and 10-year survivals of patients of both genders together, diagnosed in the four 5-year periods, are presented in Figure 2. The observed and relative 1-, 3- and 5-year survivals for each gender separately are presented in Table 3. 5-year relative survival by stage is

Preživetje dodatno osvetljujeta še dva podatka, zapisana ob koncu uvodnega dela: pogojno petletno relativno preživetje in preživetje bolnikov, pri katerem je proučevani rak edina rakava bolezen. Pogojno preživetje je petletno relativno preživetje tistih bolnikov, ki so preživeli prvo leto po postavitvi diagnoze. Praviloma je večje od tistega, ki ga računamo od datuma diagnoze. Pri nekaterih rakavih boleznih pričakujemo še druge in naslednje primarne rake; bolniki, pri katerih je bila proučevana rakava bolezen edini rak, imajo praviloma večje preživetje.

Ob koncu uvodnega dela prikazujemo petletno relativno preživetje slovenskih bolnikov, bolnikov v Evropi in v nekaterih območjih ZDA. Vrednosti so povzete po raziskavi EUROCARE-4, v kateri so združili podatke 31 registrov raka iz 15 evropskih držav ter podatke iz ZDA, ki jih posreduje program SEER ameriškega Državnega inštituta za raka (13 registrov raka). Vsi bolniki so zboleli v obdobju 2000–2002, stari so 15 let in več, za izračun pa je bila uporabljena metoda obdobnega relativnega preživetja. Zaradi različne starostne razporeditve bolnikov z rakom v posameznih področjih so v raziskavi EUROCARE-4 obdobno relativno preživetje tudi starostno standardizirali. V naši knjigi pri večini anatomskih mest prikazujemo starostno standardizirane vrednosti iz te raziskave. Pri sedmih anatomskih mestih, kjer je bilo v Sloveniji malo primerov (ustno in spodnje žrelo, jetra, trebušna slinavka, modo, možgani in akutna limfoblastna levkemija), je starostna standardizacija tako spremenila številčne vrednosti, da ne ustrezajo dejanskemu stanju, zato objavljamo pravilnejše, nestandardizirane vrednosti.

Analizi podatkov, ki smo jo pripravili v RRS, sledi komentar strokovnjakov klinikov, ki se dnevno ukvarjajo s specifičnim zdravljenjem bolnikov z rakom na OI Ljubljana in klinikah UKC Ljubljana. Razpravljajo o spremembah v metodah diagnostike in zdravljenja, ki so lahko vplivale na preživetje slovenskih bolnikov, in opozarjajo na pomanjkljivosti, ki bi morda, če bi jih odpravili, še izboljšale preživetje naših bolnikov.

VIRI
Literature

Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer 1996; 78: 2004–10.

Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961; 6: 101–21.

EUROCARE-1 do EUROCARE-4: vsi prispevki dosegljivi na: http://www.eurocare.it/.

Incidenca raka v Sloveniji (1986–2005). Ljubljana: Onkološki inštitut, Register raka za Slovenijo, 1989–2008.

Inštitut za varovanje zdravja RS. Mednarodna klasifikacija bolezni in sorodnih zdravstvenih problemov za statistične namene. 10. revizija (International Statistical Classification of Diseaseses and Related health Problems). Ljubljana: Inštitut za varovanje zdravja, 1995.

Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–81.

Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19: 335–51 (correction: 2001; 20: 655).

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents. Vol 8. Lyon: International Agency for Research on Cancer, 2002 (IARC Sci Publ 155).

Pohar M, Stare J. Relative survival analysis in R. Computer Methods and Programs in Biomedicine 2006; 81: 272–8.

Pompe-Kirn V, Zakotnik B, Volk N, Benulič T, Škrk J. Preživetje bolnikov z rakom v Sloveniji 1963–1990 (Cancer Patients' Survival in Slovenia 1963–1990). Ljubljana: Onkološki inštitut, Register raka za Slovenijo, 1995.

Pompe-Kirn V, Zakotnik B, Zadnik V. Preživetje bolnikov z rakom v Sloveniji 1983–1997 (Cancer Patients' Survival in Slovenia 1983–1997). Ljubljana: Onkološki inštitut, Register raka za Slovenijo, 2003.

Primic-Žakelj M, Pompe-Kirn V, Škrlec F, Šelb-Šemerl J. Can we rely on cancer mortality data? Checking the validity of cervical cancer mortality data for Slovenia = So podatki o umrljivosti za rakom verodostojni – analiza podatkov o umrljivosti zaradi raka materničnega vratu. Radiol Oncol 2001; 35: 243–7.

R Development Core Team, R. A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2005. Available at: http://www.R-project.org.

World Health Organisation. International Calssification of Diseases for Oncology. Geneva: World Health Organisation, 2000.

Žagar T. Lifetables for Slovenia 1982–2004. Rostock: Max Planck, 2005. 94 str. http://www.lifetable.de/cgi-bin/Country.plx?Country=Slovenia.

shown in Figure 3 and by age in Figure 4. In both figures the survival of all patients together is added for comparison.

The survival is additionally pointed out by the data given at the end of the introductory part: conditional 5-year relative survival and the survival of patients with the studied cancer as the only cancer. Conditional survival is the 5-year relative survival of patients surviving the first year from diagnosis. As a rule, it is greater than that calculated from the date of diagnosis. In certain cancers, a second and further primary cancers may be expected; patients with the studied cancer as the only primary cancer will generally have better survival.

By the end of the introductory part we present the 5-year relative survival of patients in Slovenia, in Europe and in certain regions of the USA. The results are summarized from the EUROCARE-4 study, where the data from 31 cancer registries of 15 European countries are pooled with the data from the USA reported by the SEER program of American National Cancer Institute (13 registries). All the patients were diagnosed in the period 2000–2002, they were aged 15 years or more and their survival was calculated according to the period relative survival method. Owing to different age distribution of cancer patients in individual areas, in EUROCARE-4 study the period relative survival was also age-standardized. In this publication, age-standardized values are presented for most cancer sites. In seven cancer sites with only few cases in Slovenia (oropharynx and hypopharynx, liver, pancreas, testis, brain and acute lymphoblastic leukemia), age standardization changed the values so much that they did not correspond to the actual situation, and therefore more correct, non-standardized values are published instead.

The data analyses prepared in the CRS are followed by commentaries of expert-clinicians daily dealing with specific treatment of cancer patients at the IO Ljubljana as well as at various departments of the UMC Ljubljana. They discuss the changes in diagnostic and therapeutic methods that might have influenced the survival of the Slovenian patients, and point out the drawbacks, which – if eliminated – may further improve the survival of our patients.

RAK PRI ODRASLIH

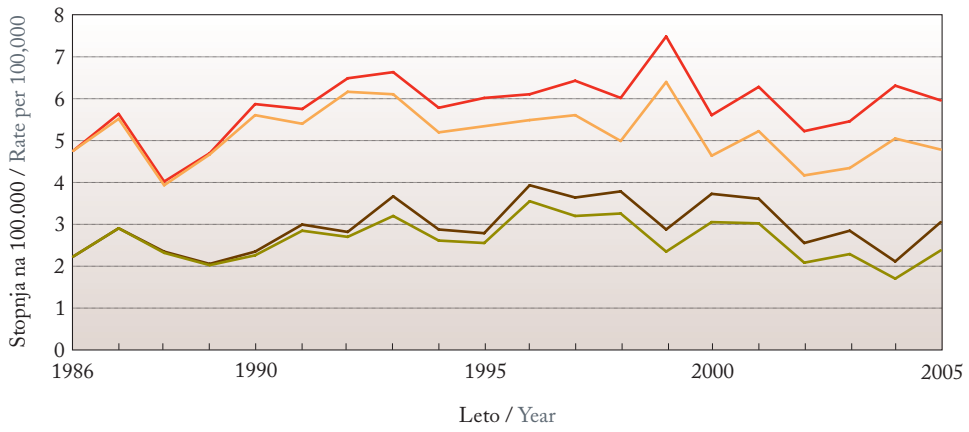
CANCER IN ADULTS

USTNO ŽRELO

MKB 10: C01, C05, C09, C10

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom ustnega žrela zbolelo 1834 ljudi, od tega 1629 moških in 205 žensk. Kot je razvidno s Slike 1, se tako grobe kot starostno standardizirane incidenčne in umrljivostne stopnje od leta 1991 zmanjšujejo. Groba incidenčna stopnja se zmanjšuje povprečno za 0,4 % letno, groba umrljivostna stopnja pa povprečno za 1,0 % letno. Starostno standardizirani stopnji se zmanjšujeta še nekoliko hitreje, saj v zadnjih letih zboli več starejših bolnikov (Tabela 1).



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka ustnega žrela, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of oropharyngeal cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1818 primerov; 15 bolnikov (0,8 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, enega, mlajšega od 20 let, pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. Pri polovici bolnikov je rak nastal prav v ustnem žrelu, pri 24 % v tonzilah, po 13 % pa jih je imelo raka na bazi jezika ali na nebu.

Manj kot 1 % bolnikov v vsakem obdobju ni imel mikroskopsko potrjene bolezni. Skoraj vsi primeri mikroskopsko potrjene bolezni (95 %) so bili ploščatocelični karcinomi.

Tabela 1: *Število bolnikov z rakom ustnega žrela po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of oropharyngeal cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	553	25,1	72,9	2,0	57	12,3	71,9	15,8
1996–2000	563	23,3	73,2	3,6	63	27,0	60,3	12,7
2001–2005	501	21,6	72,7	5,8	81	21,0	61,7	17,3

OROPHARYNX

ICD 10: C01, C05, C09, C10

EPIDEMIOLOGY

In the period 1991–2005, a total of 1834 persons were diagnosed with oropharyngeal cancer, of these 1629 males and 205 females. As evident from Figure 1, since 1991, crude as well age-standardized incidence and mortality rates have been decreasing. The estimated annual percentage decrease in crude incidence rate was 0.4% and in crude mortality rate 1.0%. Age-standardized rates have been decreasing even faster, as more elderly patients have been diagnosed in recent years (Table 1).

The survival analysis included 1818 cases; 15 patients (0.8%) diagnosed only after death were not considered in the analysis, one patient under 20 years of age is presented in the chapter on the survival of children and adolescents. In half of the patients cancer occurred in the oropharynx, in 24% in the tonsils, while cancer in the tongue base and the oral palate occurred in 13% each.

Approximately 1% of patients in each time period did not have microscopically confirmed disease. Practically all microscopically confirmed cancers (95%) were planocellular carcinomas.

Age of the majority of patients at diagnosis ranged between 50 and 74 years. In males, the proportion of those aged 75 years or older was low all the time while in females it reached 17% in the recent period. In both genders, 21% of patients developed the disease before the age of 50 (Table 1). The proportion of patients in individual age groups did not change significantly with time.

In all three time-periods, the majority of patients were diagnosed with regional disease; in the period 2001–2005 there were 79% such patients in both genders (Table 2). The remaining majority of patients had the disease diagnosed at a localized stage. A minimum proportion of patients, in whom stage at diagnosis was not determined, is encouraging. The proportion of patients in individual stages did not change significantly with time.

In the period 2001–2005, 6% of patients did not receive specific treatment. In all the observed 15-year period the proportion of untreated patients has remained practically unchanged. In the period 2001–2005, 91% of patients with specific treatment received radiotherapy. Radiotherapy alone was used in 36% of patients, one third received radiotherapy in combination with surgery and 21% in combination with chemotherapy, while 11% of the irradiated patients had surgery combined with chemotherapy. There were 8% of patients treated by surgery alone.

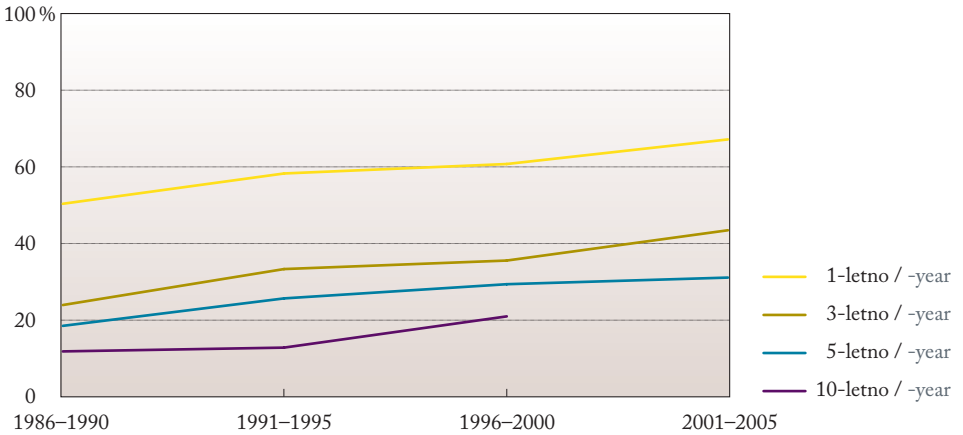
In the period 2001–2005, practically all patients started their treatment in one of the three leading Slovenian health institutions: 56% at the IO Ljubljana, 30% in the UMC Ljubljana, and 14% in the UMC Maribor.

The relative survival of patients with oropharyngeal cancer has been increasing; in 15 years, the 5-year relative survival increased by 5% (Figure 2), in males more than in females, although the 5-year relative survival in females was considerably better (Table 3). The relevance of stage

Tabela 2: *Število bolnikov z rakom ustnega žrela po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of oropharyngeal cancer patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	553	15,9	80,1	2,9	1,1	57	19,3	75,4	1,8	3,5
1996–2000	563	17,2	79,4	2,3	1,1	63	19,0	79,4	1,6	0,0
2001–2005	501	17,4	78,8	3,2	0,6	81	18,5	79,0	2,5	0,0



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom ustnega žrela po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of oropharyngeal cancer patients by period of diagnosis.*

Največji delež zbolelih je bil ob diagnozi star med 50 in 74 let. Delež starih 75 let in več je pri moških ves čas majhen, pri ženskah pa v zadnjem obdobju dosega 17 %. Pri obeh spolih pred 50. letom zboli 21 % bolnikov (Tabela 1). Deleži bolnikov v posameznih starostnih skupinah se s časom niso bistveno spreminjali.

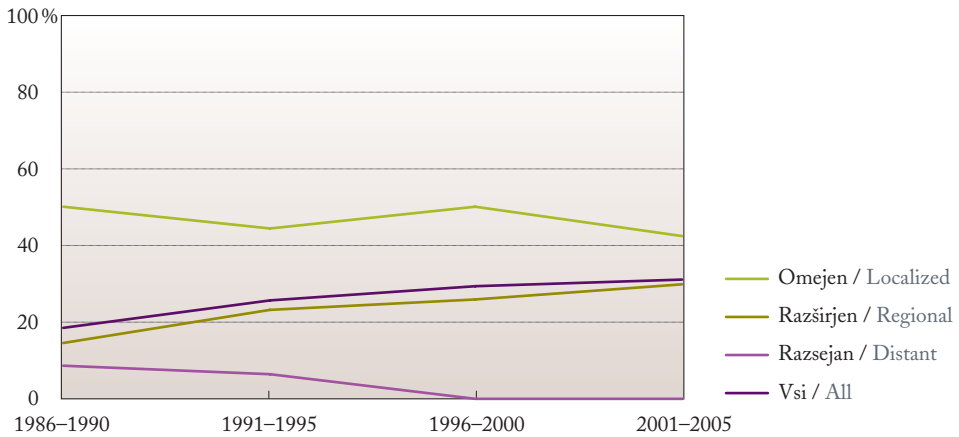
V vseh treh obdobjih je imelo največ bolnikov ob diagnozi razširjeno bolezen; v obdobju 2001–2005 je bilo takih bolnikov pri obeh spolih 79 % (Tabela 2). Večini preostalih bolnikov je bila bolezen odkrita v omejenem stadiju. Razveseljuje pa dejstvo, da le pri majhnem deležu bolnikov stadij ob diagnozi ni bil določen. Deleži posameznih stadijev se s časom niso bistveno spreminjali.

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom ustnega žrela po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of oropharyngeal cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	55,9 (51,9–60,2)	29,3 (25,7–33,3)	21,2 (18,0–24,9)	68,4 (57,4–81,6)	47,4 (36,0–62,3)	38,6 (27,8–53,5)
1996–2000	59,0 (55,0–63,2)	30,7 (27,1–34,8)	24,0 (20,7–27,8)	63,5 (52,7–76,6)	55,6 (44,5–69,3)	46,0 (35,2–60,1)
2001–2005	64,1 (60,0–68,4)	38,0 (33,9–42,6)	24,9 (20,8–29,8)	75,3 (66,5–85,3)	56,4 (46,5–68,4)	42,0 (31,2–56,6)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	57,1 (52,8–61,5)	31,4 (27,1–35,8)	23,9 (19,7–28,1)	70,1 (56,6–83,6)	51,0 (35,0–67,1)	43,7 (26,8–60,7)
1996–2000	60,3 (56,0–64,6)	32,9 (28,6–37,3)	27,0 (22,7–31,3)	64,5 (51,2–77,7)	58,3 (43,9–72,7)	50,0 (34,7–65,3)
2001–2005	65,5 (61,1–69,9)	40,8 (35,9–45,7)	28,3 (22,8–33,9)	76,8 (66,6–87,0)	60,1 (47,3–72,9)	46,9 (30,6–63,1)

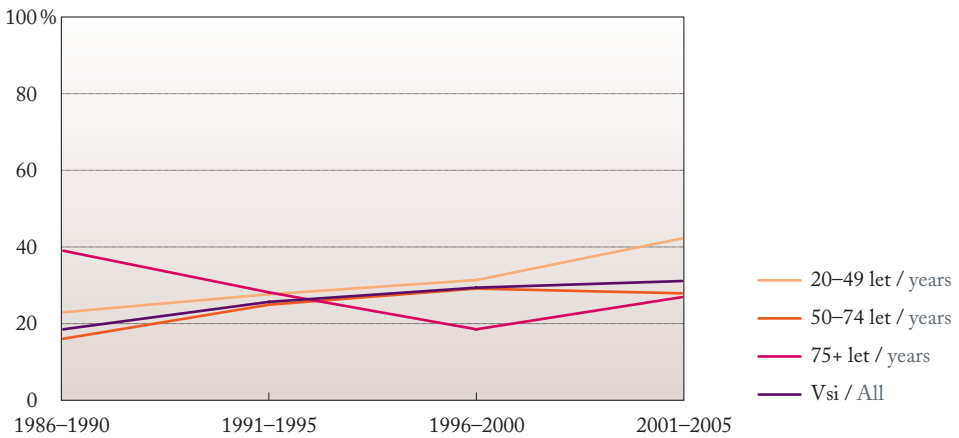


Slika 3: *Petletno relativno preživetje bolnikov z rakom ustnega žrela po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of oropharyngeal cancer patients by stage and period of diagnosis.*

at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage was 42%, while in those with regional stage at diagnosis it was 30%. Due to a small number of patients with disseminated disease, the evaluation of their survival is rather unreliable. In recent years, the greatest improvement in the survival was observed in patients with regional disease. Age is a prognostic factor as well, since the relative survival in patients over 50 years of age is considerably lower than in those diagnosed before the age of 50 years (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 31% (Figure 2); patients surviving the first year may expect to survive five years in 46%. In comparison with other cancer patients, those with cancers of the head/neck will more frequently develop a second primary cancer. Five-year relative survival of patients with oropharynx as the only primary cancer site was 40%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of Slovenian patients with oropharyngeal cancer is statistically significantly below the European average (Figure 5).



Slika 4: *Petletno relativno preživetje bolnikov z rakom ustnega žrela po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of oropharyngeal cancer patients by age and period of diagnosis.*

V letih 2001–2005 ni bilo specifično zdravljenih 6 % bolnikov. Delež nezdravljenih bolnikov ostaja v opazovanem 15-letnem obdobju skoraj enak. Med specifično zdravljenimi je bilo v letih 2001–2005 obsevanih 91 % bolnikov. Samo obsevanih je bilo 36 % bolnikov, pri tretjini je bilo obsevanje kombinirano z operacijo, pri 21 % pa s kemoterapijo; 11 % obsevanih bolnikov je poleg operacije v okviru prvega zdravljenja prejelo še kemoterapijo. Samo operiranih je bilo 8 % bolnikov.

V obdobju 2001–2005 so praktično vsi bolniki zdravljenje začeli v eni od treh vodilnih slovenskih zdravstvenih ustanov: 56 % na OI Ljubljana, 30 % v UKC Ljubljana in 14 % v UKC Maribor.

Relativno preživetje bolnikov z rakom ustnega žrela se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 5 % (Slika 2), pri moških bolj kot pri ženskah, čeprav je petletno relativno preživetje žensk precej boljše (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3; petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju 42 %, z razširjenim stadijem bolezni ob diagnozi pa 30 %. Bolnikov z razsejanim stadijem je malo, tako da je ocenjevanje njihovega preživetja precej nezanesljivo. V zadnjih letih se je najbolj izboljšalo preživetje bolnikov z razširjeno boleznijo. Napovedni dejavnik je tudi starost, saj je relativno preživetje starejših od 50 let precej manjše od preživetja zbolelih pred 50. letom starosti (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 31 % (Slika 2), tisti, ki preživijo prvo leto, pa lahko pričakujejo 46-odstotno petletno relativno preživetje. Pogosteje kot drugi bolniki z rakom zbolijo bolniki z rakom na področju glave in vratu še za drugim primarnim rakom. Bolniki, pri katerih je bil rak ustnega žrela edini rak, so imeli petletno relativno preživetje 40 %.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom ustnega žrela statistično značilno manjše od evropskega povprečja (Slika 5).

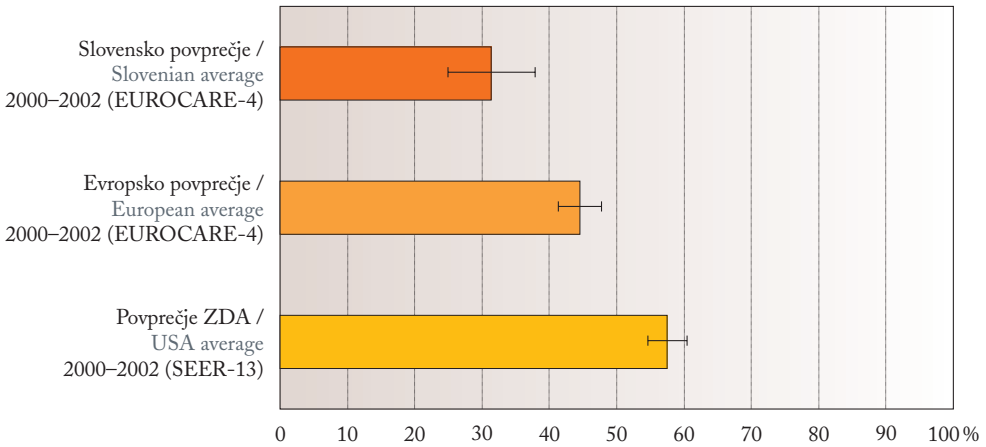
KLINIČNI KOMENTAR

Lojze Šmid
Primož Strojan
Branko Zakotnik

Na razširjenost raka ustnega žrela vpliva predvsem razširjenost kajenja; med slovenskimi moškimi se zmanjšuje, čemur sledi zmanjševanje incidence tega raka; porast incidence pri ženskah gre pripisati spremenjenim kadilskim navadam med njimi. Delež mikroskopsko potrjene bolezni je bil v opazovanem obdobju ves čas visok: pomeni dobro opredeljeno in utečeno diagnostično pot pri obravnavi bolnikov z rakom zgornjega dela dihal in prebavil v Sloveniji. Žal pa je delež napredovalih stadijev raka še vedno izjemno visok, okoli 80 %, in se v opazovanem obdobju ni prav nič spremenil, kar je svojevrsten kazalec zdravstvene ozaveščenosti v državi.

Skrajno neugodnemu izhodišču navkljub pa je moč opaziti vztrajno tendenco zniževanja umrljivosti zaradi tega raka in predvsem dejstvo, da se je preživetje bolnikov z razširjeno obliko raka ustnega žrela v opazovanem 20-letnem obdobju skoraj podvojilo! Ugoden zasuk v preživetju bolnikov obeh spolov in vseh starostnih skupin je bil dosežen z uvedbo sistemskega zdravljenja te vrste raka v rutinsko obravnavo, tako operabilnih tumorjev (pooperativna sočasna radiokemoterapija od leta 2000) kot tudi neoperabilnih tumorjev (radikalna sočasna radiokemoterapija v drugi polovici 90-ih let preteklega stoletja). K oblikovanju obstoječih načel zdravljenja napredovalega raka tega področja so pomembno prispevale tudi prospektivne randomizirane raziskave, izvedene na OI Ljubljana in na Kliniki za otorinolaringologijo in cervikofacialno kirurgijo UKC Ljubljana.

Manj spodbudni so rezultati zdravljenja omejene in razsejane oblike raka ustnega žrela. V prvem primeru, ki predstavlja okoli 15 % vseh bolnikov s to vrsto raka, se preživetje v opazovanem obdobju ni izboljšalo. Glede na to, da se obstoječi načini zdravljenja v tej skupini v zadnjih 15 letih



Slika 5: *Petletno relativno preživetje bolnikov z rakom ustnega žrela* (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of oropharyngeal* cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

* Nabor MKB10 kod v študiji EUROCARE-4 je nekoliko drugačen kot smo ga uporabili pri ostalih analizah predstavljenih v tem poglavju: v študiji EURCARE-4 so iz analize izvzete maligne neoplazme jezika (MKB10: C01) in maligne neoplazme neba (MKB10: C05).

* The ICD10 code selection in EUROCARE-4 study is slightly different in comparison to the selection applied in other analysis in this chapter: in EUROCARE-4 study the malignant neoplasm of base of tongue (ICD10: C01) and malignant neoplasm of palate (ICD10: C05) are excluded.

CLINICAL COMMENTARY

Lojze Šmid
Primož Strojan
Branko Zakotnik

The prevalence of oropharyngeal cancer is mainly influenced by the prevalence of smoking; among the Slovenian males the latter is decreasing, which is reflected in the decreasing incidence of that cancer, while an increase in the incidence among women could be attributed to their changed smoking habits. The proportion of microscopically confirmed disease was high throughout the observation period: it is indicative of a well defined and implemented diagnostics in the management of cancer patients of the upper respiratory and digestive tracts in Slovenia. Unfortunately, however, the proportion of advanced cancers is still outstandingly high (about 80%) and has not changed at all during the observation period, which can be regarded as a unique indicator of health-related awareness in the country.

Despite that extremely unfavourable situation, there is an apparent decreasing trend in the mortality due to this cancer as well as the fact that during the observed 20-year period the survival of patients with advanced stages of oropharyngeal cancer has almost doubled! A favourable shift in the survival of patients of both genders and all age groups was achieved by introducing chemotherapy into the routine management of this type of cancer, so for operable tumors (postoperative and concomitant radiochemotherapy since 2000) as well as for inoperable tumors (radical concomitant radiochemotherapy – in the second half of the 90's of the past century). An important part in the establishment of the current principles in the treatment of advanced oropharyngeal cancer should be attributed to prospective randomised studies carried out at the IO Ljubljana and at the Department of Otorhinolaryngology and Cervicofacial surgery of the UMC Ljubljana.

Treatment results in the case of localized and disseminated oropharyngeal cancer are less encouraging. In the former, which represents approximately 15% of all oropharyngeal cancers, the survival in the observed period has not changed. Considering that in the last 15 years the existing treatment approach for this group has not changed, the result was expected. No improvement

niso spremenili, je rezultat pričakovan. Preživetje bolnikov z razsejano obliko raka ustnega žrela se prav tako ni izboljšalo in je ostalo vse prej kot spodbudno. To je posledica dejstva, da zato obliko raka ni (bilo) uspešnega zdravljenja, pa tudi zaradi majhnega števila bolnikov (okoli 5 %), ki ne omogoča razpoznati manjših sprememb v preživetju bolnikov, zdravljenih z drugimi ali novimi pristopi in načini.

Pri iskanju vzrokov za slabše rezultate zdravljenja raka ustnega žrela v Sloveniji v primerjavi z zahodnoevropskimi državami in ZDA ne velja prezreti vloge HPV. S temi virusi naj bi bilo na zahodu okuženih med 40–60 % bolnikov z rakom ustnega žrela, ki predstavljajo s kliničnega in molekularnega stališča jasno ločeno skupino tumorjev z ugodnejšo prognozo kot v skupini HPV negativnih tumorjev. Žal sta v Sloveniji še vedno prevladujoča dejavnika tveganja raka ustnega dela žrela čezmerno pitje alkoholnih pijač in kajenje.

Pomembne razlike v preživetju med spoloma, ki gredo v prid ženskam, ugotavljamo pri vseh stadijih, starostnih skupinah in znotraj vseh treh opazovanih obdobij.

VIRI
Literature

Budihna M, Šoba E, Šmid L, Zakotnik B, Strojan P, Čemažar M, et al. Inoperable oropharyngeal carcinoma treated with concomitant irradiation, mitomycin C and bleomycin – long term results. Neoplasma 2005; 52: 165–74.

Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008; 100: 261–9.

Strojan P, Karner K, Šmid L, Šoba E, Fajdiga I, Jančar B, et al. Concomitant chemoradiotherapy with mitomycin C and cisplatin in advanced unresectable carcinoma of the head and neck: Phase I–II clinical study. Int J Radiat Oncol Biol Phys 2008; 72: 365–72.

Šmid L, Budihna M, Zakotnik B, Šoba E, Strojan P, Fajdiga I, et al. Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma. Int J Radiat Oncol Biol Phys 2003; 56: 1055–62.

Šmid L, Lešničar H, Zakotnik B, Šoba E, Budihna M, Furlan L, et al. Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer-preliminary report. Int J Radiat Oncol Biol Phys 1995; 32: 769–75.

Zakotnik B, Šmid L, Budihna M, Lešničar H, Šoba E, Furlan L, et al. Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. Int J Radiat Oncol Biol Phys 1998; 41: 1121–7.

Zakotnik B, Budihna M, Šmid L, Šoba E, Strojan P, Fajdiga I, et al. Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin. Int J Radiat Oncol Biol Phys 2007; 67: 685–90.

has either been achieved in the survival of patients with advanced stage of oropharyngeal cancer, which remains rather discouraging. This is attributable to the fact that there was no effective treatment available for this type of cancer, and also to the small number of patients (approximately 5%), which does not enable the detection of minor changes in the survival of patients treated by other or innovative treatment approaches and methods.

Further on, the role of HPV infection must not be overlooked when searching for the reasons of less effective treatment of hypopharingeal cancer in Slovenia in comparison to western European countries and the USA. In the west, probably about 40 to 60% of patients with hypopharingeal cancer are HPV positive. They represent a clearly different group from clinical as well as from molecular point of view and their prognosis is better than that of HPV negative patients. Unfortunately, in Slovenia the prevailing risk factors for hypopharingeal cancer are still alcohol abuse and tobacco smoking.

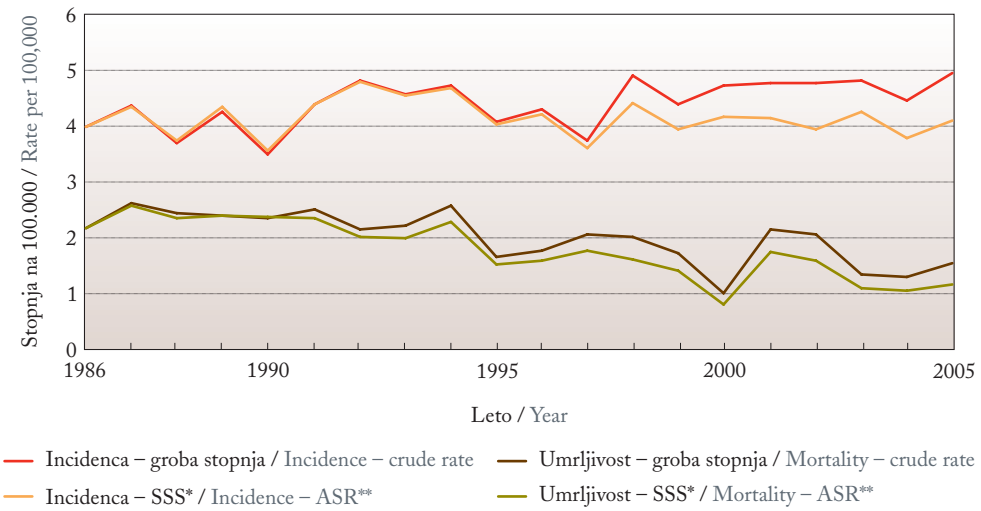
Significant differences in the survival between genders, which are in favour of women, are apparent in all stages, age groups and within all the three observation periods.

USTNA VOTLINA

MKB 10: C02, C03, C04, C06

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom ustne votline zbolelo 1374 ljudi, od tega 1126 moških in 208 žensk. Kot je razvidno s Slike 1, se razen grobe incidenčne stopnje druge mere od leta 1991 zmanjšujejo. Groba incidenčna stopnja se počasi veča, povprečno za 0,5 % letno, starostno standardizirana pa se manjša povprečno za 1 % letno. Groba umrljivostna stopnja se manjša povprečno za 3,6 % letno, starostno standardizirana pa za 5 %.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka ustne votline, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of oral cavity cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1360 primerov; 13 bolnikov (0,9 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, bolnico, ki je bila ob diagnozi mlajša od 20 let, pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. Pri 40 % bolnikov je rak nastal na ustnem dnu, pri 33 % na jeziku, pri 7 % na dlesnih, pri 20 % pa mesto nastanka ni bilo natančneje opredeljeno.

Manj kot 1 % bolnikov v vsakem obdobju ni imelo mikroskopsko potrjene bolezni. Skoraj vsi mikroskopsko potrjeni malignomi (95 %) so bili ploščatocelični karcinomi.

Tabela 1: *Število bolnikov z rakom ustne votline po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of oral cavity cancer patients by sex and period of diagnosis with their proportions by age.*

Obdobje / Period	Moški / Males				Ženske / Females			
	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	398	21,1	75,4	3,5	52	19,2	63,5	17,3
1996–2000	349	21,5	71,9	6,6	88	19,3	59,1	21,6
2001–2005	372	22,8	69,1	8,1	101	16,8	62,4	20,8

ORAL CAVITY

ICD 10: C02, C03, C04, C06

EPIDEMIOLOGY

In the period 1991–2005, a total of 1374 persons were diagnosed with cancer of the oral cavity, of these 1126 males and 208 females. As evident from Figure 1, since 1991 all rates but crude incidence rate have been decreasing. The estimated annual percentage increase in crude incidence rate was 0.5%, while age-standardized rate decreased by 1%. The estimated annual percentage decrease in crude mortality rate was 3.6% and in age-standardized 5%.

The survival analysis included 1360 cases; 13 patients (0.9%) diagnosed only after death were not considered in the analysis, one female patient under 20 years of age at diagnosis is presented in the chapter on the survival of children and adolescents. In 40% of the patients cancer occurred in the oral base, 33% in the tongue, 7% in the gum, while in 20% the origin of cancer has not been clearly defined.

Approximately 1% of patients in each time period did not have microscopically confirmed disease. Practically all microscopically confirmed cancers (95%) were planocellular carcinomas.

Age of the majority of patients at diagnosis ranged between 50 and 74 years. In males, the proportion of those aged 75 years or older was low all the time while in females it reached 21% in the recent period. In both genders approximately 20% of patients developed the disease before the age of 50 (Table 1). The proportion of patients in individual age groups did not change significantly with time.

In all three time-periods, the majority of patients were diagnosed with regional disease; in the period 2001–2005 there were 64% such patients among males and 55% among females (Table 2). The remaining majority of patients had the disease diagnosed at a localized stage. In the 15-year period, the proportion of localized stage has increased, particularly in females, on the account of a smaller proportion of regional disease.

In the years 2001–2005, 3% of patients did not receive specific treatment. In the observed 15-year period, the proportion of untreated patients has decreased by one third. Among the patients receiving specific treatment in the period 2001–2005, 40% were treated by surgery and radiotherapy, 30% underwent surgery alone, and 15% received radiotherapy alone, while 10% of the patients had surgery and radiotherapy combined with chemotherapy. Other combinations of treatments were rare. Compared to the period 1991–1995, in the recent period the proportion of patients treated by surgery alone has increased significantly in comparison with those treated by radiotherapy alone.

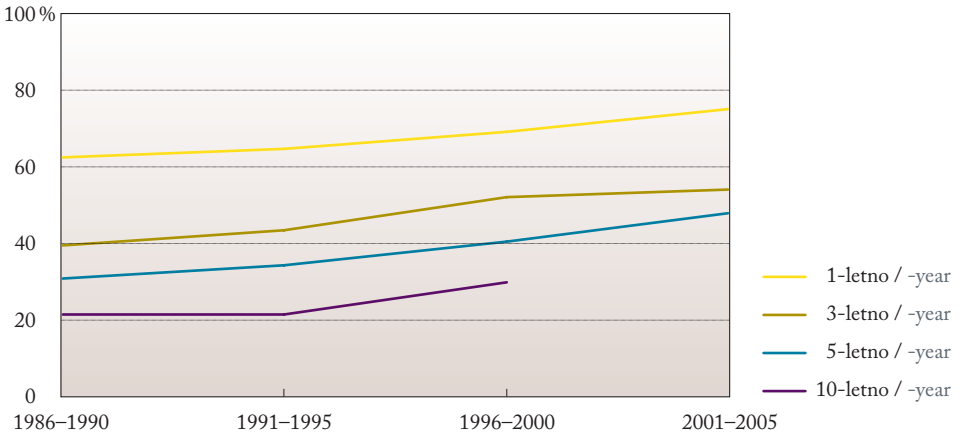
In the period 2001–2005, almost all patients started their treatment in one of the three leading Slovenian health institutions: 53% in the UMC Ljubljana, 32% at the IO Ljubljana, and 14% in the UMC Maribor.

The relative survival of patients with cancers of the oral cavity has been increasing: in 15 years, the 5-year relative survival increased by 14% (Figure 2). In comparison with males, the 5-year

Tabela 2: *Število bolnikov z rakom ustne votline po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of oral cavity cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	398	26,6	68,8	2,5	2,0	52	30,8	65,4	1,9	1,9
1996–2000	349	30,1	67,0	1,7	1,1	88	51,1	47,7	0,0	1,1
2001–2005	372	33,1	64,2	1,3	1,3	101	41,6	55,4	2,0	1,0



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom ustne votline po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of oral cavity cancer patients by period of diagnosis.*

Največ bolnikov je bilo ob diagnozi starih med 50 in 74 let. Delež starih 75 let in več je pri moških ves čas majhen, pri ženskah pa v zadnjem obdobju dosega 21 %. Pri obeh spolih pred 50. letom zboli okoli 20 % bolnikov (Tabela 1). Deleži v posameznih starostnih skupinah se s časom niso bistveno spreminjali.

V vseh treh obdobjih je imelo največ bolnikov ob diagnozi razširjeno bolezen; v obdobju 2001–2005 je bilo pri moških 64 % takih bolnikov, pri ženskah pa 55 % (Tabela 2). Pri večini preostalih bolnikov je bila bolezen odkrita v omejenem stadiju. V 15-letnem obdobju se je delež omejenega stadija povečeval, predvsem pri ženskah, na račun manjšega deleža razširjenega stadija.

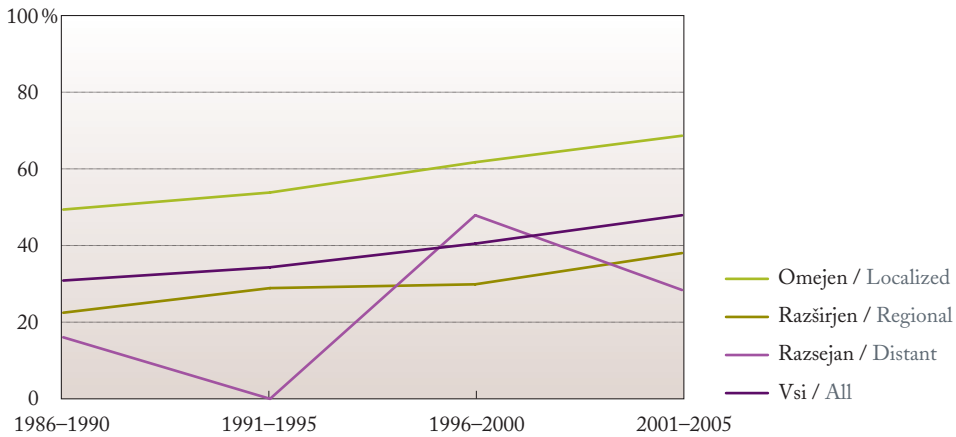
V letih 2001–2005 niso bili specifično zdravljeni 3 % bolnikov. Delež nezdravljenih bolnikov se je v opazovanem 15-letnem obdobju zmanjšal za tretjino. Med specifično zdravljenimi je

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom ustne votline po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of oral cavity cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	61,1 (56,4–66,0)	37,9 (33,5–43,0)	27,9 (23,8–32,7)	78,8 (68,5–90,8)	57,7 (45,7–72,8)	46,2 (34,4–61,9)
1996–2000	62,8 (57,9–68,0)	43,0 (38,1–48,5)	31,2 (26,7–36,5)	86,4 (79,5–93,8)	68,2 (59,1–78,6)	51,1 (41,7–62,7)
2001–2005	69,4 (64,8–74,2)	46,0 (41,2–51,4)	38,9 (33,9–44,6)	88,1 (82,0–94,7)	65,5 (56,7–75,7)	53,7 (43,4–66,4)

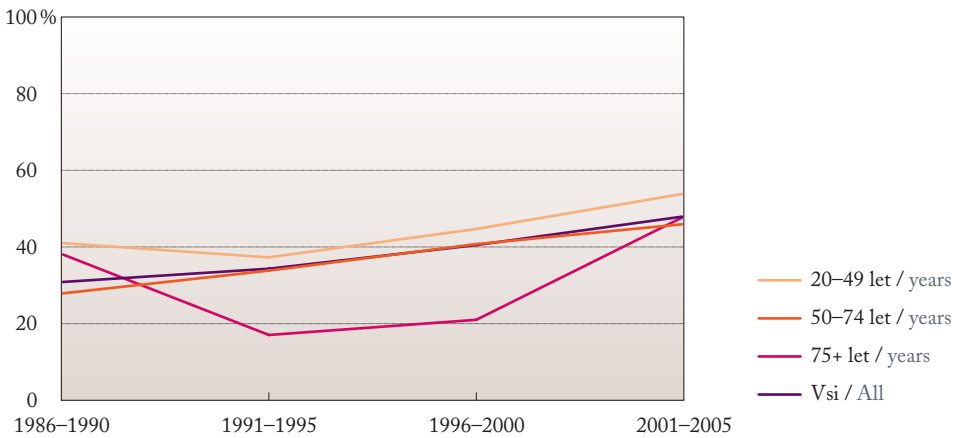
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	62,5 (57,4–67,6)	40,8 (35,3–46,3)	31,7 (26,3–37,2)	80,9 (68,7–93,2)	62,5 (46,1–78,8)	53,0 (34,9–71,1)
1996–2000	64,3 (58,9–69,7)	46,5 (40,5–52,4)	35,8 (29,8–41,8)	88,8 (81,1–96,5)	74,2 (62,8–85,6)	59,1 (45,7–72,4)
2001–2005	71,0 (66,0–76,0)	49,6 (43,8–55,4)	44,4 (37,9–50,9)	90,2 (83,5–96,9)	70,6 (59,7–81,6)	60,8 (46,4–75,2)



Slika 3: *Petletno relativno preživetje bolnikov z rakom ustne votline po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of oral cavity cancer patients by stage and period of diagnosis.*

relative survival of females is much better (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage was 69%, while in those with regional stage at diagnosis it was 38%. Due to a small number of patients with disseminated disease, the evaluation of their survival is rather unreliable. In recent years, the greatest increase in the survival was observed in patients with localized and regional disease. Age is a prognostic factor as well, since the relative survival of patients at an age between 50 to 74 years and of those aged 75 years or older is lower than in those diagnosed before the age of 50 years (Figure 4).

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 48% (Figure 2); patients surviving the first year may expect to survive five years in 63%. In comparison with the rest of cancer patients, those with cancers of the head/neck will more frequently develop a second primary cancer. Patients with oral cavity as the only primary cancer site had 57% 5-year relative survival rate.



Slika 4: *Petletno relativno preživetje bolnikov z rakom ustne votline po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of oral cavity cancer patients by age and period of diagnosis.*

bilo v letih 2001–2005 40 % bolnikov operiranih in obsevanih, 30 % je bilo samo operiranih, 15 % pa samo obsevanih; pri 10 % je bila operaciji in obsevanju dodana še kemoterapija. Ostale kombinacije so bile uporabljene redko. V primerjavi z obdobjem 1991–1995 se je v zadnjem obdobju bistveno povečal delež samo operiranih v primerjavi s samo obsevanimi.

V obdobju 2001–2005 so skoraj vsi bolniki zdravljenje začeli v eni od treh vodilnih slovenskih zdravstvenih ustanov: 53 % v UKC Ljubljana, 32 % na OI Ljubljana in 14 % v UKC Maribor.

Relativno preživetje bolnikov z rakom v ustni votlini se povečuje; v 15 letih se je petletno relativno preživetje povečalo za 14 % (Slika 2). Petletno relativno preživetje žensk je v primerjavi z moškimi precej boljše (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju 69 %, medtem ko je petletno relativno preživetje bolnikov z razširjenim stadijem bolezni ob diagnozi 38 %. Bolnikov z razsejanim stadijem je malo, tako da je ocenjevanje njihovega preživetja precej nezanesljivo. V zadnjih letih se je povečalo preživetje bolnikov z omejenim in razširjenim stadijem bolezni. Napovedni dejavnik je tudi starost, saj je relativno preživetje starih 50–74 let in starih 75 let in več podobno, a slabše kot pri zbolelih pred 50. letom starosti (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 48-odstotno (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 63-odstotno petletno relativno preživetje. Pogosteje kot ostali bolniki z rakom zbolijo bolniki z rakom na področju glave in vratu še za drugim primarnim rakom. Bolniki, pri katerih je bil rak v ustni votlini edini rak, so imeli 57-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom ustne votline statistično značilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

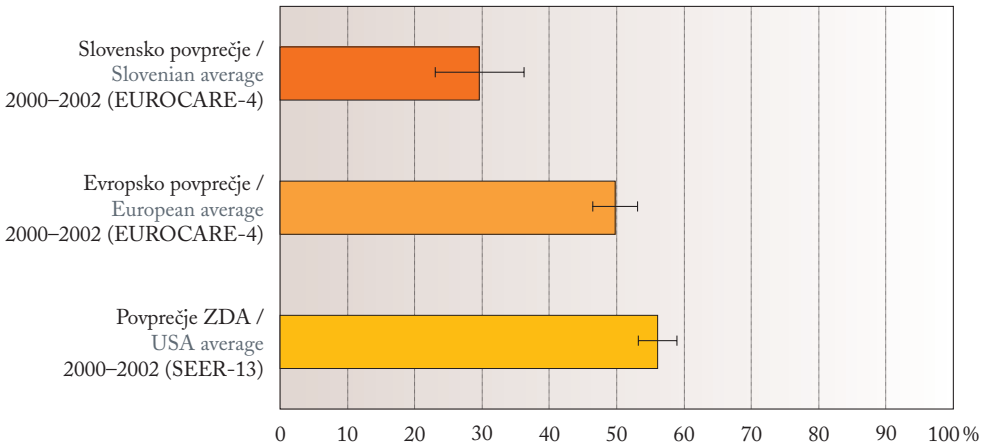
Lojze Šmid
Primož Strojan
Branko Zakotnik

Zadnja leta se je število bolnic z rakom v ustni votlini podvojilo, tako da v zadnjem obdobju predstavljajo že petino vseh obolelih za to vrsto raka. Vzrok gre iskati v spremenjenih kadilskih in morda tudi pivskih navadah žensk v zadnjih desetletjih.

Delež mikroskopsko opredeljenih rakov je izjemno velik, kar zaradi lahke dostopnosti tumorjev v ustni votlini ne preseneča. V zadnjem petletnem obdobju je tudi ugodnejša razporeditev stadijev bolezni ob diagnozi: delež omejene oblike se je vztrajno povečeval in je dosegel v obdobju 2001–2005 že tretjino vseh novih primerov raka v ustni votlini. To se je odražalo tudi pri načinu zdravljenja. V obdobju 1991–1995 je bilo samo z operacijo zdravljenih 13 % bolnikov, v letih 2001–2005 pa je bilo operiranih že 30 % vseh obravnavanih bolnikov. Nasprotno se je delež samo obsevanih bolnikov v tem času pričakovano zmanjšal, s 36 % na 15 %.

Preživetje bolnikov z rakom v ustni votlini se je v celotnem 15-letnem obdobju povečevalo, umrljivost pa se je zmanjševala, kar je gotovo posledica že omenjenih ugodnih sprememb v zastopanosti posameznih stadijev bolezni. Dodatno je v skupini omejenih tumorjev k uspehu prispeval napredek na področju kirurgije in radioterapije (izboljšanje postopkov načrtovanja in priprave bolnikov na obsevanje, uvedba naprednejših obsevalnih tehnik), v skupini razširjenih tumorjev pa poleg slednjega predvsem vključitev sistemskega zdravljenja (sočasna radiokemoterapija) v načrt zdravljenja tako operabilnih kot tudi neoperabilnih primerov raka v ustni votlini. Bolnikov z razsejano obliko bolezni je bilo na srečo malo: uspešnega zdravljenja v tej skupini ni (bilo) na voljo, njena številčnost pa ne dovoljuje zanesljivega statističnega vrednotenja.

Preživetje je bilo v vseh obdobjih, starostnih skupinah in v vseh stadijih boleznih odvisno od spola; dlje so živele bolnice. Domnevamo, da je v naši populaciji delež prognostično ugodnejših tumorjev, katerih nastanek je povezan z okužbo s HPV, nizek; žal sta prevladujoča dejavnika tveganja raka ustne votline čezmerno uživanje alikoholnih pijač in kajenje.



Slika 5: *Petletno relativno preživetje bolnikov z rakom ustne votline* (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of oral cavity cancer patients* (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

* Nabor MKB10 kod v študiji EUROCARE-4 je nekoliko drugačen kot smo ga uporabili pri ostalih analizah predstavljenih v tem poglavju: v študiji EURCARE-4 so iz analize izvzete maligne neoplazme drugih in neopredeljenih delov jezika (MKB10: C02), vključene pa so maligne neoplazme neba (MKB10: C05).

* The ICD10 code selection in EUROCARE-4 study is slightly different in comparison to the selection applied in other analysis in this chapter: in EUROCARE-4 study the malignant neoplasm of other and unspecified parts of tongue (ICD10: C01) are excluded while malignant neoplasm of palate (ICD10: C05) are included.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of Slovenian patients with cancer of the oral cavity is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Lojze Šmid
Primož Strojan
Branko Zakotnik

In the recent years the number of female patients with cancers of the oral cavity nearly doubled, so in the last time-period they represent one fifth of all patients with this type of cancer. The reason should be sought in the changed smoking and perhaps also drinking habits of women in last decades.

The proportion of microscopically confirmed cancers is extremely high, which is not surprising, considering the easy accessibility of the oral cavity. In the last 5-year period, the distribution of disease stages at diagnosis was more favourable too: the proportion of localized disease had been steadily increasing, and represented a third of all newly diagnosed oral cancer cases in the period 2001–2005. This was also reflected in the treatment modality. In the period 1991–1995, 13% of patients were treated by surgery alone, whereas in the period 2001–2005 as many as 30% of the treated patients underwent surgery. Contrary to that, in the same period the proportion of patients treated by radiotherapy alone expectedly decreased from 36% to 15%.

Throughout the 15-year period, the survival rates of patients with cancer of the oral cavity were increasing while their mortality rates were decreasing, which can probably be attributed to the already mentioned favourable changes in the stage distribution of the disease. Further success in the group of localized tumors was brought about by advances in the area of surgery and radiotherapy (improved procedures for planning and preparation of patients for radiotherapy, introduction of advanced irradiation techniques), while in the group of regional tumors – apart

VIRI
Literature

Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008; 100: 261–9.

Strojan P, Karner K, Šmid L, Šoba E, Fajdiga I, Jančar B, et al. Concomitant chemoradiotherapy with mitomycin C and cisplatin in advanced unresectable carcinoma of the head and neck: Phase I–II clinical study. Int J Radiat Oncol Biol Phys 2008; 72: 365–72.

Šmid L, Budihna M, Zakotnik B, Šoba E, Strojan P, Fajdiga I, et al. Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma. Int J Radiat Oncol Biol Phys 2003; 56: 1055–62.

Šmid L, Lešničar H, Zakotnik B, Šoba E, Budihna M, Furlan L, et al. Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer-preliminary report. Int J Radiat Oncol Biol Phys 1995; 32: 769–75.

Zakotnik B, Šmid L, Budihna M, Lešničar H, Šoba E, Furlan L, et al. Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. Int J Radiat Oncol Biol Phys 1998; 41: 1121–7.

Zakotnik B, Budihna M, Šmid L, Šoba E, Strojan P, Fajdiga I, et al. Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin. Int J Radiat Oncol Biol Phys 2007; 67: 685–90.

from the latter – the success should also be attributed to the addition of chemotherapy (concomitant radiochemotherapy) into the treatment schedule of operable as well as inoperable cancers of the oral cavity. Fortunately, there were few patients with disseminated disease: no successful treatment has been available for this group of patients, however, their small number does not allow a reliable statistical evaluation.

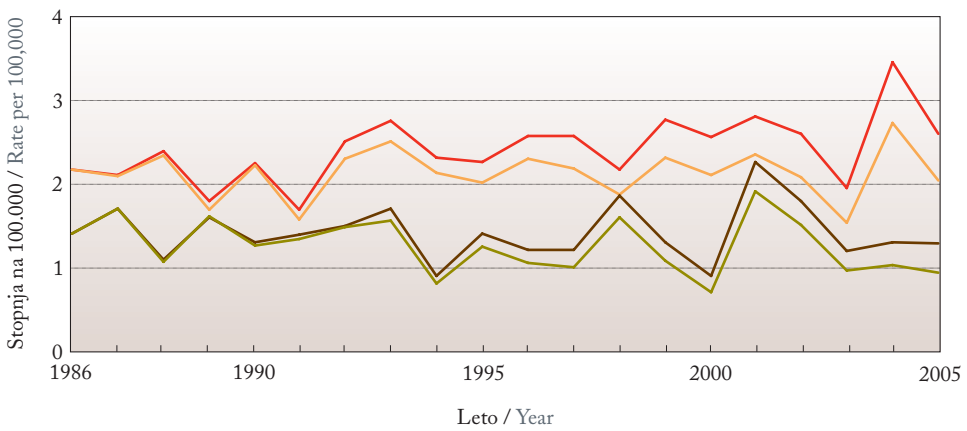
In all time periods, age groups and stages of the disease survival depended on gender: thus, female patients lived longer. We assume that the proportion of prognosticaly more favorable tumors caused by HPV infection in Slovenian patients is smaller than in western Europe; unfortunately, the prevailing risk factors are alcohol abuse and tobacco smoking.

SPODNJE ŽRELO

MKB 10: C12, C13

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom spodnjega žrela zbolelo 759 ljudi, od tega 709 moških in 50 žensk. Kot je razvidno s Slike 1, se trendi incidenčnih in umrljivostnih stopenj med seboj nekoliko razlikujejo. Obe incidenčni stopnji se povečujeta, groba v povprečju za 1,6 % letno, ravno tako groba umrljivostna stopnja povprečno za 0,2 % letno, medtem ko se starostno standardizirana umrljivostna stopnja zmanjšuje za 1,4 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka spodnjega žrela, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of hypopharyngeal cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 749 primerov; 10 bolnikov (1,3 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti. Od bolnikov, vključenih v analizo, je imelo 54 % raka piriformnega sinusa, 46 % pa raka drugih delov spodnjega žrela.

Manj kot 1 % bolnikov v vsakem obdobju ni imel mikroskopsko potrjene bolezni. Skoraj vsi mikroskopsko potrjeni malignomi (97 %) so bili ploščatocelični karcinomi.

Največji delež bolnikov je bil ob diagnozi v starostni skupini od 50 do 74 let. Delež starih 75 let in več je pri moških ves čas majhen, pri ženskah pa se je v zadnjem obdobju povečal na 23 % (Tabela 1). Pri moških se s časom manjša delež tistih, ki zbolijo mlajši od 50 let, veča pa delež

Tabela 1: *Število bolnikov z rakom spodnjega žrela po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of hypopharyngeal cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	217	25,8	71,4	2,8	13	15,4	84,6	0,0
1996–2000	238	23,5	74,4	2,1	13	53,8	38,5	7,7
2001–2005	246	13,4	80,9	5,7	22	18,2	59,1	22,7

HYPOPHARYNX

ICD 10: C12, C13

EPIDEMIOLOGY

In the period 1991–2005, a total of 759 persons were diagnosed with hypopharyngeal cancer, of these 709 males and 50 females. As evident from Figure 1, the trends in incidence and mortality rates slightly differ from each other. Both incidence and crude mortality rates have been increasing; the estimated annual percentage increase in crude incidence rate was 1.6%, while in crude mortality rate it was 0.2%. The age standardized mortality rate was decreasing by 1.4% annually on average.

The survival analysis included 749 cases; 10 patients (1.3%) diagnosed only after death were not considered in the analysis. Among the patients included in the analysis 54% had cancer of the pyriform sinus and 46% cancers of other parts of the hypopharynx.

Less than 1% of patients in each time period did not have microscopically confirmed disease. Practically all microscopically confirmed malignomas (97%) were planocellular carcinomas.

The largest proportion of patients was diagnosed at an age between 50–74 years. In males, the proportion of those aged 75 years or older was low all the time while in females it increased to 23% in the recent period (Table 1). In males, the proportion of patients under 50 years of age at diagnosis is decreasing with time, while the proportion of those diagnosed after the age of 50 and 74 is increasing (Table 1). The evaluation of time-trend in females is unreliable because of the small number of patients.

In all three time-periods, the majority of patients were diagnosed with regional disease; in the period 2001–2005 there were 83% such patients among males and 86% among females (Table 2). The remaining majority of patients had the disease diagnosed at a localized stage. The proportion of localized stage has been increasing throughout the observation period, prevailingly on the account of smaller proportion of regional disease.

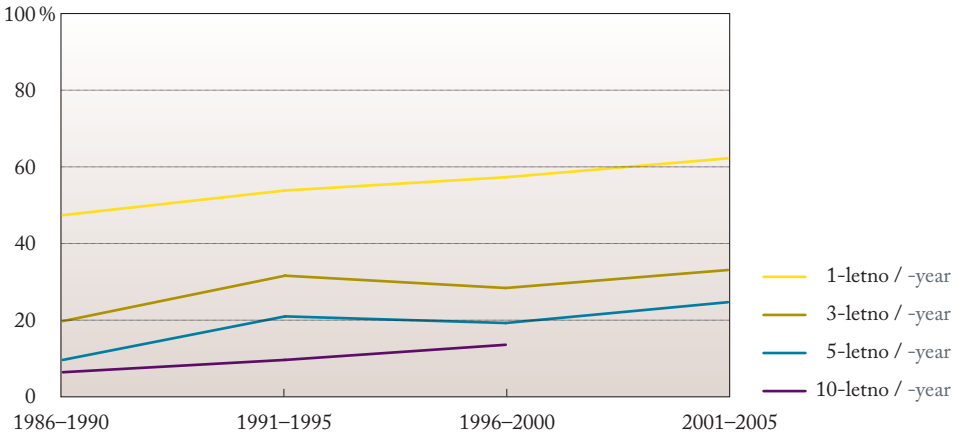
In the years 2001–2005, 7% of patients did not receive specific treatment. In the observed 15-year period the proportion of untreated patients has decreased by 2%. Among the patients receiving specific treatment in the period 2001–2005, 29% were either irradiated or treated by surgery plus radiotherapy, while 18% of patients also received chemotherapy in addition to the mentioned treatment modalities. In the 15-year period, the proportion of patients receiving chemotherapy in addition to the standard treatment by radiotherapy or radiotherapy plus surgery has undergone a four-fold increase.

In the period 2001–2005, almost all patients started their treatment in one of the three leading Slovenian health institutions: 52% at the IO Ljubljana, 33% in the UMC Ljubljana and 15% in the UMC Maribor.

Tabela 2: *Število bolnikov z rakom spodnjega žrela po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of hypopharyngeal cancer patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	217	6,0	86,6	5,5	1,8	13	0,0	84,6	15,4	0,0
1996–2000	238	7,6	87,8	4,2	0,4	13	0,0	100,0	0,0	0,0
2001–2005	246	13,0	82,9	2,8	1,2	22	13,6	86,4	0,0	0,0



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom spodnjega žrela po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of hypopharyngeal cancer patients by period of diagnosis.*

zbolelih po 50. in po 74. letu starosti. Ocenjevanje časovnega trenda pri ženskah je nezanesljivo, saj je število bolnic majhno.

V vseh treh obdobjih je imelo največ bolnikov ob diagnozi razširjeno bolezen; v obdobju 2001–2005 je imelo tako bolezen 83 % moških in 86 % žensk (Tabela 2). Pri večini ostalih bolnikov je bila bolezen odkrita v omejenem stadiju. Delež bolnikov z omejenim stadijem se ves čas opazovanja veča, predvsem na račun manjšega deleža razširjenega stadija.

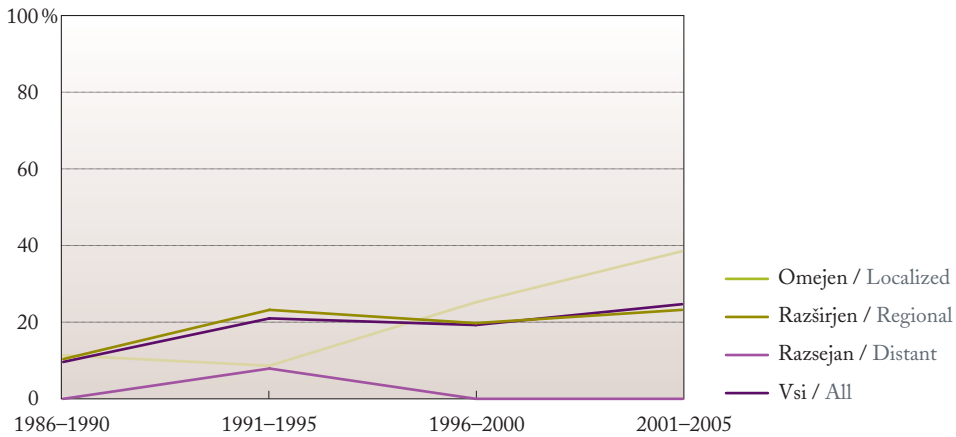
V letih 2001–2005 ni bilo specifično zdravljenih 7 % bolnikov. Delež nezdravljenih bolnikov se je v opazovanem 15-letnem obdobju zmanjšal za 2 %. Med specifično zdravljenimi je bilo v letih 2001–2005 po 29 % obsevanih ali operiranih in obsevanih, 18 % pa je dobilo poleg tega še kemoterapijo. Ostale kombinacije zdravljenj so bile uporabljene redko. Delež bolnikov, ki

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom spodnjega žrela po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of hypopharyngeal cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	52,5 (46,3–59,6)	29,0 (23,6–35,7)	18,0 (13,5–23,9)	53,8 (32,6–89,1)	38,5 (19,3–76,5)	30,8 (13,6–69,5)
1996–2000	55,9 (49,9–62,6)	26,1 (21,0–32,3)	17,2 (13,0–22,8)	61,5 (40,0–94,6)	38,5 (19,3–76,5)	15,4 (4,3–55,0)
2001–2005	61,4 (55,6–67,8)	30,7 (25,4–37,0)	21,9 (16,9–28,3)	54,5 (37,2–79,9)	31,8 (17,3–58,7)	19,1 (7,4–48,9)

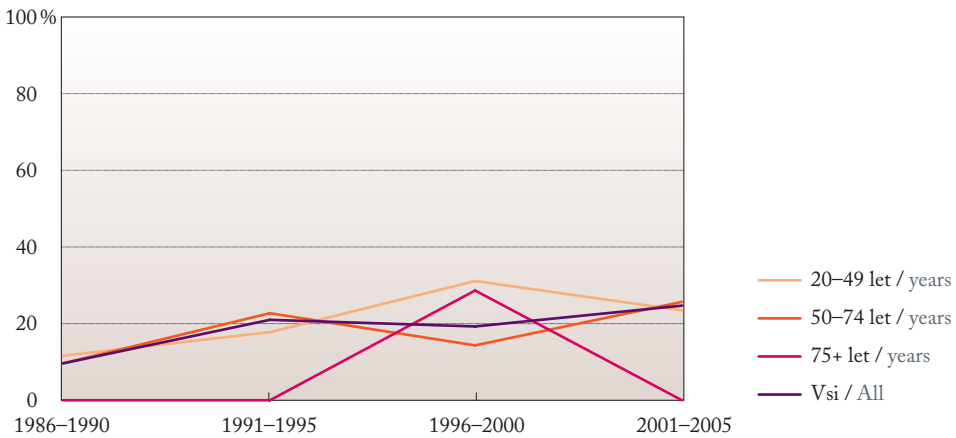
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	53,7 (46,5–61,0)	31,1 (23,9–38,3)	20,3 (13,7–27,0)	54,4 (18,8–90,0)	39,7 (0,4–79,0)	32,6 (0,0–73,7)
1996–2000	57,1 (50,3–63,9)	27,8 (21,2–34,5)	19,3 (13,1–25,6)	62,1 (28,8–95,5)	39,7 (0,4–78,9)	16,3 (0,0–58,2)
2001–2005	62,8 (56,2–69,3)	33,0 (26,1–39,8)	24,9 (17,5–32,2)	55,4 (29,7–81,2)	33,6 (5,3–62,0)	21,0 (0,0–53,9)



Slika 3: *Petletno relativno preživetje bolnikov z rakom spodnjega žrela po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of hypopharyngeal cancer patients by stage and period of diagnosis.*

The 5-year relative survival of patients with cancers of the hypopharynx has undergone a slow increase; in 15 years it has increased by 3% (Figure 2). In comparison with females, the 5-year relative survival of males is slightly better, however, the results in females being rather unreliable due to small number of patients (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage was 39%, while in those with regional stage at diagnosis it was 23%. Due to a small number of patients with disseminated disease, the evaluation of their survival is unreliable. In recent years, a considerable improvement in the survival was observed in patients with localized disease, whereas no significant improvement was noted in those with regional and disseminated disease. The survival of patients in our analysis did not depend on age at diagnosis (Figure 4).

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 25% (Figure 2); patients surviving the first year may expect to survive five years in 39%. Patients with hypopharynx as the only primary cancer site had 26% 5-year relative survival rate.



Slika 4: *Petletno relativno preživetje bolnikov z rakom spodnjega žrela po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of hypopharyngeal cancer patients by age and period of diagnosis.*

jim je bila h klasičnemu zdravljenju samo z obsevanjem ali z obsevanjem in operacijo dodana še kemoterapija, se je v 15 letih povečal za štirikrat.

V obdobju 2001–2005 so skoraj vsi bolniki, ki so bili zdravljeni, zdravljenje pričeli v eni od treh vodilnih slovenskih zdravstvenih ustanov: 52 % na OI Ljubljana, 33 % v UKC Ljubljana in 15 % v UKC Maribor.

Petletno relativno preživetje bolnikov z rakom v spodnjem žrelu se le počasi povečuje; v 15 letih se je povečalo za 3 % (Slika 2). Petletno relativno preživetje moških je v primerjavi z ženskami nekoliko boljše, vendar so rezultati pri ženskah nezanesljivi, saj je zbolelih malo (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju 39 %, medtem ko je pri bolnikih z razširjenim stadijem bolezni ob diagnozi petletno relativno preživetje 23 %. Bolnikov z razsejanim stadijem je malo, tako da je ocenjevanje njihovega preživetja nezanesljivo. V zadnjih letih se je precej izboljšalo preživetje bolnikov z omejenim stadijem bolezni, medtem ko pri bolnikih z razširjeno in razsejano boleznijo ni bistvenega napredka. Preživetje bolnikov, vključenih v našo analizo, ni bilo odvisno od starosti ob diagnozi (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 25 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 39-odstotno petletno relativno preživetje. Preživetje bolnikov, pri katerih je bil rak spodnjega žrela edini rak, so imeli petletno relativno preživetje 26 %.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom spodnjega žrela statistično neznačilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

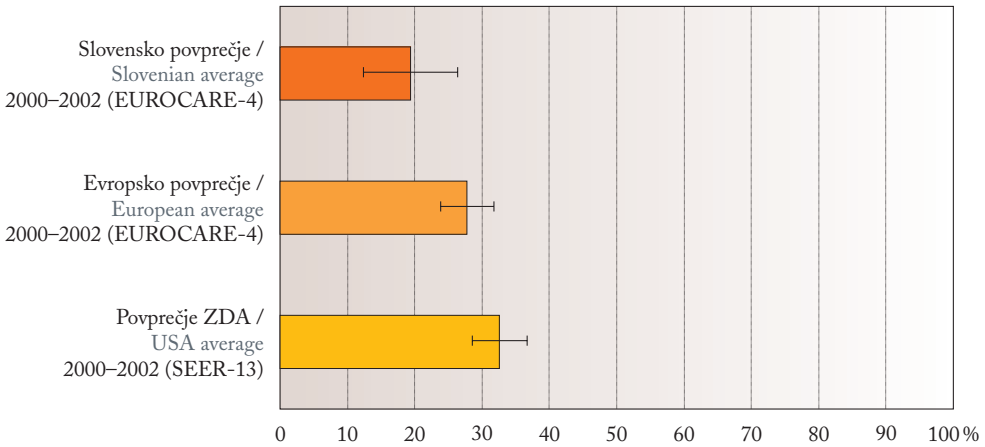
Lojze Šmid
Primož Strojan
Branko Zakotnik

Delež bolnikov z mikroskopsko potrjeno boleznijo je primerno visok in potrjuje ustreznost organizacije dela zdravstvene dejavnosti, ki obravnava to sorazmerno redko vrsto raka.

Preživetje in umrljivost bolnikov z rakom spodnjega dela žrela vseh stadijev bolezni skupaj v preučevanem 15-letnem obdobju ne kaže večje dinamike. Izjema je omejena oblika raka, kjer je napredek očiten. Predpostavljamo, da je odraz spremenjenih terapevtskih konceptov, ki so se razvili v 90. letih preteklega stoletja: očiten je namreč upad deleža bolnikov, zdravljenih samo z operacijo in obsevanjem ali celo samo z obsevanjem, in jasen porast števila bolnikov, pri katerih smo obsevanju (sledilo je operaciji ali je bilo temeljno zdravljenje) priključili sočasno kemoterapijo. Žal je skupina z omejeno obliko bolezni ob diagnozi majhna, le okoli 13 % vseh primerov raka v spodnjem žrelu.

Pri večinski, razširjeni obliki raka spodnjega žrela ostaja preživetje še vedno nesprejemljivo nizko, pri redkih bolnikih z razsejano obliko bolezni pa o dolgotrajnem preživetju niti ne moremo govoriti. Ob dejstvu, da učinkovitega zdravljenja za sistemsko razširjeno bolezen ni, slednji izsledki ne presenečajo. Nekoliko preseneča spoznanje, da tudi uvedba kemoterapije v zdravljenje razširjene oblike bolezni ob diagnozi ni privedla do boljših rezultatov zdravljenja. Zavedajoč se bioloških značilnosti poteka raka spodnjega žrela z močno izraženo težnjo k sistemski razširitvi, za katero pa, kot je bilo že omenjeno, ni učinkovitega zdravljenja, pa tak rezultat ni presenetljiv. Morda bodo izboljšanje prinesli novejši terapevtski koncepti, ki dajejo še večji poudarek sistemsko delujočim tarčnim zdravilom. Te učinkovine poleg že uveljavljenega kombiniranja z obsevanjem, katerega temeljni namen je povečanje občutljivosti tumorskih celic na ionizirajoče žarke (t. i. radiosenzibilizacija), vstopajo v zdravljenje že v uvodnem, indukcijskem delu prav zato, da bi uničile morebitne mikrozasevke v organizmu.

Spol pri raku spodnjega žrela v nasprotju z drugimi raki na področju zgornjega dela prebavne cevi in dihalnih poti nima značilne napovedne vrednosti.



Slika 5: *Petletno relativno preživetje bolnikov z rakom spodnjega žrela (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of hypopharyngeal cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of Slovenian patients with hypopharyngeal cancer is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Lojze Šmid
Primož Strojan
Branko Zakotnik

The proportion of patients with microscopically confirmed disease is correspondingly high and confirms that the organization of work in the healthcare sector dealing with this relatively rare type of cancer is adequate.

In the 15-year observation period, no major changes have been observed in the survival and mortality rates of patients with cancer of the hypopharynx of all stages. An exception is the localized disease, where improvement is quite evident. Presumably, this can be attributed to the changed therapeutic approaches developed in the 90's: there is an obvious decrease in the proportion of patient treated by either surgery or radiotherapy alone, and a clear increase in the number of patients where radiotherapy (following surgery or used as a primary treatment) has been supplemented by concomitant chemotherapy. Unfortunately, the group with localized disease at diagnosis represents only around 13% of all cancers of the hypopharynx.

Survival in the prevailing, regional stage of the hypopharyngeal cancer still remains unacceptably low, while in few patients with the disseminated disease any long-term survival is out of question. In view of the fact that there is no effective treatment available for advanced disease, such results are not surprising. Slightly unexpected though is the finding that even the introducing of chemotherapy into the treatment of patients with regional disease at diagnosis has not resulted in more favorable treatment outcomes. However, being aware of the biological characteristics of the course of hypopharyngeal cancer with strong tendency to metastasizing, which is known to lack any effective treatment, even such result should not come as a surprise. Perhaps an improvement will be brought about by new therapeutic approaches assigning greater role to systemic treatment with target drugs. These drugs – apart from the already established combinations with radiotherapy intended to enhance the sensitivity of tumor cells to ionizing irradiation

VIRI
Literature

Strojan P, Karner K, Šmid L, Šoba E, Fajdiga I, Jančar B, et al. Concomitant chemoradiotherapy with mitomycin C and cisplatin in advanced unresectable carcinoma of the head and neck: Phase I–II clinical study. Int J Radiat Oncol Biol Phys 2008; 72: 365–72.

Šmid L, Budihna M, Zakotnik B, Šoba E, Strojan P, Fajdiga I, et al. Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma. Int J Radiat Oncol Biol Phys 2003; 56: 1055–62.

Šmid L, Lešničar H, Zakotnik B, Šoba E, Budihna M, Furlan L, et al. Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer-preliminary report. Int J Radiat Oncol Biol Phys 1995; 32: 769–75.

Zakotnik B, Budihna M, Šmid L, Šoba E, Strojan P, Fajdiga I, et al. Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin. Int J Radiat Oncol Biol Phys 2007; 67: 685–90.

Zakotnik B, Šmid L, Budihna M, Lešničar H, Šoba E, Furlan L, et al. Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. Int J Radiat Oncol Biol Phys 1998; 41: 1121–7.

(radiosensibilization) – are used already in the initial, induction therapy, in order to destroy possible micrometastases in the body.

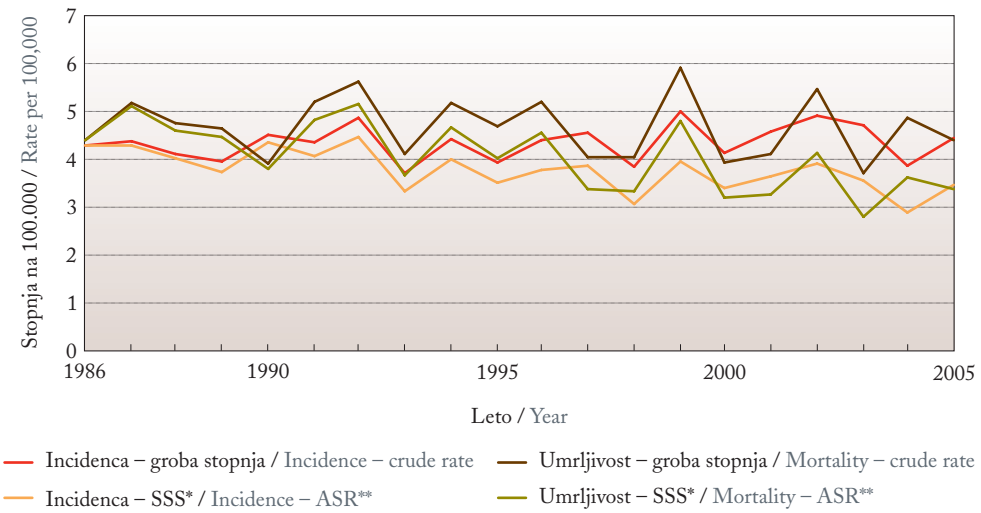
For the difference from other cancers of the upper respiratory and digestive tract in the case of hypopharynx, gender does not have a significant prognostic value.

POŽIRALNIK

MKB 10: C15

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom požiralnika zbolelo 1398 ljudi, od tega 1155 moških in 243 žensk. Kot je razvidno s Slike 1, je groba incidenčna stopnja ustaljena, groba umrljivostna stopnja pa se manjša povprečno za 1,0 % letno. Starostno standardizirane incidenčne in umrljivostne stopnje pa se od leta 1991 zmanjšujejo (incidenčne za 1,3 %, umrljivostne pa za povprečno 2,6 % letno), saj v zadnjih letih zboli več starejših bolnikov (Tabela 1). Manj natančno opredeljevanje vzroka smrti in slab izid bolezni sta verjetno glavna razloga za v nekaterih letih večjo umrljivostno stopnjo od incidenčne.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka požiralnika, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of esophageal cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1307 primerov; 91 bolnikov (6,5 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti. Med vsemi bolniki jih 57 % ni imelo natančneje opredeljenega mesta nastanka malignoma, v zadnjem obdobju 28 %. Med zbolelimi v zadnjem obdobju, ki so imeli opredeljeno mesto, je imelo 37 % bolnikov tumor v spodnji tretjini požiralnika, 26 % v srednji tretjini in 23 % v zgornji tretjini požiralnika; 4 % tumorjev se je ob diagnozi razraščalo prek več delov požiralnika.

Tabela 1: *Število bolnikov z rakom požiralnika po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of esophageal cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	363	10,5	78,2	11,3	61	3,3	55,7	41,0
1996–2000	359	11,4	79,4	9,2	75	9,3	56,0	34,7
2001–2005	370	10,0	74,6	15,4	79	5,1	54,4	40,5

ESOPHAGUS

ICD 10: C15

EPIDEMIOLOGY

In the period 1991–2005, a total of 1398 persons were diagnosed with cancer of the esophagus, of these 1155 males and 243 females. As evident from Figure 1, the crude incidence rate is stable, while crude mortality rate is decreasing with an estimated annual percentage change of 1.0%. Age-standardized incidence and mortality rates have been decreasing (1.3% estimated annual percentage decrease in incidence rate and 2.6% in mortality rate) since 1991, as more elderly patients have been diagnosed in recent years (Table 1). Mortality rate exceeds incidence rate in some years, which can be explained most probably by less accurate definition of the causes of death and poor prognosis of the disease.

The survival analysis included 1307 cases; 91 patients (6.5%) diagnosed only after death were not considered in the analysis. Among all patients, 57% did not have the origin of malignoma more precisely defined, in the last period the proportion of such patients being 28%. Among those diagnosed in the last period and who had the site precisely defined, there were 37% of patients with tumors of the lower third of the esophagus, 26% with the middle third and 23% with tumors of the upper third of the esophagus; at the time of diagnosis, 4% of tumors were found to spread over more segments of the esophagus.

In the period 2001–2005, 93% of cancers were microscopically verified. In comparison with the period 1991–1995, the proportion of microscopically confirmed disease has increased by 5%. In all three observation periods the majority of patients had planocellular carcinoma (70%). The number of patients with adenocarcinomas is increasing every year: thus, in the period 2001–2005 their proportion represented already 14% (in the period 1991–1995 only 7%).

At the time of diagnosis most patients were aged 50–74 years. Approximately three-fourths of male and slightly over a half of female patients belonged to this age group; approximately 40% of females were aged 75 years or older, and less than 10% of patients were younger than 50 years (Table 1). The proportion of patients in individual age groups did not change significantly with time.

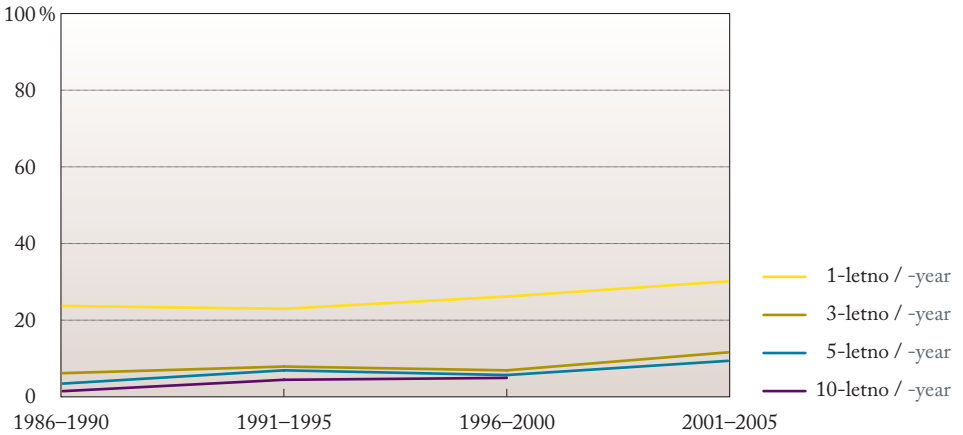
In all three time-periods, the majority of patients were diagnosed with regional disease; in the period 2001–2005 there were 38% males and 44% females (Table 2). A greater proportion of disseminated stage in both genders evidenced in the last period is mainly on the account of a smaller proportion of patients with localized stage; in almost 15% of patients the stage at diagnosis was not determined.

In the years 2001–2005, 37% of patients did not receive specific treatment. In comparison with the period 1991–1995, the proportion of untreated patients has decreased by 6%. In the period 2001–2005, 62% of patients with specific treatment received radiotherapy. In almost a half of them irradiation was combined with chemotherapy, while 10% of irradiated patients were

Tabela 2: *Število bolnikov z rakom požiralnika po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of esophageal cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	363	28,4	43,0	16,3	12,4	61	19,7	42,6	14,8	23,0
1996–2000	359	32,9	35,9	15,3	15,9	75	37,3	30,7	13,3	18,7
2001–2005	370	20,3	38,4	27,6	13,8	79	22,8	44,3	15,2	17,7



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom požiralnika po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of esophageal cancer patients by period of diagnosis.*

V obdobju 2001–2005 je bilo 93 % primerov raka mikroskopsko potrjenih. Delež mikroskopsko potrjenih primerov se je v primerjavi z obdobjem 1991–1995 povečal za 5 %. V vseh treh obdobjih je imelo največ bolnikov ploščatocelični karcinom (70 %). Vsako leto je večje število bolnikov z adenokarcinomom: v obdobju 2001–2005 je bil njihov delež že 14 % (le 7 % v obdobju 1991–1995).

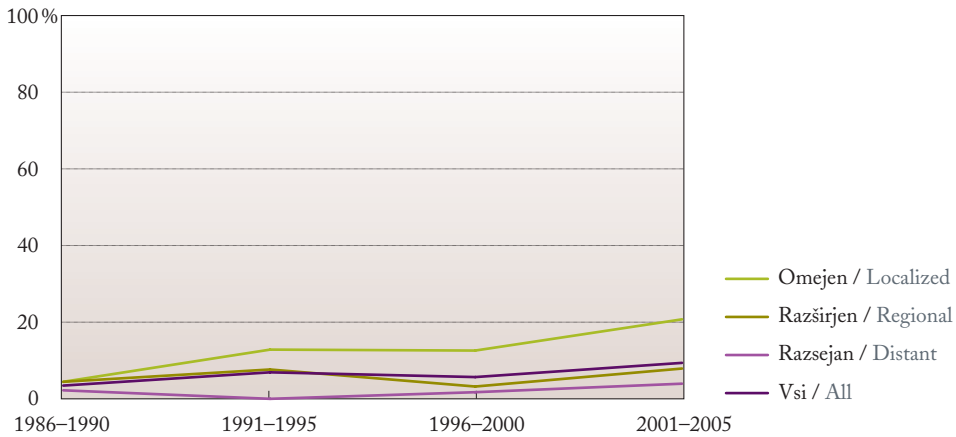
Največji delež zbolelih je bilo ob diagnozi starih med 50 in 74 let. Med moškimi je v tej starostni skupini približno tri četrtine zbolelih, med ženskami pa nekaj več kot polovica. Okrog 40 % žensk je ob diagnozi starih 75 let in več, pred 50. letom pa zboli manj kot 10 % bolnikov (Tabela 1). Deleži v posameznih starostnih skupinah se s časom niso bistveno spreminjali.

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom požiralnika po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of esophageal cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	20,7 (16,9–25,3)	6,1 (4,0–9,1)	5,0 (3,2–7,8)	29,5 (20,0–43,5)	13,1 (6,9–25,0)	9,8 (4,6–21,0)
1996–2000	25,9 (21,7–30,9)	6,1 (4,1–9,2)	4,2 (2,5–6,9)	22,7 (14,9–34,4)	6,7 (2,9–15,5)	6,7 (2,9–15,5)
2001–2005	28,6 (24,4–33,6)	9,3 (6,8–12,8)	6,3 (4,1–9,7)	30,4 (21,8–42,4)	14,9 (8,7–25,4)	13,2 (7,4–23,7)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	21,5 (16,7–26,2)	6,8 (3,4–10,2)	5,9 (2,6–9,3)	31,1 (16,4–45,8)	15,5 (1,4–29,6)	12,7 (0,0–27,2)
1996–2000	26,8 (21,6–31,9)	6,8 (3,4–10,2)	5,0 (1,8–8,2)	23,8 (11,5–36,2)	7,7 (0,0–18,0)	8,5 (0,0–19,8)
2001–2005	29,7 (24,5–34,9)	10,5 (6,5–14,4)	7,8 (3,6–11,9)	31,9 (19,3–44,6)	17,3 (5,1–29,6)	17,3 (3,6–30,9)

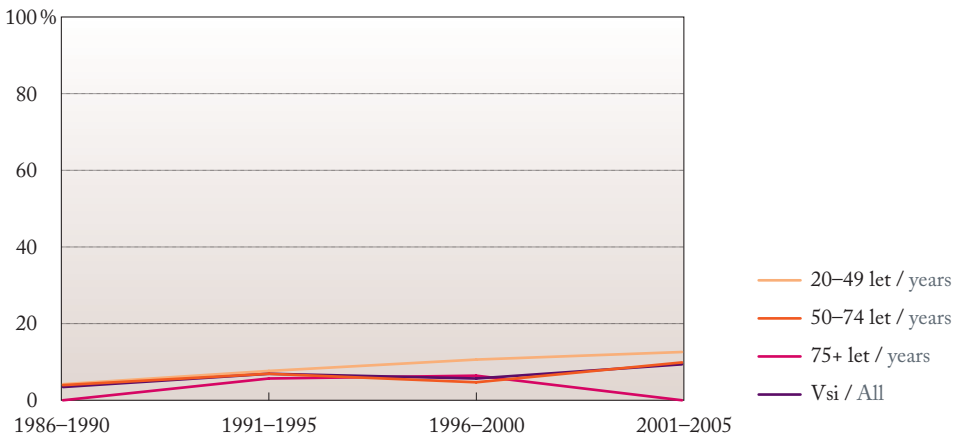


Slika 3: *Petletno relativno preživetje bolnikov z rakom požiralnika po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of esophageal cancer patients by stage and period of diagnosis.*

also treated by surgery and chemotherapy. There were 21% of all patients treated by surgery and 7% by chemotherapy as single-modality treatment.

In the period 2001–2005, practically all patients started their treatment in one of the three leading Slovenian health institutions: 64% at the IO Ljubljana, 27% in the UMC Ljubljana and 9% in the UMC Maribor.

The relative survival rate of patients with esophageal cancer has been increasing very slowly: in 15 years, the 5-year relative survival rate increased by 2% only (Figure 2), in females slightly more than in males (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage has exceeded 20%. However, 5-year survival of patients with regional and disseminated stages is still lower than 10%. Age is a prognostic factor as well, since the relative survival is the lowest in patients aged 75 years or older, while the survival of those diagnosed at an age between 50 and 74 years has been lagging slightly behind the relative survival of those diagnosed before the age of 50 throughout the observation period (Figure 4).



Slika 4: *Petletno relativno preživetje bolnikov z rakom požiralnika po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of esophageal cancer patients by age and period of diagnosis.*

V vseh treh obdobjih je imelo največ bolnikov ob diagnozi razširjeno bolezen; v obdobju 2001–2005 38 % moških in 44 % žensk (Tabela 2). Večji delež razsejanega stadija v zadnjem obdobju pri obeh spolih gre na račun manjšega deleža bolnikov z omejenim stadijem; skoraj 15 % bolnikov ob diagnozi ni imelo določenega stadija.

V letih 2001–2005 ni bilo specifično zdravljenih 37 % bolnikov. Delež nezdravljenih se je v primerjavi z obdobjem 1991–1995 zmanjšal za 6 %. Med specifično zdravljenimi jo bilo v letih 2001–2005 obsevanih 62 % bolnikov. Pri skoraj polovici je bilo obsevanje kombinirano še s kemoterapijo, 10 % med vsemi obsevanimi pa je bilo operiranih in zdravljenih še s kemoterapijo. Samo operiranih je bilo 21 % vseh bolnikov, le kemoterapijo pa jih je prejelo 7 %.

V obdobju 2001–2005 so praktično vsi bolniki, ki so bili zdravljeni, zdravljenje pričeli v eni od treh vodilnih slovenskih zdravstvenih ustanov: 64 % na OI Ljubljana, 27 % v UKC Ljubljana in 9 % v UKC Maribor.

Preživetje bolnikov z rakom požiralnika se povečuje zelo počasi; v 15 letih se je petletno relativno preživetje povečalo le za 2 % (Slika 2), nekoliko bolj pri ženskah (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju preseglo 20 %. Petletno relativno preživetje bolnikov z razširjenim in razsejanim stadijem pa je še vedno manjše od 10 %. Napovedni dejavnik je tudi starost, saj je relativno preživetje najslabše pri starejših od 75 let, preživetje pri zbolelih med 50. in 74. letom pa ves čas opazovanja rahlo zaostaja za relativnim preživetjem pri zbolelih pred 50. letom starosti (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 9 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 30-odstotno petletno relativno preživetje.

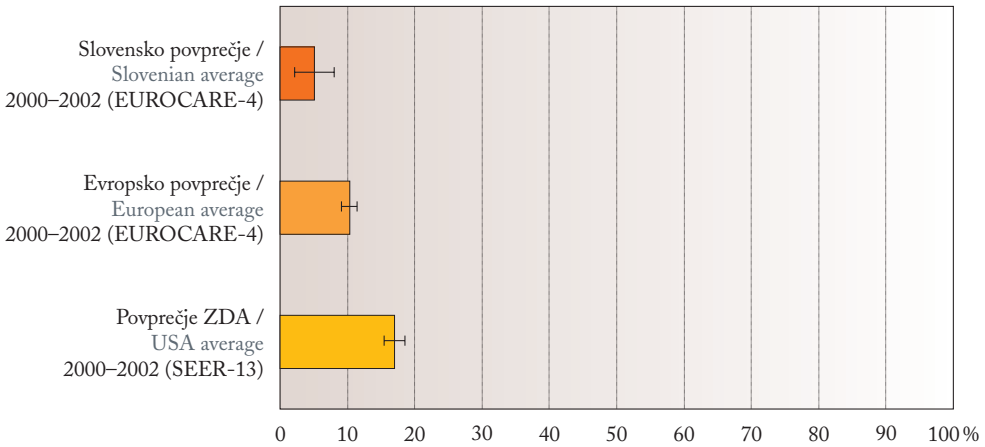
Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom požiralnika statistično značilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

Miha Sok

Preživetje bolnikov z rakom požiralnika v treh obdobjih od leta 1991 do leta 2005 ostaja slabo. Minimalni trend izboljšanja preživetja gre na račun boljšega preživetja pri bolnikih, mlajših od 50 let, in pri bolnikih z rakom v omejenem stadiju. To je skupina bolnikov, ki smo jih zdravili kirurško. Zgodnja diagnostika je tako še vedno najpomembnejša, a velikih premikov na tem področju žal ni. V zadnjem obdobju je bilo v primerjavi s prejšnjimi obdobji registriranih celo manj bolnikov z omejeno obliko in več bolnikov z razsejano obliko. Manj omejenega raka kaže po eni strani na zelo maligno naravo raka požiralnika, po drugi strani pa na natančnejšo diagnostiko v zadnjem obdobju. Sodobna diagnostika pa še vedno ni optimalna, saj sta sicer najprimernejši preiskavi za zamejitev bolezni, CT prsnega koša in zgornjega trebuha ter endoskopska ultrazvočna preiskava, netočni kar v 60 % oz. 30 %. Omejene oblike raka požiralnika so pravzaprav izjemne, še posebej če vemo, da rak požiralnika v stadiju T1 metastazira v bezgavke že v 30 %, praviloma pa dobimo v ambulanto bolnike s stadijem T2. Manj omejenih oblik se kaže tudi v manjšem številu resekcij. Tako smo v obdobju od 1991–1995 operirali kar 42 % vseh bolnikov z rakom požiralnika, v obdobju od 2001–2005 pa le 21 %. Boljše preživetje bolnikov z omejeno obliko, ki smo jih operirali, pa gre tudi na račun manjše pooperacijske smrtnosti. V raziskovalnem projektu Kirurgija raka prebavil smo od leta 2003–2007 beležili manj kot 2-odstotno pooperacijsko smrtnost.

Kirurško zdravljenje še vedno ostaja metoda izbire. Pri tem se vedno vprašamo, ali lahko naredimo radikalno resekcijo, a tudi, ali bolnika sploh smemo operirati. Radikalno resekcijo lahko naredimo zelo redko, saj so požiralnik in področne bezgavke za kirurga slabo dostopen organ. Pogosto je tudi aktualno vprašanje, ali sploh smemo operirati, ker gre največkrat za starejše bolnike s številnimi pridruženimi boleznimi in slabo telesno zmogljivostjo. Protokoli kombiniranega



Slika 5: *Petletno relativno preživetje bolnikov z rakom požiralnika (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of esophageal cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 9% (Figure 2); patients surviving the first year may expect to survive five years in 30%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, survival of Slovenian patients with esophageal cancer is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Miha Sok

In the three observation periods, from 1991 to 2005, the survival of patients with esophageal cancer remains poor. A trend of slight improvement in the survival is attributable to better survival of patients under 50 years of age and in those with localized stage. These are the patients that were treated surgically. Therefore, early diagnosis is still most important, but unfortunately no relevant advances in this area have been achieved. In comparison with the previous periods, among the patients registered in the last period there were even fewer with localized than with disseminated form of the disease. On the one hand, smaller proportion of localized disease reflects the highly malignant nature of esophageal cancer, and on the other, more accurate diagnostics available in the last period. However, the current diagnostic protocol is still not optimal, since the most suitable methods for staging of the disease, i. e. CT scan of the chest and upper abdomen and endoscopic ultrasonography, turn out inaccurate in as many as 60% and 30% of cases respectively. The localized forms of esophageal cancer are actually exceptional, particularly in view of the fact that stage T1 esophageal cancer metastasizes into the lymph nodes already in 30% of cases, while as a rule the patients seen in our outpatient clinic present with stage T2. Smaller proportion of localized disease is also reflected in a smaller number of cancer resections. Thus, in the period 1991–1995, as many as 42% of all esophageal cancer patients were treated by surgery, whereas in the period 2001–2005 there were only 21% of them. Better survival of patients with localized disease, who underwent surgery, is also attributable to lower postoperative lethality rates. The study on surgery of gastrointestinal cancer in the period 2003–2007 revealed a postoperative lethality rate of less than 2%.

Surgery still remains the method of choice. Nevertheless, there is always a question whether we can perform a radical resection and whether we can operate on the patient at all. Radical

zdravljenje z radioterapijo, kemoterapijo in kirurgijo se zadnjih deset let niso spremenili. Čakamo na nova zdravila, na učinkovitejše sheme, ki bodo nudile večje upanje za ozdravitev.

VIRI
Literature

Chang HK, Young TK, Sang-Hoon J, Sook-Whan S, Joo HK. Lymphadenectomy extent is closely related to long-term survival in esophageal cancer. Eur J Cardiothorac Surg 2007; 31: 154–60.

Graham AJ, Shrive FM, Ghali WA, Manns BJ, Grondin SC, Finley RJ, et al. Defining the Optimal Treatment of Locally Advanced Esophageal Cancer: A Systematic Review and Decision Analysis. Ann Thorac Surg 2007; 83: 1257–64.

Imdahl I, Bognar G, Schulte-Mönting J, Schöffe U, Farthmann EH, Ihling C. Predictive factors for response to neoadjuvant therapy in patients with oesophageal cancer. Eur J Cardiothorac Surg 2002; 21: 657–63.

Satoshi Y, Kawahara K, Maekawa T, Shiraishi T, Shirakusa T. Minimally Invasive Esophagectomy for Stage I and II Esophageal Cancer. Ann Thorac Surg 2005; 80: 2070–5.

KLINIČNI KOMENTAR
Franc Anderluh

Karcinom požiralnika je, žal, tako pri nas kot tudi drugje po svetu še vedno bolezen z zelo slabo napovedjo izida. Incidenca adenokarcinoma se povečuje zaradi spremenjenih življenjskih navad. Ugotavljamo, da bolniki kljub večji ozaveščenosti pomoč pri zdravniku žal še vedno iščejo prepozno, saj v zadnjem opazovanem obdobju, pri obeh spolih, narašča delež bolnikov, pri katerih so ob postavitvi diagnoze prisotni tudi že oddaljeni zasevki, njihovo zdravljenje pa je praviloma lahko le simptomatsko. Razveseljuje dejstvo, da se v zadnjem obdobju izboljšuje preživetje bolnikov z omejenim in razširjenim rakom (na ta račun tudi preživetje vseh bolnikov z rakom požiralnika), pri katerih je možno kurativno zdravljenje.

Čeprav je delež bolnikov, ki so bili deležni kombiniranega zdravljenja z obsevanjem, kemoterapijo in operacijo v zadnjih letih glede na obdobje 1996–2000 nekoliko manjši, pa se preživetje teh bolnikov izboljšuje, kar verjetno lahko pripišemo bolj natančnemu načrtovanju obsevanja in vedno manjši ob- in pooperativni smrtnosti. Pri teh bolnikih smo namreč vpeljali trodimenzionalno načrtovanje obsevanja, ki nam omogoča natančnejše obsevanje tumorja in področnih bezgavk ter boljšo zaščito zdravih organov. Kljub temu so rezultati zdravljenja, žal, še vedno daleč nezadovoljivi. V svetu potekajo številne klinične raziskave, s katerimi poskušajo izboljšati preživetje predvsem z dodatkom novih citostatikov že uveljavljenim kurativnim terapevtskim shemam, vendar pa zaenkrat zdravljenje s 5-FU v nepretrgani infuziji in s cisplatinom, ki ga izvajamo tudi pri nas, še vedno ostaja standardno.

Poleg tega ugotavljamo, da so bili v zadnjem opazovanem obdobju praktično vsi slovenski bolniki, ki so bili zaradi karcinoma požiralnika deležni kakršnega koli zdravljenja, obravnavani na OI Ljubljana in/ali v UKC Ljubljana in/ali v UKC Maribor, kar je verjetno edino smiselno, saj gre za ustanove, ki imajo z zdravljenjem tovrstnih bolnikov največ izkušenj, zato so bolniki dejansko lahko deležni multidisciplinarne obravnave.

VIRI
Literature

Bosset JF, Lorchel F, Mantion G, Buffet J, Crehange G, Bosset M, et al. Radiation and chemoradiation for esophageal adenocarcinoma. J Surg Oncol 2005; 92: 239–45.

Kaklamanos IG, Walker GR, Ferry K, Franceschi D, Livingston AS. Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: A meta-analysis of randomized clinical trials. Ann Surg Oncol 2003; 10: 754–61.

Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seebwe S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005; 23: 2310–7.

resection is feasible only very rarely as the esophagus and regional lymph nodes are not easily accessible to surgery. Another question that turns up frequently is whether we may perform surgery at all, since these are generally older patients with several concomitant diseases and a poor general condition. The protocols of combined treatment with radiotherapy, chemotherapy and surgery have not changed over the last decade. We expect new medications and more effective treatment schedules that would hold more promise of cure.

CLINICAL COMMENTARY

Franc Anderluh

Unfortunately, in Slovenia as elsewhere in the world, carcinoma of the esophagus still remains a disease with rather poor prognosis. The incidence of adenocarcinoma is increasing due to changed lifestyles. It turns out that – despite of raising awareness – the patients still seek medical help too late. Namely, in the last observation period the proportion of patients presenting with distant metastases at diagnosis, when treatment options are reduced to symptomatic treatment only, has been increasing in both genders. It is encouraging to note that in the last period the survival of patients with localized and locoregionally advanced disease (and thus also the survival of all esophageal cancer patients), in whom curative treatment is still feasible, has improved.

Although in last years the proportion of patients treated with a combination of radiotherapy, chemotherapy and surgery has slightly decreased as compared to the period 1996–2000, the survival of these patients has been improving, which can probably be attributed to a more precise irradiation planning as well as to steadily decreasing peri- and postoperative lethality rates. Namely, in these patients we introduced a 3-D irradiation planning system, which facilitates more accurate irradiation of the tumor and regional lymph nodes and also provides a better protection of healthy organs. Nevertheless, the treatment results are unfortunately still far from satisfactory. Several clinical studies are underway worldwide, which are aimed at improving the patient survival particularly by introducing new cytotostatic drugs into the already established curative therapeutic schedules. However, the treatment with 5-FU in a continued infusion with cis-platinum, which is used also in our institution, still remains a standard treatment approach.

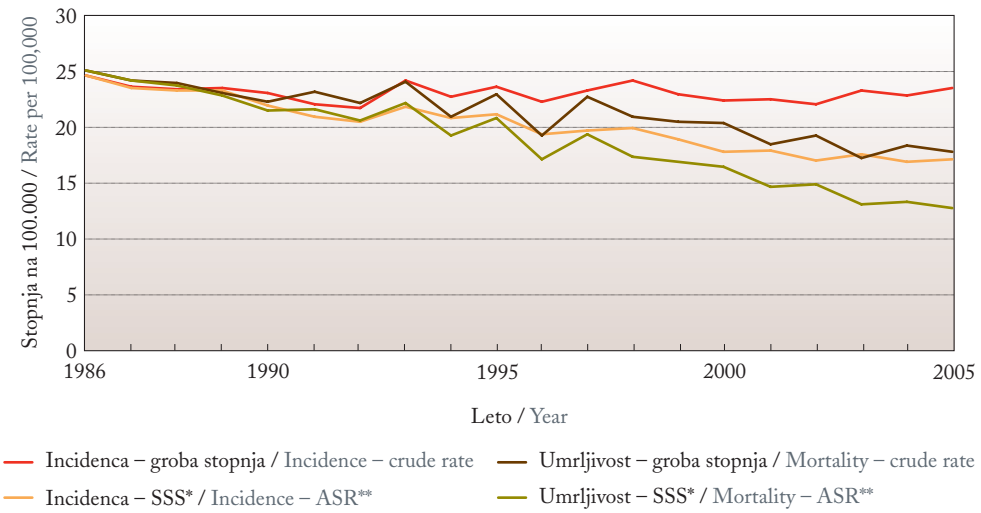
Furthermore, it has been established that in the last observation period practically all patients receiving any kind of treatment for carcinoma of the esophagus were treated either at the IO Ljubljana and/or UMC Ljubljana and/or UMC Maribor, which seems only reasonable, since these are the institutions with most experience in the treatment of such patients, and thus able to offer the patients a multidisciplinary treatment approach.

ŽELODEC

MKB 10: C16

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za želodčnim rakom zbolelo 7345 ljudi, 4435 moških in 2910 žensk. Kot je razvidno s Slike 1, je bila v opazovanem obdobju groba incidenčna stopnja stabilna, druge stopnje so se zmanjševale, predvsem obe starostno standardizirani meri; incidenčna stopnja se je zmanjševala za povprečno 1,8 % letno, umrljivostna pa za povprečno 3,9 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja želodčnega raka, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of stomach cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 6833 primerov; 508 (6,9 %) jih nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 4 mlajše od 20 let obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. V obdobju 2001–2005 je imelo 1447 primerov (od 2278) natančneje opredeljeno mesto vznika tumorja v želodcu. Najpogosteje je bil to antrum (31 %), sledijo kardija (21 %), korpus (20 %), mala krivina (7 %), velika krivina in pilorus s po 2 %; pri 17 % je bila bolezen tako razširjena, da mesta nastanka ni bilo mogoče določiti. Deleži opredeljenih mest vznika tumorja se v zadnjih desetih letih niso bistveno spreminjali.

Odstotek mikroskopsko potrjenih primerov se je povečal z 92 % v letih 1991–1995 na 96 % v letih 2001–2005. V vseh treh obdobjih je bilo več kot tri četrtine žleznih karcinomov, v zadnjem

Tabela 1: *Število bolnikov z želodčnim rakom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of stomach cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	1364	8,9	68,4	22,7	911	9,2	56,1	34,7
1996–2000	1387	8,6	66,8	24,7	893	11,4	55,2	33,4
2001–2005	1397	8,3	63,7	28,0	881	9,5	47,4	43,0

STOMACH

ICD 10: C16

EPIDEMIOLOGY

In the period 1991–2005, a total of 7345 persons were diagnosed with cancer of the stomach, of these 4435 males and 2910 females. As evident from Figure 1, in the observed time period the crude incidence rate was stable, while other rates have been decreasing, especially the age-standardized rates; the estimated annual percentage decrease in age-standardized incidence rate was 1.8% and 3.9% in age-standardized mortality rate.

The survival analysis included 6833 cases; 508 patients (6.9%) diagnosed only after death were not considered in the analysis, 4 patients less than 20 years of age are presented in the chapter on the survival of children and adolescents. In the period 2001–2005, 1447 patients (out of total 2278) had the site of tumor origin in the stomach more precisely defined. This was most frequently the antrum (31%), followed by cardia (21%), corpus (20%), lesser curvature (7%), greater curvature and pylorus (2% each); in 17% the disease was so advanced that the site of origin could not be determined. The proportion of undefined site of origin has not been changing much in the last years.

The percentage of microscopically confirmed cases increased from 92% in the period 1991–1995 to 96% in the period 2001–2005. In all three time-periods, more than three-quarters of cancers were adenocarcinomas; in the last period they represented 88% of the total, their proportion increasing mainly on the account of undefined carcinomas, while in all three periods other defined histological types represent less than 1%. Among adenocarcinomas, according to Lauren's classification, there were 34% adenocarcinomas of intestinal and 16% of diffuse type.

In fifteen years, the proportion of younger patients (20–49 years) has not changed significantly while the proportion of patients aged 75 years or older, particularly among females, has been increasing (Table 1). In all three time-periods, almost three quarters of patients were diagnosed with regional or disseminated disease (Table 2).

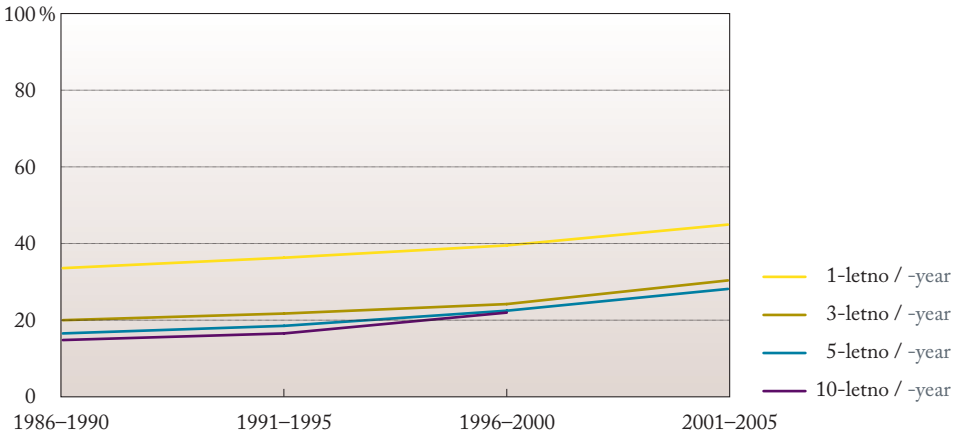
The stage of disease at diagnosis is probably the main reason that in the period 2001–2005 40% (1,375) patients did not receive specific treatment, which was 10% less that in the first period; more than three fourths of these patients were diagnosed with disseminated disease or their stage was not determined at all.

In the period 2001–2005, 55% (1,248) of all patients included in the analysis underwent surgery, i. e. 91% of all that received specific treatment in this period. In the 15-year period, the proportion of patients treated by surgery alone has decreased from 85% to 68%; the proportion of those treated additionally with a combination of irradiation and chemotherapy (15% in the period 2001–2005) or chemotherapy alone (7%) has been gradually increasing; 7% were treated by chemotherapy as single modality treatment and 3% with other combinations.

Tabela 2: *Število bolnikov z želodčnim rakom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of stomach cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	1364	19,6	37,6	30,1	12,7	911	21,4	33,3	30,4	14,9
1996–2000	1387	20,5	37,7	32,4	9,4	893	22,3	34,6	31,2	11,9
2001–2005	1397	19,3	40,4	33,9	6,4	881	24,0	37,3	27,7	11,0



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z želodčnim rakom po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of stomach cancer patients by period of diagnosis.*

obdobju 88 %; njihov delež se veča predvsem na račun zmanjševanja deleža neopredeljenih karcinomov, drugih opredeljenih histoloških vrst je v vseh obdobjih manj kot 1 %. Med žleznimi karcinomi želodca jih je bilo glede na klasifikacijo po Laurenu 34 % intestinalnega tipa in 16 % difuznega tipa.

V petnajstih letih se delež mlajših bolnikov (20–49 let) ni bistveno spremenil, povečuje pa se delež bolnikov, starejših od 75 let, zlasti med ženskami (Tabela 1). V vseh treh obdobjih so imele ob diagnozi skoraj tri četrtine bolnic in bolnikov razširjeno ali razsejano bolezen (Tabela 2).

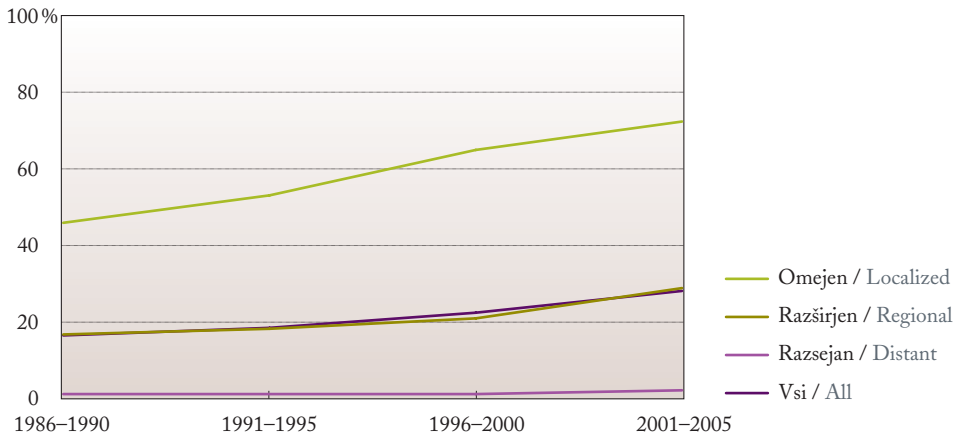
Razširjenost bolezni ob diagnozi je verjetno najpomembnejši vzrok, da tudi v obdobju 2001–2005 ni bilo specifično zdravljenih 40 % (1375) bolnikov, kar pa je 10 % manj kot v prvem obdobju;

Tabela 3: *Opazovano in relativno preživetje bolnikov z želodčnim rakom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of stomach cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	34,4 (32,0–37,0)	18,8 (16,8–21,0)	14,3 (12,6–16,3)	34,9 (31,9–38,1)	18,8 (16,4–21,5)	14,5 (12,4–17,0)
1996–2000	37,1 (34,6–39,7)	19,4 (17,4–21,6)	15,9 (14,1–18,0)	38,2 (35,1–41,5)	23,2 (20,6–26,1)	19,9 (17,5–22,7)
2001–2005	42,4 (39,9–45,1)	24,4 (22,3–26,8)	19,9 (17,7–22,3)	43,5 (40,3–46,9)	28,6 (25,7–31,8)	24,4 (21,6–27,7)

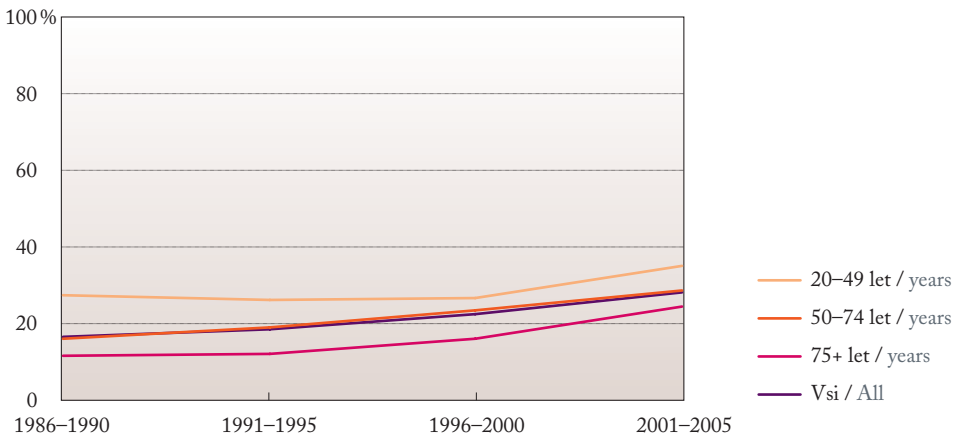
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	36,2 (33,5–39,0)	22,0 (19,4–24,6)	18,7 (16,1–21,3)	36,5 (33,1–39,9)	21,6 (18,4–24,7)	18,3 (15,2–21,5)
1996–2000	39,1 (36,3–41,8)	22,8 (20,2–25,4)	20,9 (18,2–23,6)	39,9 (36,4–43,3)	26,4 (23,1–29,8)	24,8 (21,3–28,3)
2001–2005	44,7 (41,9–47,6)	28,8 (26,0–31,6)	26,4 (23,2–29,6)	45,4 (41,8–48,9)	32,8 (29,1–36,4)	31,0 (26,9–35,1)



Slika 3: *Petletno relativno preživetje bolnikov z želodčnim rakom po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of stomach cancer patients by stage and period of diagnosis.*

In the period 2001–2005, near to 40% of patients started their treatment in the UMC Ljubljana (similar as in the previous years), 21% in the UMC Maribor, 13% at the IO Ljubljana and 6% in the GH Celje; the remaining 20% were operated on in the general hospitals of Jesenice (4%), Novo mesto (4%), Murska Sobota (4%), Slovenj Gradec (3%), Nova Gorica (2%), Izola (2%) and Ptuj (1%).

The relative survival has been gradually increasing, particularly in the last period; in 15 years, the 5-year relative survival increased by 9% (Figure 2), by 13% in females and 8% in males (Table 3). The relevance of stage at diagnosis is shown in Figure 3. Compared to the period 1991–1995, in the last period the 5-year relative survival of patients with localized stage was already above 70%, thus having increased by 20%, while the 5-year relative survival of patients with regional disease has increased by 11%. Age is a prognostic factor as well, since in the last period all the patients under 50 years of age had 10% higher relative survival than those aged 75 years or older (Figure 4).



Slika 4: *Petletno relativno preživetje bolnikov z želodčnim rakom po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of stomach cancer patients by age and period of diagnosis.*

pri več kot treh četrtinah nezdravljenih bolnic in bolnikov je šlo za razsejano bolezen ali pa stadij sploh ni bil določen. V letih 2001–2005 je bilo operiranih 55 % (1248) od vseh v analizo vključenih primerov oz. 91 % od vseh, ki so bili v tem obdobju specifično zdravljeni. Delež samo operiranih se je v petnajstletnem obdobju zmanjšal s 85 % na 68 %, postopno se veča delež dodatno zdravljenih z obsevanjem in kemoterapijo v kombinaciji (15 % v letih 2001–2005) ali samo s kemoterapijo (7 %), 7 % je bilo zdravljenih samo s kemoterapijo, 3 % pa z drugimi kombinacijami.

V letih 2001–2005 je blizu 40 % bolnikov zdravljenje pričelo v UKC Ljubljana (podobno tudi v prejšnjih letih), 21 % v UKC Maribor, 13 % na OI Ljubljana in 6 % v SB Celje, preostalih 20 % pa je bilo operiranih v bolnišnicah Jesenice (4 %), Novo mesto (4 %), Murska Sobota (4 %), Slovenj Gradec (3 %), Nova Gorica (2 %), Izola (2 %) in Ptuj (1 %).

Relativno preživetje se postopno povečuje, predvsem v zadnjem obdobju; v 15 letih se je petletno relativno preživetje povečalo za 9 % (Slika 2), za 13 % pri ženskah in za 8 % pri moških (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: v zadnjem obdobju je petletno relativno preživetje bolnikov z omejenim stadijem že več kot 70-odstotno in se je v primerjavi z obdobjem 1991–1995 povečalo za 20 %, za 11 % se je povečalo tudi petletno relativno preživetje bolnikov z razširjeno boleznijo. Napovedni dejavnik je tudi starost, saj so v zadnjem obdobju mlajši od 50 let imeli za 10 % večje relativno preživetje kot stari 75 let in več (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 28 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 60-odstotno relativno petletno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z želodčnim rakom skoraj enako evropskemu povprečju (Slika 5).

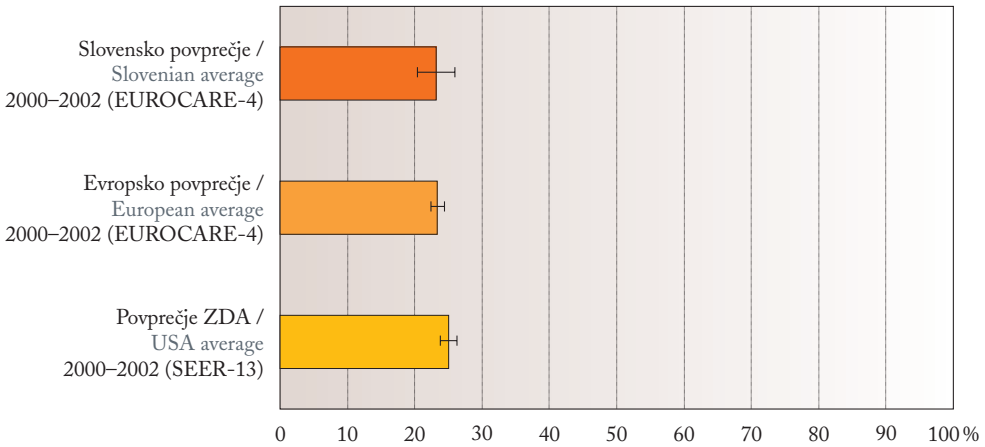
KLINIČNI KOMENTAR

Stane Repše

Razvoj in stanje kirurškega zdravljenja želodčnega raka v Sloveniji v letih 1983–1997 je bilo opisano v zadnji izdaji monografije *Preživetje bolnikov z rakom v Sloveniji* leta 2003. Ali je takratno mnenje, da se bodo strokovna prizadevanja na področju želodčnega raka po letu 1980 (strokovni sestanki, nacionalne ankete, multidisciplinarni timi, delavnice in simpoziji, publikacije) pokazala z boljšimi rezultati preživetja na državni ravni šele v sedanjem obdobju, pravilno?

V obdobju, ki je sedaj analizirano in prikazano s petletnim preživetjem, smo se kirurgi v Sloveniji držali doktrinarnih načel za obravnavo bolnikov z želodčnim rakom, ki smo jih izdelali v začetku devetdesetih let in so bila objavljena v publikaciji *Priporočila za zdravljenje bolnikov z rakom prebavil* leta 1997. Resekcija, radikalna in/ali paliativna, je imela absolutno prednost, ne glede na starost bolnika. Vrsta operacije – distalna subtotalna resekcija oz. totalna gastrektomija s sistematično limfadenektomijo vseh bezgavk 1. in 2. skupine (D2 limfadenektomija) – je bila odvisna od mesta procesa na želodcu (tretjine) in od histološkega tipa po Laurenu. D2 limfadenektomija je bila sestavni del radikalne operacije ne glede na kategorijo T. Neoadjuvantna kemoterapija in/ali radioterapija pri napredovalem stadiju (T3, T4) sta bili bolj izjema kot pravilo, prav tako tudi adjuvantno onkološko zdravljenje.

Po letu 2000 se je doktrina zdravljenja želodčnega raka pri nas začela ponovno postopoma spreminjati v smislu bolj individualizirane kirurgije – »tailored surgery« (mukozektomija pri tumorjih T1N0, samo D1 limfadenektomija pri tumorjih T1Nx) in neoadjuvantne radiokemoterapije pri tumorjih v kategorijah nad T2bNxMx. Sprva posamezni primeri so postajali vse številnejši. Kirurgija, ki je bila edino zdravljenje v obdobju 1996–2000 pri 83 % bolnikov, se je v obdobju 2001–2005 zmanjšala na 68 %, povečal pa se je odstotek kombiniranega zdravljenja. Tudi delež bolnikov, ki jih ni bilo mogoče operirati in so bili zdravljeni samo s kemoterapijo, se je povečal s 3 % v prvem obdobju na 7 % v tretjem. Rezultati ankete, ki smo jo naredili med kirurškimi



Slika 5: *Petletno relativno preživetje bolnikov z želodčnim rakom (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of stomach cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 28% (Figure 2); patients surviving the first year may expect to survive five years in 60%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of Slovenian patients is nearly equal to the European average (Figure 5).

CLINICAL COMMENTARY

Stane Repše

The development and the state-of-the-art of surgical treatment for stomach cancer in Slovenia in the period 1983–1997 was presented in the last edition of the monograph *Cancer Patients Survival in Slovenia* issued in 2003. How correct were we then by presuming that the results of endeavors in the area of stomach cancer after the year 1980 (expert meetings, national surveys, multidisciplinary teams, workshops and symposia, publications) would be reflected in better survival rates at the national level only in the current period?

In the period, which is subject to the current analysis and is presented by 5-year survival, the surgeons in Slovenia followed the doctrinaire principles of stomach cancer patient treatment, which were adopted in the beginning of 90's and published in 1997 under the title *Recommendations for a Comprehensive Treatment of Patients with Cancers of Digestive Organs*. Resection, either radical and/or palliative, was the treatment of choice, irrespective of the patient's age. The type of resection – distal subtotal resection or total gastrectomy with systematic lymphadenectomy of all groups 1 and 2 lymph nodes (D2 lymphadenectomy) depended on the site of process in the stomach (thirds) as well as on histological type by Lauren. D2 lymphadenectomy was an integral part of radical surgery, regardless the T category. At an advanced stage (T3, T4), neoadjuvant chemotherapy and/or radiotherapy were the exception rather than the rule, and so was also adjuvant oncological therapy.

After the year 2000, the principle of stomach cancer treatment in Slovenia again started to change gradually in terms of a more individualized surgery, the so-called »tailored surgery« (mucosectomy in T1N0 tumors, D1 lymphadenectomy alone in T1Nx tumors) and neoadjuvant radiochemotherapy in categories above T2bNxMx. Initially, this approach was used in individual cases only, but later on it became more and more frequent. In the period 1996–2000,

oddelki slovenskih bolnišnic, kažejo, da se je pooperacijska smrtnost reseciranih bolnikov postopoma zmanjševala; leta 1994 je bila 6 %, leta 2004 pa 4 %.

Kot smo napovedali, se napredek naših skupnih prizadevanj na državni ravni kaže šele v tem obdobju. Petletno relativno preživetje bolnikov z želodčnim rakom v Sloveniji se je postopoma povečevalo: od 17 % v obdobju 1986–1990 in 19 % v obdobju 1991–1995 na 23 % v obdobju 1996–2000 in 28 % v obdobju 2001–2005.

Boljši rezultati kliničnih serij iz UKC v Ljubljani in v Mariboru, kjer je t. i. resektabilnost bistveno večja, pooperativna smrtnost manjša in petletno preživetje večje od slovenskega povprečja, so zagotovilo, da bo tudi naslednje obdobje prineslo izboljšanje, še posebej, če bomo uspeli regionalizirati kirurško zdravljenje želodčnega raka. Tretjino bolnikov, ki so sedaj operirani v 9 regionalnih bolnišnicah (okrog 80 do 100 bolnikov), bi lahko operirali v treh največjih bolnišnicah, v Ljubljani, Mariboru in Celju, morda še v treh regijskih, v Novi Gorici, Izoli in Novem mestu. To bi se gotovo pokazalo s povečanjem sedanjega, še vedno slabega, populacijskega preživetja.

VIRI
Literature

Juvan R, Omejc M, Jelenc F, Repše S. Rezultati operacijskega zdravljenja želodca v obdobju 1993–2002. In: Omejc M, Repše S, eds. Kirurgija želodca – standardi in novosti: zbornik simpozija. Ljubljana, Kirurška klinika, 2005; 210–6.

Omejc M, Repše S. Rak želodca v Sloveniji 2004. In: Omejc M, Repše S, eds. Kirurgija želodca – standardi in novosti: zbornik simpozija. Ljubljana, Kirurška klinika, 2005; 128–33.

Potrč S, Horvat M, Ivanez A, Hazabend M. Kaj smo se naučili pri kirurškem zdravljenju adenokarcinoma želodca: primerjava dveh obdobij. In: Omejc M, Repše S, eds. Kirurgija želodca – standardi in novosti: zbornik simpozija. Ljubljana, Kirurška klinika, 2005; 197–09.

Repše S, Juvan R. Kirurgija raka želodca v Sloveniji. In: Repše, ed. Kirurgija želodca: zbornik simpozija. Ljubljana, Kirurška šola, Kirurške klinike, 1995; 101–12.

Repše S, Omejc M, Juvan R, Jelenc F. Napredovali rak želodca – standardna resekcija danes. In: Omejc M, Repše S, eds. Kirurgija želodca – standardi in novosti: zbornik simpozija. Ljubljana, Kirurška klinika, 2005; 154–60.

Repše S, Žitko T, Kocijančič B, Lamovec J, Golouh R, Jelenc F, et al. Rak želodca. In: Repše S, ed. Priporočila za celostno obravnavo bolnikov z rakom prebavil. Ljubljana: Ministrstvo za zdravstvo R Slovenije, 1997; 13–21.

KLINIČNI KOMENTAR
Irena Oblak

Čeprav se incidenca želodčnega raka po svetu in v Sloveniji zmanjšuje, sodi ta bolezen med najpogostejše vzroke smrti zaradi raka. Zanimivo je, da se v zadnjih letih povečuje incidenca karcinoma, ki vznikne na kardiji, predvsem v razvitih zahodnih državah.

Že ob diagnozi ima več kot dve tretjini bolnikov razširjeno ali metastatsko bolezen. Po podatkih iz literature je pri 40–50 % bolnikih ob postavitvi diagnoze bolezen ocenjena kot neresektabilna, njihovo srednje preživetje pa je 6 mesecev do 1 leta. V primeru, da je operacija izvedljiva, je osnovno zdravljenje radikalna resekcija tumorja s pripadajočimi področnimi bezgavkami. Na žalost se bolezen ponovi kar v 75 % primerih, od tega pri 40–65 % primerov lokalno in/ali področno.

Leta 2001 smo v Sloveniji uvedli dopolnilno zdravljenje s pooperativno radiokemoterapijo (fluoropirimidini ± cisplatin), ki izboljša preživetje bolnikov po radikalni resekciji želodčnega raka stadijev Ib–IV brez oddaljenih zasevkov. V naši skupini bolnikov smo dosegli odličen lokalni nadzor, saj se kar pri 81 % bolnikov bolezen po petih letih ni ponovila ne lokalno ne področno. Petletno preživetje brez ponovitve bolezni je bilo pri naših bolnikih 51 %, za bolezen specifično preživetje 51 % in skupno 49 %. Kot je že splošno znano, tudi v naši raziskavi ugotavljamo, da imajo bolniki z večjimi tumorji in tisti s tumorji, ki so vzniknili na kardiji želodca, slabšo napoved izida bolezni.

83% of patients were treated by surgery alone, whereas in the period 2001–2005 their proportion deceased to 68% while the percentage of combined treatment increased. The proportion of inoperable patients treated by chemotherapy alone increased from 3% in the first observation period to 7% in the third. The results of the survey carried out in all surgical departments in Slovenia show that postoperative lethality rates of the resected patients gradually decreased, from 6% in 1994 to 4% in 2004.

Consistent with our projections, the progress resulting from our joint endeavors at the national level is evident only in the last observed period. The 5-year relative survival of patients with stomach cancer in Slovenia has gradually increased: from 17% in the period 1986–1990 and 19% in the period 1991–1995 to 23% in the period 1996–2000 and 28% in the period 2001–2005.

Better results of the clinical series of the UMC Ljubljana and UMC Maribor, where resectability is significantly higher, postoperative lethality lower and 5-year survival above the Slovenian average, justify the expectation that the following period too will bring further improvement, particularly if we manage to reorganize the surgical treatment for stomach cancer. A third of the patients that currently undergo surgical treatment in nine regional hospitals (approximately 80 to 100 patients) could have surgery in three major hospitals – in Ljubljana, Maribor and Celje, and perhaps also in three regional hospitals – in Nova Gorica, Izola and Novo mesto. Undoubtedly, this would result in an increase in the currently still poor population survival.

CLINICAL COMMENTARY

Irena Oblak

Although the incidence of stomach cancer in Slovenia has been decreasing, this disease still remains among the most frequent cancer-related causes of deaths. It is interesting, however, that in recent years the incidence of carcinoma stemming from the cardia has been increasing particularly in the developed countries of the West.

More than two thirds of patients will have regional or metastatic disease already at the time of diagnosis. In as many as 40–50% of patients the disease is assessed as nonresectable at diagnosis; the median survival of these patients is 6 months to 1 year. In the case of resectable disease the basic treatment comprises a radical resection of the tumor with relevant regional lymph nodes. Unfortunately, the disease will recur in as many as 75% of cases, 40–65% of these recurrences being local and/or regional.

In 2001, an adjuvant treatment with postoperative radiochemotherapy (fluoropirimidins with or without cisplatin) was introduced in Slovenia. This treatment regimen improves the survival of patients after radical resection for stomach cancer stage Ib–IV without distant metastases. In our group of patients, an excellent local response has been achieved, as in 81% of patients the disease did not recur, neither locally nor regionally. The 5-year recurrence-free survival in our patient's group was 51%, the disease specific survival 51% and the overall survival 49%. As elsewhere, also our patients with larger tumors and those with tumors arising at cardia have worse prognosis.

Recently, the use of preoperative systemic chemotherapy and/or radiochemotherapy has become increasingly more frequent. In the last two years in Slovenia too we started to treat patients with operable stomach cancer by preoperative systemic chemotherapy according to ECF schedule (epidoxorubicin, cisplatin and 5-fluorouracil in continuous infusion), which is followed by surgery and afterwards by the same schedule as maintenance chemotherapy. When tumors were not resectable, the patients received radiochemotherapy prior to surgery. Such preoperative treatment is aimed at reducing the tumor mass and increasing the possibility of radical resection. Study results show that such treatment approach facilitates surgical removal of the tumor and regional lymph nodes (R0 resection) in more than 80% of patients, while a complete pathologic response and tumor disappearance is achieved in 20–30% of cases.

V zadnjem času se vse bolj uveljavlja predoperativno zdravljenje s sistemsko terapijo in/ali radiokemoterapijo. Tudi v Sloveniji smo v zadnjih dveh letih pričeli zdraviti bolnike z operabilnim rakom želodca s predoperativno sistemsko kemoterapijo po shemi ECF (epidoksorubicin, cisplatin in 5-FU v trajni infuziji), ki ji sledi operacija in nato ista vzdrževalna kemoterapija. Če tumorji niso bili resektabilni, so bili bolniki pred operacijo zdravljeni z radiokemoterapijo. Namen predoperativnega zdravljenja je zmanjšati tumor in povečati možnost za radikalno operacijo. Po izsledkih raziskav ta način zdravljenja omogoča popolno kirurško odstranitev tumorja in področnih bezgavk (resekcija R0) pri več kot 80 % bolnikov, pri 20–30 % pa že s tem postopkom tumor v celoti uničimo.

Izboljšanje preživetja bolnikov z želodčnim rakom v zadnjih letih pripisujemo tako izboljšani kirurški tehniki, kot tudi dodatnemu zdravljenju s kemo- in/ali radioterapijo. Tudi pri bolnikih z oddaljenimi zasevki in tistih, pri katerih tumor kljub intenzivnemu zdravljenju ostane neoperabilen, s paliativnim zdravljenjem (operacijo, radioterapijo in/ali sistemskim zdravljenjem) izboljšamo kakovost življenja, povečamo pa lahko tudi preživetje.

VIRI
Literature

Ajani JA, Mansfield PF, Janjan N, Morris J, Pisters PW, Lynch PM, et al. Multi-Institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol 2004; 22: 2774–80.

Cunningham D, Allum WH, Stenning SP, Thomson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl Med 2006; 355: 11–20.

Gunderson LL, Sosin H. Adenocarcinoma of the stomach: Areas of failure in a reoperation series (second or symptomatic look); clinicopathological correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1982; 8: 1–11.

Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345: 725–30.

Oblak I, Velenik V, Anderluh F, Strojan P. Results of adjuvant radiochemotherapy for gastric adenocarcinoma in Slovenia. Eur J Surg Oncol 2007; 33: 982–7.

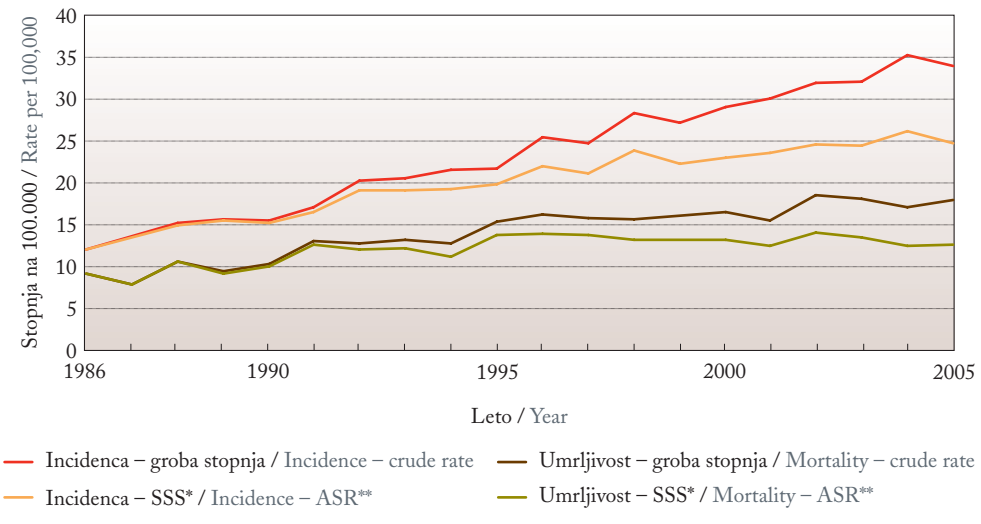
The improved survival of patients with stomach cancer in recent years is attributable to more advanced surgical techniques as well as to the use of adjuvant chemo and/or radiotherapy. Thus, even in patients with distant metastases and in those whose tumors remain inoperable despite intensive therapy, palliative therapy (surgery, radiotherapy and/or systemic therapy) is able to improve their quality of life and even increase their survival.

DEBELO ČREVO

MKB 10: C18

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom debelega črevesa zbolelo 8208 ljudi, od tega 4326 moških in 3882 žensk. Kot je razvidno s Slike 1, se groba in starostno standardizirana incidenčna stopnja od leta 1991 povečujeta, groba stopnja povprečno za 4,9 % letno, starostno standardizirana pa za 2,8 %. Groba umrljivostna stopnja se od leta 1996 veča v povprečju za 2,6 % letno, starostno standardizirana pa v povprečju za 0,5 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka debelega črevesa, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of colon cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 7934 primerov; 274 bolnikov (3,3 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti. V obdobju 2001–2005 je imela večina bolnikov (97 %) natančneje opredeljeno mesto vznika tumorja v debelem črevesu. Najpogosteje je bilo to esasto debelo črevo (44 %), sledijo slepo črevo (15 %), ascendentni kolon (13 %), jetrni zavoj in prečno debelo črevo, vsak z 8 %, vranični zavoj (7 %), descendentni kolon (6 %) in slepič z 1 %.

Odstotek mikroskopsko potrjenih primerov se je z 92 % v letih 1991–1995 povečal na 96 % v letih 2001–2005. V vseh treh obdobjih je bilo več kot tri četrtine žleznih karcinomov, v zadnjem

Tabela 1: *Število bolnikov z rakom debelega črevesa po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of colon cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	1018	8,4	69,5	22,0	995	8,4	62,7	28,8
1996–2000	1413	9,1	69,3	21,6	1252	8,0	57,3	34,7
2001–2005	1767	6,2	69,2	24,6	1489	5,9	56,1	37,9

COLON

ICD 10: C18

EPIDEMIOLOGY

In the period 1991–2005, a total of 8208 persons were diagnosed with colon cancer, of these 4326 males and 3882 females. As evident from Figure 1, since 1991 the crude and age standardized incidence rates have been increasing (4.9% estimated annual percentage increase in crude and 2.8% in age-standardized rate). From 1996 on, crude mortality rate has been increasing by 2.6% yearly, while in the same period, age-standardized mortality rate has been decreasing by 0.5% on average.

The survival analysis included 7934 cases; 274 patients (3.3%) diagnosed only after death were not considered in the analysis. In the period 2001–2005, the majority of patients (97%) had the site of tumor origin in the colon more precisely defined. The most frequent site was the sigmoid colon (44%), followed by the caecum (15%), ascending colon (13%), hepatic flexure and transverse colon (8% each), spleen flexure (7%), descending colon (6%) and the appendix (1%).

The percentage of microscopically confirmed cases increased from 92% in the period 1991–1995 to 96% in the period 2001–2005. In all three time-periods, more than three-quarters of cancers were adenocarcinomas, in the last period they represented 97% of the total, their proportion increasing mainly on the account of decrease in undefined carcinomas, while in all three periods other defined histological types represent less than 1%.

Age of the majority of patients at diagnosis ranged between 50 and 74 years. Less than 10% of patients developed the disease before the age of 50 (Table 1). Particularly in females, the proportion of patients aged 75 years or older is increasing with time, while the proportion of those aged 50–74 years is decreasing (Table 1).

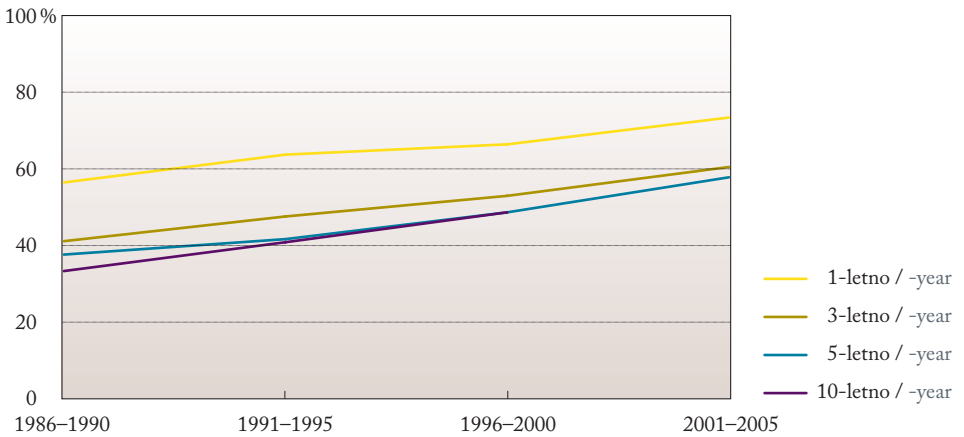
In all three time-periods, the majority of patients were diagnosed with regional disease; in the period 2001–2005 there were 60% such patients. In approximately 10% of patients the disease was diagnosed in the localized stage, while in more than 20% it was found to be disseminated. The proportions of individual stages have not changed significantly with time; an increase in the proportion of patients with regional stage is attributable to the decrease in the proportion of cancers with undefined stage in all periods (Table 2).

In the period 2001–2005, 13% of patients did not receive specific treatment. The proportion of untreated patients was slightly decreasing throughout the period of analysis; among those diagnosed in the years 1991–1995 there were 20% of patients without specific treatment. Practically all patients among the specifically treated in the period 2001–2005 underwent surgery; only 5% of patients with advanced disease at diagnosis were not treated by surgery. In 63% of patients primary treatment consisted of surgery alone, while 32% had surgery plus chemotherapy. In the period 2001–2005, 34% of patients started their treatment in the UMC Ljubljana, 17% in the UMC Maribor, 8% in GH Celje, 7% in GH Jesenice, 6% in GH Murska

Tabela 2: *Število bolnikov z rakom debelega črevesa po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of colon cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	1018	13,5	51,6	28,0	7,0	995	11,8	57,4	22,4	8,4
1996–2000	1413	10,5	59,1	26,3	4,2	1252	13,3	58,4	22,9	5,4
2001–2005	1767	11,6	60,0	26,0	2,4	1489	11,8	61,4	23,1	3,8



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom debelega črevesa po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of colon cancer patients by period of diagnosis.*

obdobju 97 %; njihov delež se veča predvsem na račun zmanjšanja deleža neopredeljenih karcinomov. Drugih opredeljenih histoloških vrst je v vseh obdobjih manj kot 1 %.

Starost največjega deleža zbolelih je bila ob diagnozi 50–74 let. Pred 50. letom zboli manj kot 10 % bolnikov (Tabela 1). Predvsem pri ženskah se s časom veča delež starih 75 let in več, manjša pa delež starih 50–74 let.

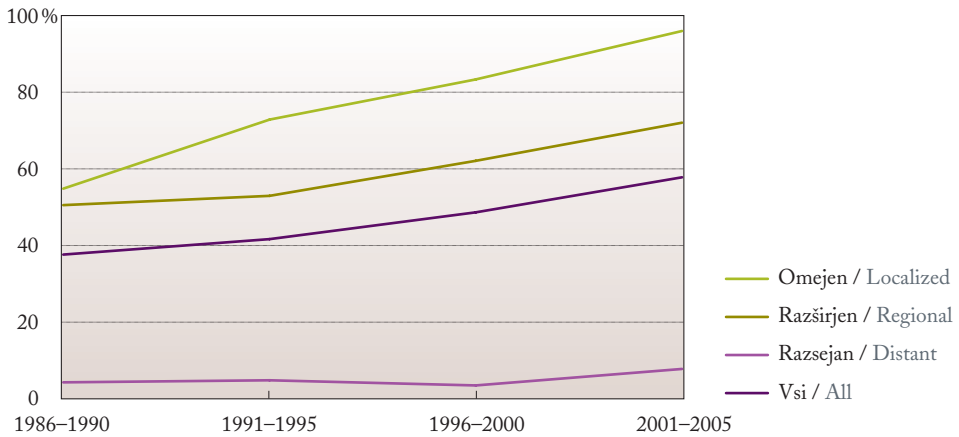
V vseh treh obdobjih je imelo največ bolnikov ob diagnozi razširjeno bolezen; v obdobju 2001–2005 je bilo takih 60 % bolnikov. Pri približno 10 % bolnikov je bila bolezen odkrita v omejenem stadiju, pri več kot 20 % pa v razsejanem. Deleži posameznih stadijev se s časom niso bistveno spreminjali; večanje deleža bolnikov z razširjenim stadijem gre predvsem na račun manjšanja deleža bolnikov z neopredeljenim stadijem v vseh obdobjih (Tabela 2).

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom debelega črevesa po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of colon cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	59,5 (56,6–62,6)	39,2 (36,3–42,3)	29,8 (27,1–32,7)	62,2 (59,3–65,3)	43,8 (40,8–47,0)	36,1 (33,2–39,2)
1996–2000	62,8 (60,4–65,4)	44,9 (42,3–47,5)	36,7 (34,3–39,3)	64,1 (61,5–66,8)	47,4 (44,7–50,2)	40,3 (37,6–43,1)
2001–2005	69,7 (67,6–71,8)	52,1 (49,8–54,5)	44,7 (42,3–47,3)	71,0 (68,7–73,3)	53,4 (50,9–56,0)	46,2 (43,5–49,0)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	62,7 (59,4–65,9)	45,8 (42,2–49,5)	38,8 (35,0–42,6)	64,6 (61,4–67,8)	49,3 (45,7–52,9)	44,1 (40,3–47,9)
1996–2000	66,0 (63,3–68,7)	52,2 (49,1–55,3)	47,5 (44,2–50,9)	66,8 (63,9–69,6)	53,7 (50,5–56,9)	49,8 (46,3–53,3)
2001–2005	73,1 (70,8–75,4)	60,7 (57,9–63,5)	58,3 (55,0–61,7)	73,8 (71,4–76,2)	60,4 (57,5–63,4)	57,1 (53,6–60,5)

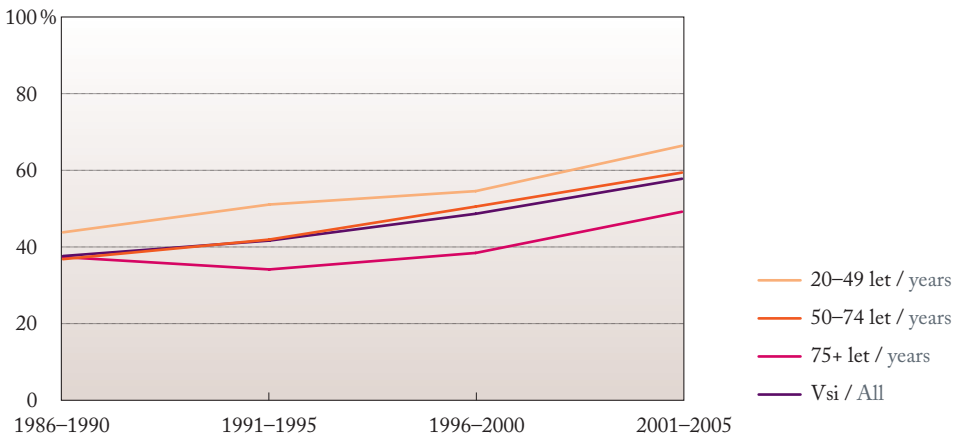


Slika 3: *Petletno relativno preživetje bolnikov z rakom debelega črevesa po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of colon cancer patients by stage and period of diagnosis.*

Sobota and 5% in GH Nova Gorica, while 18% of patients were admitted to almost all other Slovenian hospitals.

The relative survival rate of patients with colon cancer has been increasing: in 15 years, the 5-year relative survival increased by 16% (Figure 2), in males slightly more than in females (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, the 5-year relative survival of patients with localized stage has reached near to 96%. The 5-year relative survival of patients with regional stage of the disease is near to 72%, whereas patients with disseminated disease had only a rate of 8%. Age is a prognostic factor as well, since the relative survival is the lowest in patients aged 75 years or older, while survival in the age group 50–74 years was lagging behind the relative survival of those diagnosed before the age of 50 throughout the observation period (Figure 4).

The relative 5-year survival rate of all patients diagnosed in the period 2001–2005 was 58% (Figure 2); patients surviving the first year may expect to survive five years in 77%.



Slika 4: *Petletno relativno preživetje bolnikov z rakom debelega črevesa po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of colon cancer patients by age and period of diagnosis.*

V obdobju 2001–2005 ni bilo specifično zdravljenih 13 % bolnikov. Delež nezdravljenih bolnikov se je skozi vse obdobje analize počasi zmanjševal; med bolniki, zbolelimi v obdobju 1991–1995, jih je bilo brez specifičnega zdravljenja še 20 %. Med specifično zdravljenimi so bili v letih 2001–2005 praktično vsi bolniki operirani; brez kirurškega zdravljenja je ostalo 5 % bolnikov z napredovalo boleznijo ob diagnozi. Pri 63 % bolnikov je bilo prvo zdravljenje zaključeno z operacijo, 32 % pa jih je poleg operacije prejelo še kemoterapijo.

V obdobju 2001–2005 se je 34 % bolnikov pričelo zdraviti v UKC Ljubljana, 17 % v UKC Maribor, 8 % v SB Celje, 7 % v SB Jesenice, 6 % v SB Murska Sobota in 5 % v SB Nova Gorica, 18 % bolnikov je začelo zdravljenje v skoraj vseh drugih slovenskih bolnišnicah.

Relativno preživetje bolnikov z rakom debelega črevesa se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 16 % (Slika 2), pri moških nekoliko več kot pri ženskah (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem se je v zadnjem obdobju približalo 96 %. Petletno relativno preživetje bolnikov z razširjenim stadijem se približuje 72 %, pri bolnikih z razsejano boleznijo ob diagnozi pa je petletno relativno preživetje le 8 %. Napovedni dejavnik je tudi starost, saj je relativno preživetje najmanjše pri starih 75 let in več, preživetje ob diagnozi starih 50–74 let pa ves čas opazovanja zaostaja za relativnim preživetjem zbolelih pred 50 letom starosti (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 58 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 77-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom debelega črevesa statistično značilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

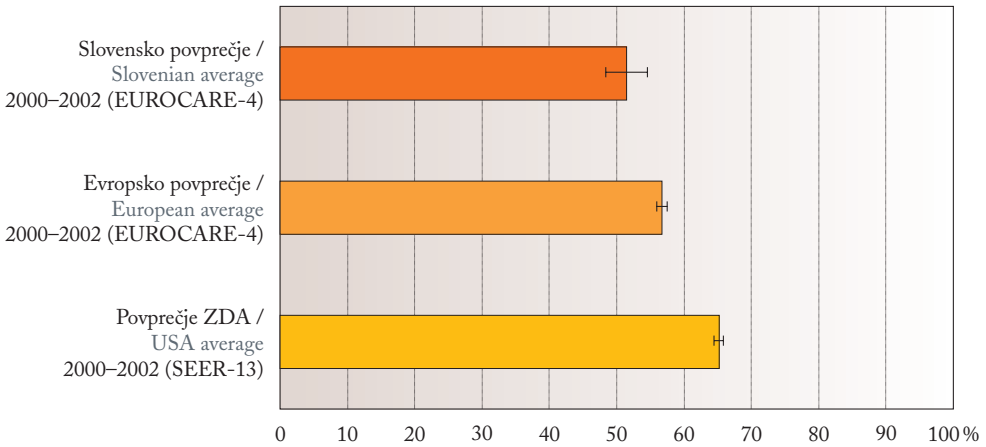
Stane Repše

Razvoj in stanje kirurškega zdravljenja raka debelega črevesa v Sloveniji v obdobju 1983 do 1997 je bilo opisano v zadnji izdaji *Preživetje bolnikov z rakom v Sloveniji* leta 2003. Takrat smo menili, da se bodo posledice prizadevanja na področju raka debelega črevesa po letu 1980 (strokovni sestanki, nacionalne ankete, multidisciplinarni timi, delavnice in simpoziji, publikacije) pokazale z boljšimi rezultati preživetja na državni ravni šele v sedanjem obdobju.

V obdobju, ki je sedaj analizirano in je prikazano s petletnim preživetjem, smo kirurgi v Sloveniji spoštovali doktrinarna načela obravnave bolnikov z rakom debelega črevesa, ki smo jih izdelali v začetku 90. let in so bila objavljena v publikaciji *Priporočila za celostno obravnavo bolnikov z rakom prebavil* leta 1997. Standardna resekcija obolelega dela črevesa in razširjena resekcija z radikularno ligaturo žil ter limfadenektomijo je bila kirurški standard. Pooperativna adjuvantna kemoterapija pri stadiju III je bila splošno sprejeta, pri stadiju II pa je bila dovoljena samo v okviru kliničnih raziskav.

Vseh kirurških podatkov za raka debelega črevesa in za raka danke ni mogoče dobro prikazati ločeno. V nadaljevanju prikazujemo podatke za obe mesti raka skupaj. Po podatkih ankete *Rak debelega črevesa in danke v Sloveniji 2005* je bilo zdravljenih na vseh kirurških oddelkih v Sloveniji 1121 bolnikov: 449 (40 %) v Ljubljani, 233 (20 %) v Mariboru in Celju ter 452 (40 %) na kirurških oddelkih drugih bolnišnic. Operiranih je bilo 1102 od 1121 (operabilnost 98 %), reseciranih pa 1014 od 1102 (resektabilnost 92 %).

Če primerjamo podatke te ankete s podatki enake ankete iz leta 1995 (803 bolniki), vidimo, da je bila operabilnost enaka (98 %), resektabilnost pa manjša, samo 82 %. Tudi delež bolnikov po kraju zdravljenja je bil skoraj enak: Ljubljana 43 %, Maribor in Celje 22 %, vse preostale bolnišnice pa 36 %. Pooperacijska smrtnost reseciranih bolnikov se je v zadnjem obdobju nekoliko povečala (leta 1995 3 %, leta 2005 5 %), kar pa je zaradi 10 % večje resektabilnosti razumljivo.



Slika 5: *Petletno relativno preživetje bolnikov z rakom debelega črevesa (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of colon cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, survival of Slovenian patients with colon cancer is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Stane Repše

The development and the state-of-the-art of surgical treatment for colon cancer in Slovenia in the period 1983–1997 was presented in the last edition of the publication *Cancer Patients Survival in Slovenia* issued in 2003. Then we presumed that the results of endeavors in the area of colon cancer after the year 1980 (expert meetings, national surveys, multidisciplinary teams, workshops and symposia, publications) would be reflected in better survival rates at the national level only in the current period.

In the period, which is subject to the current analysis and is presented by 5-year survival, the surgeons in Slovenia followed the doctrinary principles of colon cancer patient treatment, which were adopted in the 90's and published in 1997 under the title *Recommendations for a Comprehensive Treatment of Patients with Cancers of Digestive Organs*. Thus, standard resection of the affected part of the colon and extended resection with radicular artery ligation and lymphadenectomy represented a surgical standard. While in stages III and IV postoperative adjuvant chemotherapy was commonly accepted, in stage II it was approved only within the framework of clinical trials.

It is not possible to present all the surgical data for colon cancer and rectal cancer separately. Therefore, in this commentary the data for both sites are presented together. According to the survey on the colorectal cancer in Slovenia in 2005, there were 1121 patients treated in all surgical departments in Slovenia: 449 (40%) in UMC Ljubljana, 233 (20%) in UMC Maribor and GH Celje, and 452 (40%) at surgical departments of other hospitals. Out of the total of 1121 patients, 1102 underwent surgery (98% operability), 1014 of 1102 had a resection (92% resectability).

When comparing the data of this survey with the data of the same survey carried out in 1995 (803 patients), the operability turns out to be equal (98%) while the resectability was lower,

Rezultati naših skupnih prizadevanj na državni ravni v zadnjih dveh desetletjih prejšnjega stoletja so se dejansko pokazali v sedanjem obdobju, saj se je populacijsko petletno relativno preživetje bolnikov v 10 letih povečalo za 16 %. Rezultati v posamezni ustanovi so lahko pri tem bistveno boljši od državnega povprečja. Tako je v seriji 1478 reseciranih bolnikov z rakom debelega črevesa in danke v UKC Ljubljana iz obdobja 1991–2000 opazovano petletno preživetje vseh reseciranih (R0, R1, R2) bolnikov 55 % (Kaplan-Meier); pri reseciranih R0 zaradi raka debelega črevesa 66 % in pri raku danke 59 %.

Ker tudi populacijski podatki kažejo, da petletno relativno preživetje bolnikov z omejenim stadijem po letu 1996 presega 80 %, lahko pričakujemo nadaljnje izboljševanje preživetja na državni ravni, če se bo s presejalnim programom SVIT več primerov bolezni odkrilo v omejenem stadiju.

VIRI
Literature

Markovič S, Štabuc B, Zakotnik B, Benulič T, Čalić M, Žakelj B, et al. Rak debelega črevesa in danke. In: Repše S, ed. Priporočila za celostno obravnavo bolnikov z rakom prebavil. Ljubljana: Ministrstvo za zdravstvo R Slovenije, 1997; 23–32.

Repše S, Jelenc F, Štor Z, Omejc M, Juvan R. Kirurgija raka debelega črevesa in danke v Sloveniji v obdobju 1995 do 2005. In: Repše S, Štor Z, eds. Kirurgija raka debelega črevesa in danke – standardi in novosti: zbornik simpozija. Ljubljana, Kirurška klinika, 2006; 3–13.

Repše S, Štor Z, Juvan R. Kirurgija raka širokega črevesa in danke v Sloveniji. In: Repše S, ed. Kirurgija želodca: zbornik simpozija. Ljubljana, Kirurška šola, Kirurške klinike, 1996; 118–26.

Štor Z, Jelenc F, Juvan R, Omejc M, Bunc M, Repše S. Improved Outcome of Patients with Colorectal Cancer: The Ljubljana University Medical Centre Experience. Dig Surg 2008; 25: 158–63.

Štor Z, Repše S. Kirurgija raka debelega črevesa in danke v Sloveniji – rezultati ankete 2005. In: Repše S, Štor Z, eds. Kirurgija raka debelega črevesa in danke – standardi in novosti: zbornik simpozija. Ljubljana, Kirurška klinika, 2006; 95–103.

KLINIČNI KOMENTAR
Janja Ocvirk

Presejalnega programa za raka debelega črevesa v obdobju 1991–2005 v Sloveniji ni bilo, kakor tudi ne dejavnosti za ozaveščanje prebivalstva, kar se zrcali v velikem številu bolezni, odkrite v napredovalem stadiju. Samo 10–13 % bolnikov je bilo odkritih z boleznijo v omejenem stadiju, kar je veliko manj kot v drugih evropskih državah, veliko več pa je bolnikov z razširjeno (50–60 %) in razsejano boleznijo (22–28 %). V vseh petletnih obdobjih delež omejene bolezni ostaja enako majhen in delež razsejane bolezni enako velik, manj pa je bolnikov, za katere stadij ni znan, kar lahko pripišemo boljšim diagnostičnim postopkom. Temu pripisujemo tudi večji delež mikroskopsko potrjenih primerov raka. Kolonoskopija z biopsijo je uveljavljena že od 80. let, izboljšale pa so se preiskave za natančnejšo opredelitev razširjenosti bolezni: UZ, CT in MR. Bolnike z rakom debelega črevesa so operirali in jih še operirajo v vseh slovenskih bolnišnicah, vendar pa jih največ operirajo v UKC Ljubljana, nekaj več kot 30 %, sledita UKC Maribor in SB Celje. Skupaj je bila v treh največjih centrih za abdominalno kirurgijo operirana več kot polovica bolnikov.

Incidenca raka debelega črevesa se iz leta v leto veča v vseh starostnih skupinah, vendar največ med bolniki, starimi 75 let in več, katerih delež se zato veča. Spodbuden je podatek, da se umrljivost veča veliko manj kot incidenca.

Petletno relativno preživetje bolnikov se veča v vseh obdobjih že od leta 1991; tako preživetje vseh bolnikov kakor tudi bolnikov z omejeno in razširjeno boleznijo. Za vse večje preživetje vseh naštetih skupin so pomembni tako boljša diagnostika, boljše in standardizirane operativne tehnike in dodatno sistemsko zdravljenje. Pri bolnikih z razširjeno boleznijo, ki so bili poleg operativnega zdravljenja deležni še adjuvantne kemoterapije, pa večanje preživetja pripisujemo tudi tej, saj se je delež tako zdravljenih močno povečal. V obdobju 1991–1995 se je samo 8 % bolnikov po operaciji tudi dodatno zdravilo s kemoterapijo, medtem ko se je ta delež v obdobju 2001–2005

being 82% only. The proportion of patients by place of treatment was similar: Ljubljana 43%, Maribor and Celje 22%, and all other hospitals 36%. In the last period, postoperative mortality of the resected patients has slightly increased (in 1995 it was 3% and in 2005, 5%), which is understandable, considering the 10% greater resectability.

The results of our joint endeavors at the national level, achieved in the last two decades of the previous century, have become apparent in the present period, since in a 10-year period, the population-based relative 5-year relative survival increased by 16%. Results of an individual institution may be significantly better than the national average. Thus, in the series of 1478 patients with colon and rectum cancer resected in the UMC Ljubljana, in the period 1991–2000, the observed 5-year survival rate of all the resected patients (R0, R1, R2) was 55% (Kaplan-Meier); in the R0 group resected for colon cancer it was 66% and in rectal cancer patients it was 59%.

As population data show that 5-year relative survival of patients with localized disease after 1996 exceeds 80%, we can expect further improvement in survival at the national level, particularly if by means of SVIT screening program more cases of the disease will be diagnosed at a localized stage.

CLINICAL COMMENTARY

Janja Ocvirk

In the period 1991–2005 there was no screening program for colon cancer in Slovenia and neither any awareness-raising activity in this respect, which is reflected in a high number of cases diagnosed at an advanced stage. In only 10–13% of patients the disease was diagnosed at a localized stage, which is far less than in other European countries; accordingly, the proportion of patients with regional (50–60%) and disseminated disease (22–28%) was much greater. In all 5-year time-periods, the proportion of localized disease remains equally low and the proportion of disseminated disease equally high, while the number of patients with undefined stage is lower, which is attributable to better diagnostic procedures. The same applies to the higher proportion of microscopically confirmed cancers. Colonoscopy with biopsy has been established since the 80's, however, the methods for more precise staging of the disease have improved; thus ultrasonography is used along with computer tomography and magnetic resonance. Patients with colon cancer used to be and still are treated surgically in all Slovenian hospitals, however, most of them (more than 30%) undergo surgery in the UMC Ljubljana; following in descending order are UMC Maribor and GH Celje. Altogether, more than a half of these patients were operated on in the three largest centers for abdominal surgery.

The incidence of colon cancer has been increasing every year in all age groups, however most steeply in patients aged 75 or older, whose proportion is therefore getting larger. It is encouraging to note that the mortality rate is increasing less than the incidence.

The 5-year relative survival of patients has been improving in all time periods since 1991; this applies to the survival of all patients as well as of those with localized and regional disease. The increasingly better survival of all these groups can be ascribed to better diagnostics, more advanced and standardized surgical techniques and to adjuvant systemic therapy. In patients with regional disease treated by surgery in combination with adjuvant chemotherapy the increasing survival rates should be actually attributed to the latter treatment modality, since the proportion of thus treated patients has markedly increased. In the period 1991–1995, only 8% of patients were treated by adjuvant chemotherapy after surgery, whereas in the period 2001–2005 this proportion increased to almost 32%, thanks to the generally recognized knowledge on the effectiveness of adjuvant therapy, up-to-dated recommendations for such treatment and, last but not least, to a better multidisciplinary approach to patient treatment. The effectiveness of such treatment is also reflected in better survival of these patients.

povečal na skoraj 32 %, kar lahko pripišemo spoznanjem o učinkovitosti adjuvantne terapije, posodobljenim priporočilom za tovrstno zdravljenje in seveda boljši multidisciplinarni obravnavi bolnika. Učinkovitost takega zdravljenja se kaže tudi v večjem preživetju teh bolnikov.

Petletno preživetje bolnikov z razsejano boleznijo se je začelo večati šele po letu 2001, ko smo v zdravljenje vpeljali prvo izmed skupine novih zdravil – irinotekan, kateremu so v nadaljnjih letih sledili še kapecitabin, oksaliplatin, cetuksimab in bevacizumab, vendar se bo vpliv zadnjih treh bolj opazil šele v naslednjem obdobju.

VIRI
Literature

Luzar B, Cerar A, Štabuc B, eds. Tumorji debelega črevesa in danke. Ljubljani: Inštitut za patologijo, Medicinska fakulteta; 2008.

Ocvirk J. Novosti v zdravljenju metastatskega raka debelega črevesa in danke. Onkologija 2006; 10: 24–6.

Ocvirk J. Sistemsko zdravljenje bolnikov z rakom debelega črevesa in danke. In: Repše S, Štor Z, eds. Kirurgija raka debelega črevesa in danke – standardi in novosti: zbornik simpozija. Ljubljana, Kirurška klinika, 2006; 170–8.

Ocvirk J. Sistemsko zdravljenje inoperabilnih jetrnih zasevkov raka debelega črevesa in danke. In: Repše S, Stanisavljević D, eds. Kirurgija jeter in vranice: zbornik simpozija. Ljubljana: Kirurška klinika, 2004; 107–16.

Ocvirk J. Zdravljenje bolnikov z rakom debelega črevesa. In: Kopčavar Guček N, Petek D, eds. Kakovostna obravnava bolnika v družinski medicini: zbornik predavanj. Ljubljana: Združenje zdravnikov družinske medicine, 2006; 111–5.

Program SVIT: www.program-svit.si.

Reberšek M, Hlebanja Z, Ocvirk J. Priporočila za adjuvantno zdravljenje bolnikov z rakom debelega črevesa. Onkologija 2007; 11: 26–7.

Reberšek M, Hlebanja Z, Ocvirk J. Priporočila za sistemsko zdravljenje bolnikov z napredovalim rakom debelega črevesa in danke. Onkologija 2007; 11: 28–31.

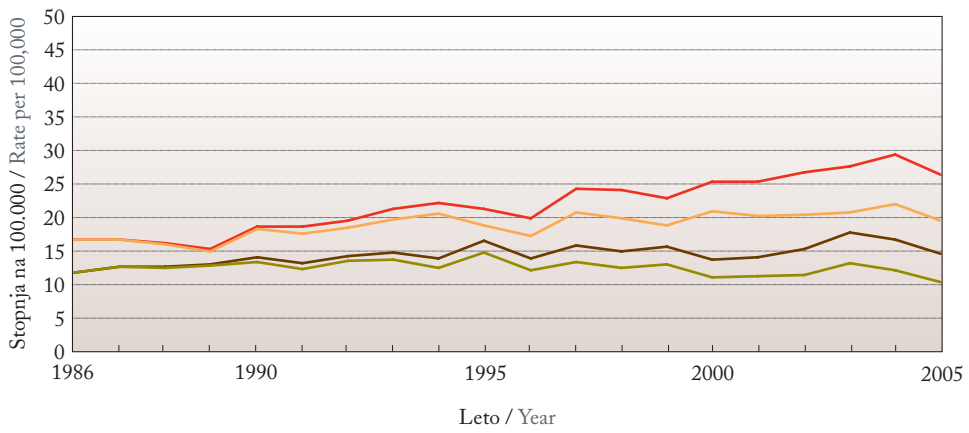
The 5-year survival of patients with disseminated disease has started to improve only after the year 2001, when the first in the group of new cancer drugs – irinotecan was introduced into therapy, followed over the years by capecitabin, oxaliplatin, cetuximab and bevacizumab. However, the impact of the latter drugs will be noticeable only in the next observation period.

DANKA

MKB10: C19–C21

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom danke zbolelo 7309 ljudi, od tega 4121 moških in 3188 žensk. Kot je razvidno s Slike 1, se groba in starostno standardizirana incidenčna stopnja od leta 1991 povečujeta, groba stopnja se veča hitreje, povprečno za 2,9 % letno, kot starostno standardizirana (0,9 %). Groba umrljivostna stopnja se je v letih 1991–2005 povečevala za 0,9 % letno, starostno standardizirana umrljivostna stopnja pa se je manjšala v povprečju za 1,2 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka danke, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of rectal cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 7066 primerov; 243 bolnikov (3,3 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 1 mlajši od 20 let pa je vključen v poglavje o preživetju pri otrocih in mladostnikih. V zadnjem obdobju je imelo 78 % bolnikov tumor ampule danke, 19 % tumor rektosigmoidne zveze in 3 % tumor zadnjika ali zadnjičnega kanala.

V obdobju 2001–2005 je bilo 97 % primerov raka mikroskopsko potrjenih. Delež mikroskopsko potrjenih se je v primerjavi z obdobjem 1991–1995 povečal za 5 %. Večina mikroskopsko potrjenih malignomov je bila adenokarcinomov, drugih histoloških vrst je bilo manj kot 2 %.

Tabela 1: *Število bolnikov z rakom danke po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of rectal cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	1122	8,8	69,2	22,0	927	8,0	63,9	28,2
1996–2000	1304	6,5	73,4	20,1	1004	7,4	62,5	30,1
2001–2005	1595	7,4	70,4	22,2	1114	5,9	56,0	38,1

RECTUM

ICD 10: C19–C21

EPIDEMIOLOGY

In the period 1991–2005, a total of 7309 persons were diagnosed with cancer of the rectum, of these 4121 males and 3188 females. As evident from Figure 1, since 1991 the crude and age standardized incidence rates have been increasing, the crude rate more rapidly than the age-standardized rate (2.9% vs. 0.9% estimated annual percentage increase, respectively). In the period 1991–2005 the crude mortality rate was increasing by 0.9%, while the age-standardized mortality rate was decreasing by an estimated annual percentage change of 1.2%.

The survival analysis included 7066 cases; 243 patients (3.3%) diagnosed only after death were not considered in the analysis, 1 patient younger than 20 years is included in the chapter on the survival of children and adolescents. In the last period, 78% of patients had tumor situated in the rectal ampulla, 19% in the rectosigmoid junction and 3% in the anus or anal canal.

In the period 2001–2005, 97% of rectal cancers were microscopically verified. In comparison with the period 1991–1995 the proportion of microscopically confirmed cases has increased by 5%. The majority of microscopically confirmed malignomas were adenocarcinomas; other histological types represented less than 2% of cases.

Age of the majority of patients at diagnosis ranged between 50–74 years. Less than 10% of patients developed the disease before the age of 50 (Table 1). Except for the increased proportion of females in the oldest age group, the proportion of patients in individual age groups did not change significantly with time.

In all three time-periods, the majority of patients were diagnosed with regional disease; in the period 2001–2005 there were 57% such patients. Approximately 20% of patients were diagnosed either with localized or disseminated stage. The proportion of patients with individual stages has not changed significantly with time, however the proportion of patients with undefined stage has been decreasing (Table 2).

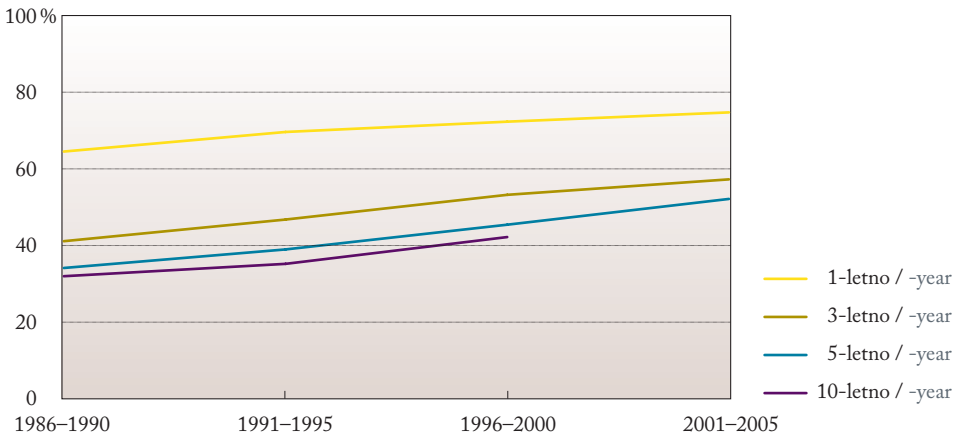
In the period 2001–2005, 15% of patients did not receive specific treatment. The proportion of untreated patients was gradually decreasing throughout the observation periods; among those diagnosed in the period 1991–1995 there were 23% of patients without specific treatment. Practically all patients among the specifically treated in the period 2001–2005 underwent surgery; only 7% of patients with advanced disease at diagnosis were not treated by surgery. In 42% of patients primary treatment consisted of surgery alone, 30% were additionally treated by irradiation and chemotherapy, 14% had surgery combined with chemotherapy, while 6% received only radiotherapy.

In the period 2001–2005, 25% of patients started their treatment at the IO Ljubljana, 21% in the UMC Ljubljana, 10% in the UMC Maribor, 5% each in GH Celje and GH Novo mesto, while less than 5% of patients were admitted to almost all other Slovenian general hospitals.

Tabela 2: *Število bolnikov z rakom danke po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of rectal cancer patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	1122	19,3	50,9	20,6	9,3	927	17,0	51,6	19,6	11,8
1996–2000	1304	17,5	53,4	22,8	6,4	1004	21,6	52,7	18,1	7,6
2001–2005	1595	17,1	58,1	21,4	3,4	1114	18,4	56,1	19,9	5,6



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom danke po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of rectal cancer patients by period of diagnosis.*

Starost največjega deleža zbolelih je bila ob diagnozi 50–74 let. Pred 50. letom zboli manj kot 10 % bolnikov (Tabela 1). Razen povečanega deleža najstarejših žensk se deleži v posameznih starostnih skupinah s časom niso bistveno spreminjali.

V vseh treh obdobjih je imelo ob diagnozi največ bolnikov razširjeno bolezen; v obdobju 2001–2005 jih je bilo 57 %. Z omejenim in razsejanim stadijem je bilo diagnosticiranih približno po 20 % bolnikov. Deleži bolnikov s posameznimi stadiji se s časom niso bistveno spreminjali, se pa manjša delež bolnikov, pri katerih stadij ni bil opredeljen (Tabela 2).

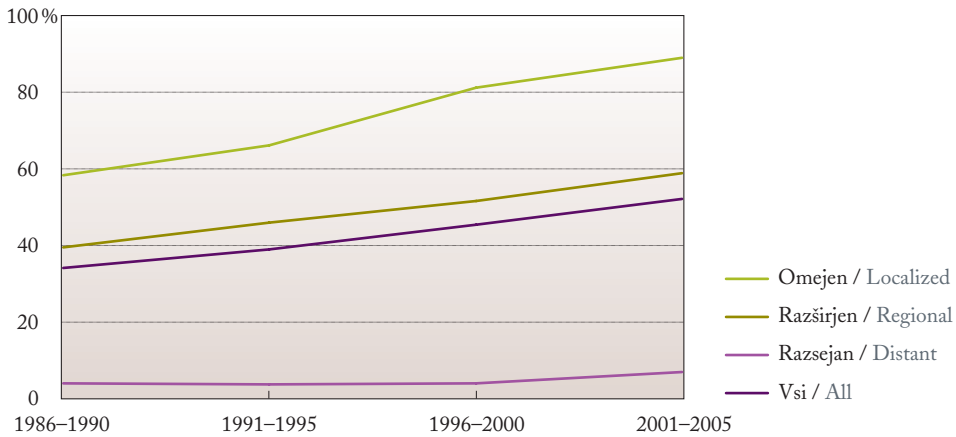
V obdobju 2001–2005 se ni specifično zdravilo 15 % bolnikov. Delež nezdravljenih bolnikov se je v vseh obdobjih počasi zmanjševal; med bolniki, zbolelimi v letih 1991–1995, se jih ni specifično zdravilo 23 %. Med specifično zdravljenimi so bili v letih 2001–2005 praktično vsi

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom danke po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of rectal cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	66,9 (64,2–69,7)	40,4 (37,6–43,4)	29,9 (27,3–32,7)	65,8 (62,8–68,9)	41,3 (38,3–44,6)	31,9 (29,1–35,1)
1996–2000	68,8 (66,3–71,4)	45,2 (42,6–48,0)	34,4 (31,9–37,1)	69,8 (67,0–72,7)	49,0 (46,0–52,2)	38,9 (36,0–42,1)
2001–2005	71,9 (69,7–74,2)	50,9 (48,5–53,5)	42,2 (39,7–45,0)	71,1 (68,5–73,8)	49,3 (46,4–52,3)	40,2 (37,2–43,5)

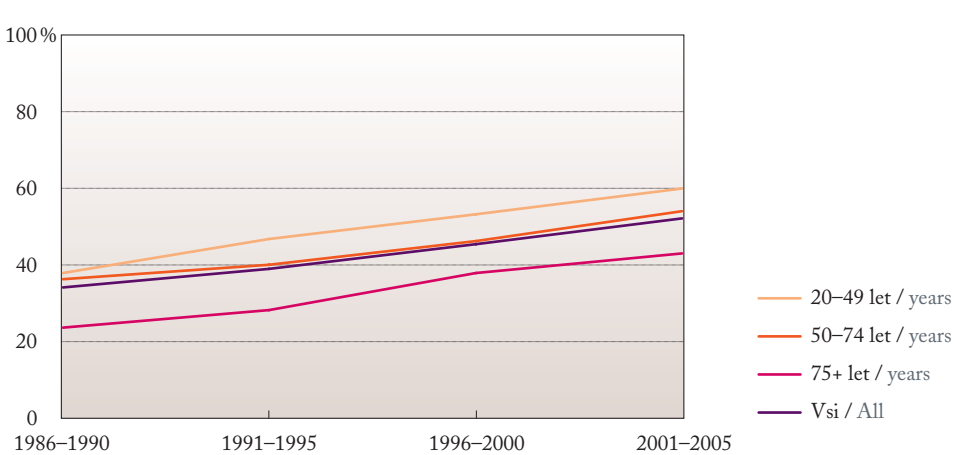
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	70,4 (67,4–73,3)	47,0 (43,5–50,5)	38,5 (34,9–42,1)	68,5 (65,2–71,7)	46,7 (43,0–50,4)	39,2 (35,3–43,1)
1996–2000	72,1 (69,4–74,8)	52,2 (49,0–55,4)	44,1 (40,6–47,5)	72,4 (69,4–75,4)	54,7 (51,1–58,3)	47,1 (43,3–50,9)
2001–2005	75,2 (72,9–77,6)	58,7 (55,8–61,7)	54,3 (50,8–57,8)	73,8 (71,0–76,6)	55,5 (52,1–58,9)	49,5 (45,5–53,6)



Slika 3: *Petletno relativno preživetje bolnikov z rakom danke po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of rectal cancer patients by stage and period of diagnosis.*

Within the primary treatment, many patients – after having received initial preoperative chemo and/or radiotherapy at the IO Ljubljana – underwent surgery at their local hospitals. In the period 2001–2005 the majority of surgical procedures in rectal cancer patients were performed in the UMC Ljubljana (34%). The percentage of surgeries for rectal cancer performed in the UMC Maribor was a half of that (17%); 8% of patients were operated on at the IO Ljubljana and 7% each in the general hospitals of Celje, Novo mesto and Murska Sobota. In the 5-year period, over a 100 patients were operated on in the general hospitals of Jesenice and Slovenj Gradec (5% of all such patients). Four percents of all patients underwent surgery in the general hospitals of Nova Gorica and Izola, while individual patients were also operated on elsewhere.

The relative survival rate of patients with rectal cancer has been gradually increasing: in 15 years, the 5-year relative survival increased by 13% (Figure 2), in males slightly more than in females (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage has reached near to 90%. The 5-year relative survival of patients with regional stage of the disease is near to 60%, whereas patients with



Slika 4: *Petletno relativno preživetje bolnikov z rakom danke po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of rectal cancer patients by age and period of diagnosis.*

bolniki operirani; operiranih ni bilo 7 % bolnikov z napredovalo boleznijo ob diagnozi. Pri 42 % primerov se je prvo zdravljenje zaključilo z operacijo, 30 % jih je bilo dodatno še obsevanih in zdravljenih s kemoterapijo, 14 % jih je poleg operacije prejelo kemoterapijo, 6 % pa samo radioterapijo.

V obdobju 2001–2005 se je 25 % bolnikov začelo zdraviti na OI Ljubljana, 21 % v UKC Ljubljana, 10 % v UKC Maribor, po 5 % pa v SB Celje in SB Novo mesto; manj kot 5 % bolnikov so začeli zdraviti v skoraj vseh drugih slovenskih splošnih bolnišnicah. V okviru prvega zdravljenja se je veliko bolnikov, ki so se začeli zdraviti s predoperativno kemo- in/ali radioterapijo na OI Ljubljana, na kirurški poseg vrnilo v matično bolnišnico. Največ kirurških posegov pri bolnikih z rakom danke so v obdobju 2001–2005 naredili v UKC Ljubljana (34 %). Polovico manj kirurških posegov pri bolnikih s tumorji danke so naredili v UKC Maribor (17 % vseh operacij), 8 % so jih operirali na OI Ljubljana, po 7 % pa v splošnih bolnišnicah v Celju, Novem mestu in Murski Soboti. Več kot 100 bolnikov v petletnem obdobju (po 5 % med vsemi) so operirali še v SB Jesenice in SB Slovenj Gradec. V SB Nova Gorica in v SB Izola so operirali 4 % vseh bolnikov, posamezni bolniki pa so bili operirani tudi drugod.

Relativno preživetje bolnikov z rakom danke se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 13 % (Slika 2), pri moških malo več kot pri ženskah (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem se je v zadnjem obdobju približalo 90 %. Petletno relativno preživetje bolnikov z razširjenim stadijem se približuje 60 %, pri bolnikih z razsejano boleznijo ob diagnozi pa je petletno relativno preživetje le 7 %. Napovedni dejavnik je tudi starost, saj je relativno preživetje najslabše pri starih 75 let in več, preživetje zbolelih med 50–74 leti pa ves čas opazovanja nekoliko zaostaja za relativnim preživetjem zbolelih pred 50. letom (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 52 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 68-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom danke statistično značilno manjše od evropskega povprečja (Slika 5).

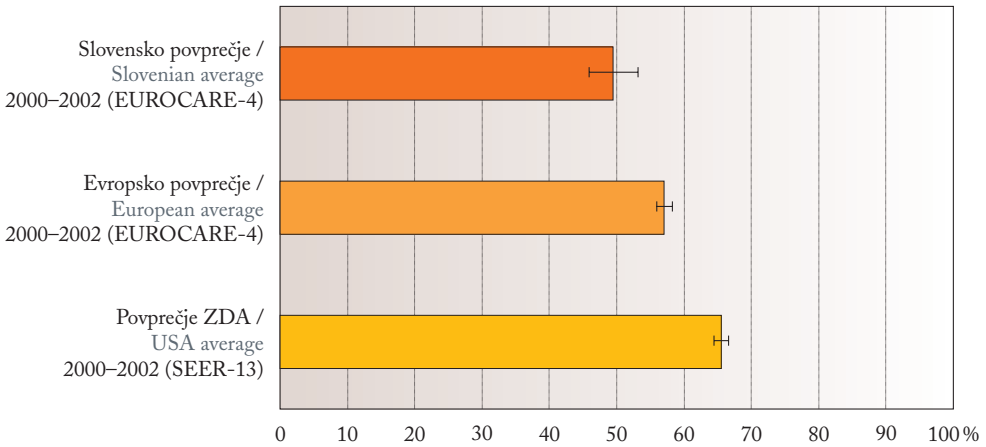
KLINIČNI KOMENTAR

Ibrahim Edhemović

Iz priloženih podatkov je razvidno, da se je preživetje bolnikov z rakom danke v Sloveniji v zadnjem opazovanem obdobju izboljšalo, vendar ne v zadovoljivem obsegu. Za to sta dva temeljna razloga: napredovali stadij ob diagnozi in razpršeno kirurško zdravljenje po vseh kirurških oddelkih v Sloveniji.

Skoraj tri četrtine bolnikov ima že ob diagnozi razširjeni ali razsejani stadij – takšni bolniki imajo slabšo napoved izida oz. slabše preživetje. Pričakujemo, da bo letos začeti presejalni program za zgodnje odkrivanje raka debelega črevesa in danke (SVIT) povečal delež bolnikov z nižjimi stadiji ob diagnosticiranju in s tem tudi povečal preživetje.

Rezultati zdravljenja raka danke so izrazito odvisni od samega kirurga, oz. od njegove strokovne izpopolnjenosti in izkušenj, ki jih lahko nabere le z ustreznim dodatnim izobraževanjem in velikim številom operacij. V Sloveniji adjuvantno in neoadjuvantno zdravljenje izvajajo izključno zdravniki na OI Ljubljana, zato ni razpršenosti, s tem sta tudi zagotovljena kakovost in nadzor. Kar se tiče kirurgije, pa opažamo, da bolnike z rakom danke operirajo v skoraj vseh bolnišnicah v Sloveniji – tudi na oddelkih, kjer na leto opravijo 10 ali manj operacij. Če bi te operacije šteli na posameznega kirurga, bi bile številke še manjše. Kirurgi, ki niso dodatno izobraženi s področja kirurgije raka danke in naredijo malo operacij, ne morejo kakovostno izvesti operacije (totalna mezorektalna ekscizija), kar pa je temeljni pogoj za dobre rezultate zdravljenja. Drugi razlog, zaradi katerih je treba bolnike koncentrirati v večjih centrih, je lažja dostopnost do preiskave MRI, ki je danes nepogrešljiva za pravilno načrtovanje predoperativnega zdravljenja



Slika 5: *Petletno relativno preživetje bolnikov z rakom danke (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of rectal cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

disseminated disease at diagnosis have only a rate of 7%. Age is a prognostic factor as well, since the relative survival is the lowest in patients aged 75 years or older, while the survival of those diagnosed between 50–74 years of age was lagging behind the relative survival of the patients diagnosed before the age of 50 throughout the observation period (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 52% (Figure 2); patients surviving the first year may expect to survive five years in 68%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, survival of Slovenian patients with rectal cancer is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Ibrahim Edhemović

The data presented indicate, that in the last observation period the survival of rectal cancer patients in Slovenia has improved, though not to a sufficient extent. There are two basic reasons for that: advanced stage at diagnosis and surgical treatment, which is dispersed practically through all surgical departments in Slovenia.

Almost three fourths of patients present with regional or disseminated disease at diagnosis, and such patients have worse prognosis. It is expected that the screening program for early colorectal cancer detection (SVIT) launched this year will contribute to a greater proportion of patients with lower stages and thus also to a better survival.

The results of rectal cancer treatment very much depend on the surgeon, i. e. on his professional skills and experience, which can only be obtained through additional training and sufficient number of surgeries performed. In Slovenia, adjuvant and neoadjuvant therapy is performed exclusively by specialized doctors at IO Ljubljana, which ensures that there is no dispersion and that adequate quality and supervision are maintained. However, as regards surgery we note that rectal cancer patients are operated on in almost all hospitals throughout Slovenia, thus also in departments with a turnover of less than 10 such surgeries per year. If these procedures

in operacije same. Poleg tega v večjih centrih posvečajo posebno pozornost prehranskemu zdravljenju v pred- in pooperativnem obdobju, kar zaradi pozitivnega vpliva na imunsko stanje bolnika izboljšuje tudi preživetje. Poseben pomen ima tudi obdelava preparata po Quirkejevem protokolu na oddelkih za patologijo, ki jo opravljajo skoraj izključno na oddelku za patologijo na OI Ljubljana, drugje pa le izjemoma. V prihodnje bi bilo treba po bolnišnicah poleg preživetja registrirati tudi število lokalnih in oddaljenih ponovitev ter razmerje med kontinuitetnimi in nekontinuitetnimi operacijami. Ti parametri so merljivi in predstavljajo osnovo za oceno kakovosti zdravljenja raka danke. Na ta način bi lahko ugotovili, katere ustanove ne izpolnjujejo minimalnih standardov kakovosti zdravljenja in bi morale bolnike preusmeriti v ustanove, kjer je večja verjetnost ozdravitve.

Boljše preživetje v zadnjem opazovanem obdobju je lahko posledica večjega deleža bolnikov, ki so bili neoadjuvantno zdravljeni. K temu je prispevalo tudi sodobno sistemsko pooperativno zdravljenje. Zavedati pa se moramo, da brez odlične kirurgije tudi vrhunska kemoterapija in radioterapija ne moreta bistveno izboljšati preživetja.

VIRI
Literature

Beets-Tan RG, Lettinga T, Beets GL. Pre-operative imaging of rectal cancer and its impact on surgical performance and treatment outcome. Eur J Surg Oncol 2005; 31: 681–8.

Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH. Cooperative Clinical Investigators of the Dutch Colorectal Cancer Group. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol 2002; 20: 1729–34.

Peeters KC, van de Velde CJ. Surgical quality assurance in rectal cancer treatment: the key to improved outcome. Eur J Surg Oncol 2005; 31: 630–5.

Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr 2006; 25: 224–44.

KLINIČNI KOMENTAR
Vaneja Velenik

Rak danke je bolezen, ki jo opredeljujeta velika zbolevnost in umrljivost. Incidenca je v stalnem porastu. Rezultati zdravljenja raka danke v Sloveniji se izboljšujejo, še vedno pa so slabši kot v razvitih evropskih državah. Eden glavnih razlogov za to je, da ima ob diagnozi kar 70 % bolnikov lokalno in/ali področno razširjeno bolezen (tj. stadij II ali III). Ti bolniki potrebujejo odločno multimodalno zdravljenje, saj je napoved izida bolezni pri njih slabša kot pri tistih, pri katerih je tumor omejen na sluznico ali mišično plast danke. Presejalni program za zgodnje odkrivanje raka debelega črevesa in danke (SVIT) se je pričel sredi leta 2008; z večjim deležem bolnikov z rakom danke, odkritim v začetnem stadiju, pričakujemo v naslednjem petletnem obdobju tudi večanje preživetja.

Standardno zdravljenje lokalno ali področno napredovalega raka danke je predoperativna radioterapija ali radiokemoterapija s 5-FU. V primerjavi s pooperativno radiokemoterapijo je manj toksična, zagotavlja boljši lokalni nadzor bolezni in večji delež bolnikov z ohranjenim analnim sfinktrom. Načrtovanje obsevanja je natančnejše s pomočjo CT in računalniškega sistema z algoritmom 3D. Tako je tveganje akutnih toksičnih sopojavov manjše, verjetnost, da bodo bolniki dokončali predvideno zdravljenje, pa večja. Delež predoperativno zdravljenih bolnikov se je večal od leta 2000 pa vse do leta 2006, ko so tudi iz vseh območnih bolnišnic pričeli bolnike pošiljati na predoperativno radiokemoterapijo na OI Ljubljana. Poleg tega smo v letu 2004 pričeli kot radiosenzibilizator uporabljati kapecitabin, ki po načinu delovanja in ob dvakrat dnevnem peroralnem jemanju ves čas obsevanja posnema kontinuirano infuzijo 5-FU, zdravljenje pa je za bolnika prijaznejše in varnejše.

Kljub trendu, da se kirurgija raka danke centralizira v večjih kirurških oddelkih, tega raka še vedno operirajo v skoraj vseh slovenskih bolnišnicah. Rezultati zdravljenja bi bili verjetno boljši, če bi bolnike operiralo omejeno število strokovno usposobljenih in v onkološki kirurgiji

were scored by individual surgeons the number would be even lower. Surgeons that are not additionally qualified in the area of rectal cancer surgery and themselves perform but few operations, are not able to carry out a quality surgical intervention such as the total mesorectal excision, which is a prerequisite for favorable treatment outcome. Next reason why the patients should be referred to bigger centers is in better accessibility of MR imaging, which is nowadays indispensable for correct planning of preoperative treatment and surgery. Moreover, in bigger centers due attention is paid to dietetic therapy in the preoperative as well as postoperative period, which – through its favorable impact on the patients' immune response – contributes to their better survival. Next, the importance of histological sample processing according to the Quirke's protocol should be pointed out too, the method being practiced almost exclusively at the Pathology Department of the IO Ljubljana and only exceptionally elsewhere. In the future, besides the survival statistics, the data on the number of local and distant recurrences and the ratio between continuity and discontinuity surgeries should be registered as well. These parameters are measurable and provide a basis for the quality assessment of rectal cancer treatment. In this way it could be established which institutions fail to meet the minimum standards for quality treatment, and the patients be referred to the institutions where the chances for their cure would be greater.

Better survival in the last observation period may be attributed to a greater proportion of patients receiving neoadjuvant therapy. Besides, the survival results were also favorably influenced by up-to-date postoperative systemic therapy. However, we should keep in mind that without excellent surgery even the state-of-the-art chemotherapy and radiotherapy are unable to significantly improve the survival rates.

CLINICAL COMMENTARY

Vaneja Velenik

Rectal cancer is a disease that is characterized by high incidence and mortality rates. The incidence is constantly increasing. The results of rectal cancer treatment in Slovenia have been improving, however they are still below those in the developed European countries. One of the main reasons lies in the fact that as many as 70% of patients present with locally and/or regionally advanced disease at diagnosis (i. e., stage II or III). These patients require an aggressive multimodality treatment since their prognosis is worse than in those with tumors limited to the mucosa or muscular layer of the rectum. A screening program for early colorectal cancer detection (SVIT) was launched in the middle of 2008; it is expected that a greater proportion of rectal cancer patients detected at an earlier stage of the disease will contribute to a better survival in the next five-year period.

Standard therapy for locally or regionally advanced rectal cancer consists of preoperative radiotherapy or radiochemotherapy with 5-FU. In comparison with postoperative radiotherapy, the former is less toxic and provides better local control of the disease as well as a greater number of patients with preserved anal sphincter. Using CT scan and 3D computer vision algorithms, irradiation planning has become more accurate. Thus the risk of acute toxic side effects is lower and the probability that patients may complete the anticipated therapy is accordingly higher. The proportion of preoperatively treated patients had been increasing from 2000 all until 2006, when all peripheral hospitals started to refer their patients for radiochemotherapy to the IO Ljubljana. Furthermore, in 2004 we started to use capecitabin as radiosensitizer; with twice daily oral application, this drug imitates the effects of 5-FU in continuous infusion throughout the course of irradiation while the treatment for the patient is safer and easier to tolerate.

Despite the tendency to centralize surgery for rectal cancer in bigger surgical departments, these procedures are still carried out in almost all Slovenian hospitals. The treatment results would probably be better if the patients were operated on by a limited number of adequately qualified surgeons with skills and experience in oncological surgery. The mortality of our patients is

izkušenih kirurgov. Zaradi sistemskega razsoja bolezni je umrljivost naših bolnikov še vedno velika. V iskanju možnosti za izboljšanje preživetja uvajamo v predoperativno zdravljenje nove kombinacije citostatikov in tarčnih zdravil.

VIRI
Literature

Luzar B, Cerar A, Štabuc B, eds. Tumorji debelega črevesa in danke. Ljubljani: Inštitut za patologijo, Medicinska fakulteta; 2008.

Program SVIT: www.program-svit.si.

Velenik V, Anderluh F, Oblak I, Strojan P, Zakotnik B. Capecitabine as a radiosensitizing agent in neoadjuvant treatment of locally advanced resectable rectal cancer: prospective phase II trial. Croat Med J 2006; 47: 693–700.

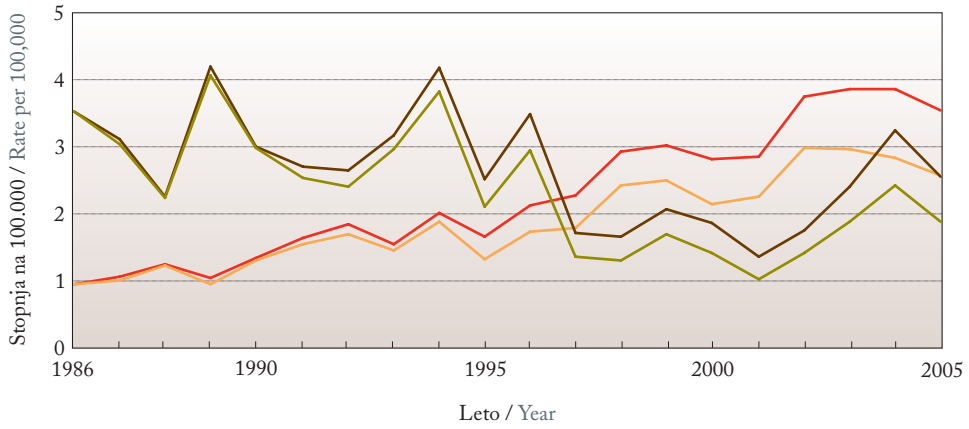
still high due to systemic dissemination of the disease. In an attempt to improve their survival, new combinations of cytostatics and target medications are being introduced into preoperative treatment schedules.

JETRA, jetnocelični rak

MKB 10: C22.0

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za jetnoceličnim rakom zbolelo 893 ljudi, 698 moških in 195 žensk. Kot je razvidno s Slike 1, se tako groba kot starostno standardizirana incidenčna stopnja od leta 1991 večata; groba stopnja za povprečno 7,1 % letno, starostno standardizirana pa za 5,3 % letno. Trend umrljivostnih stopenj je težko ovrednotiti, saj je leta 1997 očitno prišlo do spremembe v kodiranju vzrokov smrti; do takrat so med primarni jetnocelični rak uvrščali tudi jetrne metastaze, zato časovnega trenda umrljivosti ni mogoče pravilno interpretirati.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja jeternoceličnega karcinoma, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of hepatocellular carcinoma, Slovenia 1986–2005.*

V analizo preživetja je vključenih 791 primerov; 102 bolnikov (11 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

V obdobju 2001–2005 je bilo 70 % primerov raka mikroskopsko potrjenih. Delež mikroskopsko potrjenih primerov se je v primerjavi z obdobjem 1991–1995 zmanjšal za 19 %.

Tabela 1: *Število bolnikov z jeternoceličnim karcinomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of hepatocellular carcinoma patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	137	13,9	78,1	8,0	37	10,8	73,0	16,2
1996–2000	189	7,9	80,4	11,6	71	7,0	73,2	19,7
2001–2005	283	7,4	74,2	18,4	74	9,5	56,8	33,8

LIVER, hepatocellular carcinoma

ICD 10: C22.0

EPIDEMIOLOGY

In the period 1991–2005, a total of 893 persons were diagnosed with hepatocellular carcinoma, of these 698 males and 195 females. As evident from Figure 1, since 1991 the crude and age standardized incidence rates have been increasing, the crude rate by 7.1% and the age-standardized by 5.3% annually on average. The trend in mortality rates is difficult to assess since in 1997 obviously a change occurred in the cause-of-death coding system; until then liver metastases had also been included among primary liver cancer, and therefore time trends in mortality cannot be interpreted correctly.

The survival analysis included 791 cases; 102 patients (11%) diagnosed only after death were not considered in the analysis.

In the period 2001–2005, 70% of cancers were microscopically verified. In comparison with the period 1991–1995, the proportion of microscopically confirmed cancers has decreased by 19%.

Age of the majority of patients at diagnosis ranged between 50 and 74 years. In the last period, approximately three-fourths of male- and slightly over a half of female patients belonged to this age group (Table 1). An increased proportion of patients aged 75 or more can be observed in the last period.

In all three time-periods, the majority of patients were diagnosed with localized disease; in the period 2001–2005 there were 53% males and 41% females (Table 2); in almost 15% of patients stage at diagnosis was not determined.

In the years 2001–2005, 71% of patients did not receive specific treatment. In comparison with the period 1991–1995, the proportion of untreated patients has not changed significantly. Among the patients receiving specific treatment in the period 2001–2005, 49% underwent surgery; in 37% of them surgery was the only treatment while 12% also received chemotherapy; chemotherapy alone was used in 37% of patients; 9% of patients were treated by radiotherapy and 3% received chemotherapy besides irradiation treatment.

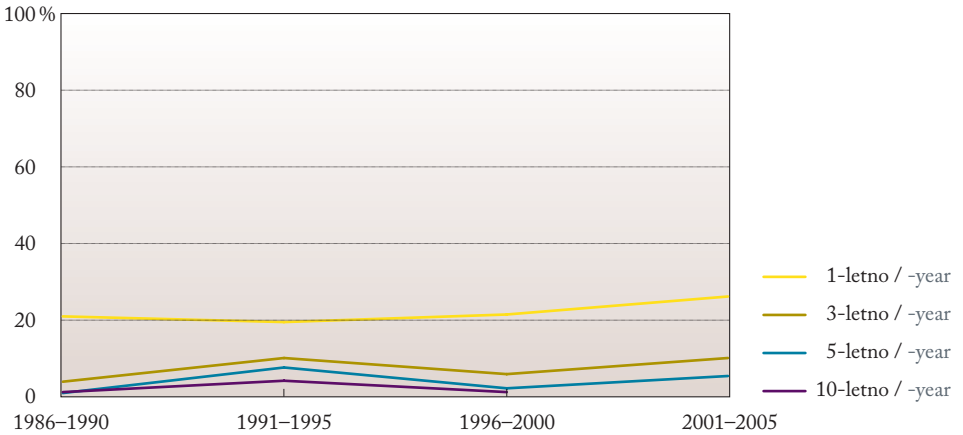
In the period 2001–2005, almost all patients started their treatment in one of the three leading Slovenian health institutions: 59% in the UMC Ljubljana, 23% in the UMC Maribor and 17% at the IO Ljubljana.

The trend in the survival of patients with liver cancer is difficult to assess as the number of patients in individual time-periods is small; in the last periods the 5-year relative survival

Tabela 2: *Število bolnikov z jeternoceličnim karcinomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of hepatocellular carcinoma patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	137	57,7	13,9	22,6	5,8	37	27,0	27,0	29,7	16,2
1996–2000	189	55,6	18,0	17,5	9,0	71	46,5	18,3	19,7	15,5
2001–2005	283	52,7	14,1	20,1	13,1	74	40,5	21,6	21,6	16,2



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z jeternoceličnim karcinomom po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of hepatocellular carcinoma patients by period of diagnosis.*

Največ zbolelih je ob diagnozi starih med 50 in 74 let. Med moškimi je v tej starostni skupini približno tri četrtine zbolelih, med ženskami pa v zadnjem obdobju nekaj več kot polovica (Tabela 1). V zadnjih letih opažamo povečanje deleža starih 75 let in več.

V vseh treh obdobjih je imelo največ bolnikov ob diagnozi omejeno bolezen; v obdobju 2001–2005 53 % moških in 41 % žensk (Tabela 2); skoraj 15 % bolnikov stadija ob diagnozi ni imelo določenega.

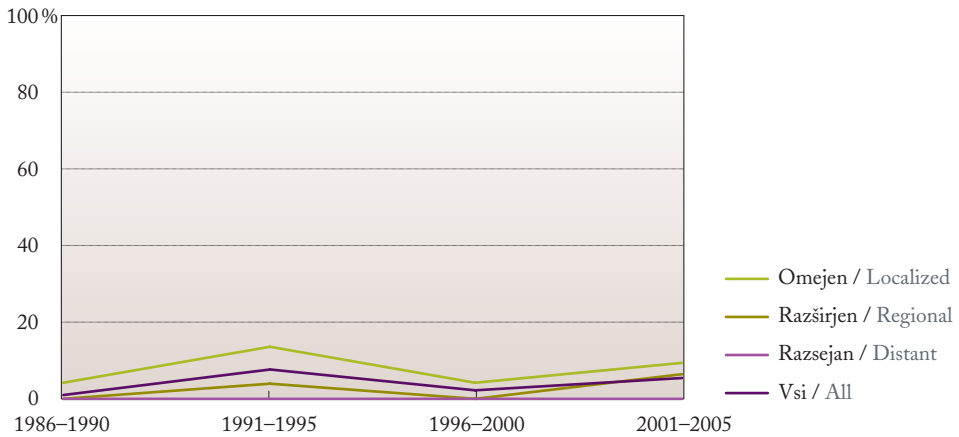
V letih 2001–2005 ni bilo specifično zdravljenih 71 % bolnikov. Delež nezdravljenih se v primerjavi z obdobjem 1991–1995 ni bistveno spremenil. Med specifično zdravljenimi je bilo v letih 2001–2005 operiranih 49 % bolnikov; pri 37 % je bil to edini način zdravljenja, 12 % je

Tabela 3: *Opazovano in relativno preživetje bolnikov z jeternoceličnim karcinomom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of hepatocellular carcinoma patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	19,0 (13,4–26,8)	8,8 (5,1–15,0)	6,6 (3,5–12,4)	18,9 (9,7–36,9)	10,8 (4,3–27,3)	5,4 (1,4–20,8)
1996–2000	20,6 (15,6–27,3)	5,3 (2,9–9,7)	1,6 (0,5–4,9)	21,1 (13,5–33,1)	5,6 (2,2–14,6)	2,8 (0,7–11,0)
2001–2005	25,8 (21,2–31,4)	8,6 (5,8–12,6)	4,8 (2,3–10,1)	23,0 (15,1–34,9)	10,8 (5,6–20,8)	3,8 (0,8–19,0)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	19,6 (11,5–27,7)	9,5 (2,7–16,4)	7,9 (0,9–14,8)	19,5 (1,0–37,9)	11,7 (0,0–29,5)	6,4 (0,0–24,6)
1996–2000	21,4 (14,5–28,3)	5,9 (1,0–10,9)	1,9 (0,0–5,9)	21,7 (9,4–34,0)	6,2 (0,0–15,9)	3,3 (0,0–12,8)
2001–2005	26,8 (21,0–32,7)	9,7 (5,1–14,2)	5,9 (0,0–12,5)	23,7 (11,4–36,0)	12,0 (0,9–23,0)	4,5 (0,0–22,6)



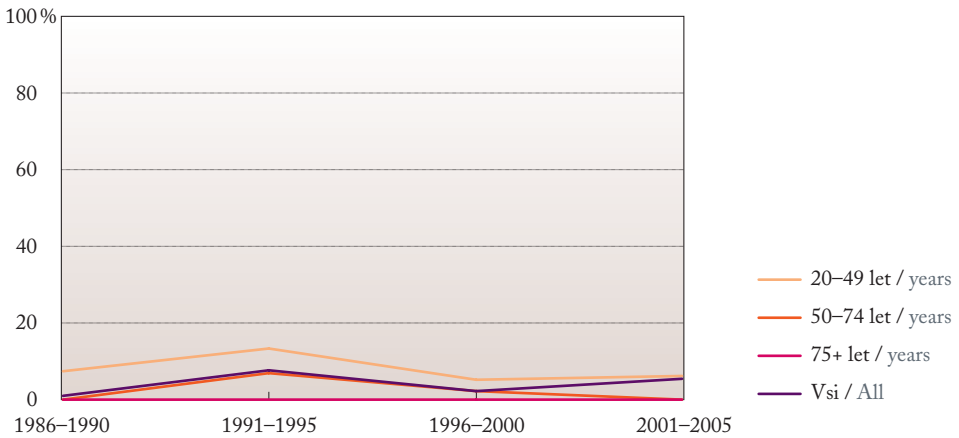
Slika 3: *Petletno relativno preživetje bolnikov z jeternoceličnim karcinomom po stadiju in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of hepatocellular carcinoma patients by stage and period of diagnosis.*

rate is slightly lower than 15 years ago (Figure 2); there were no major differences between genders (Table 3). The survival of patients with localized stage is slightly better while in the remaining stages the rates are unstable due to the small number of cases (Figure 3). The survival of patients younger than 50 years is slightly better than the survival of older patients (Figure 4).

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 5.4% (Figure 2); patients surviving the first year may expect to survive five years in 20%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of Slovenian patients with primary liver cancer is below (statistically not significant) the European average (Figure 5).



Slika 4: *Petletno relativno preživetje bolnikov z jeternoceličnim karcinomom po starosti in obdobju postavitve diagnoze.*

Figure 4: *5-year relative survival of hepatocellular carcinoma patients by age and period of diagnosis.*

prejelo še kemoterapijo; samo kemoterapijo je prejelo 37 % bolnikov. Obsevanih je bilo 9 % bolnikov, 3 % pa je poleg radioterapije prejelo še kemoterapijo.

V obdobju 2001–2005 so praktično vsi bolniki, ki so bili zdravljeni, zdravljenje pričeli v eni od treh vodilnih slovenskih zdravstvenih ustanov: 59 % v UKC Ljubljana, 23 % v UKC Maribor in 17 % na OI Ljubljana.

Trend preživetja bolnikov z jetrnoceličnim rakom je težko vrednotiti, saj je število bolnikov v posameznih obdobjih majhno; v zadnjem obdobju je vrednost petletnega relativnega preživetja nekoliko manjša kot 15 let prej (Slika 2). Med spoloma ne beležimo večjih razlik v preživetju (Tabela 2). Preživetje bolnikov z omejenim stadijem je nekoliko večje, pri ostalih stadijih pa so vrednosti nestabilne zaradi majhnega števila primerov (Slika 3). Preživetje mlajših od 50 let je nekoliko boljše od tistega pri starejših (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 5,4 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 20-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je grobo petletno relativno preživetje slovenskih bolnikov statistično neznačilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

Eldar M. Gadžijev

Čeprav se incidenčna stopnja jetrnoceličnega raka po letu 2002 ne povečuje več, predvidevamo, da še ni dosegla pričakovane incidence, ki je povezana s predvidenim velikim odstotkom okuženih z virusom hepatitisa C. Vsekakor smo še priča učinkom aktivnosti gastroenterologov za zgodnje odkrivanje jetrnoceličnega raka pri bolnikih z jetrno cirozo. Uveljavitev doktrine, da pri bolniku s cirozo, pri katerem je z ultrazvočno preiskavo vidna žariščna jetrna sprememba in imajo vrednost alfa fetoproteina (AFP) nad 400, ni potrebna citološka ali histopatološka potrditev za diagnozo raka, pa je vplivala na izrazito manjši odstotek histološko potrjene bolezni v obdobju od 2001–2005 v primerjavi s prejšnjimi obdobji.

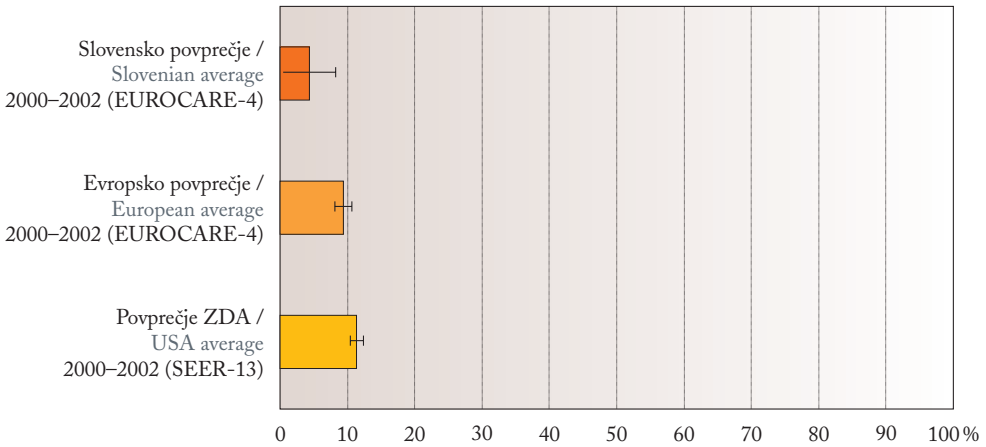
Določanje zamejitve jetrne bolezni in stadija tumorja po Child-Pughu oziroma Okudi se je dokončno uveljavilo tudi pri nas; med kirurgi pa se je uveljavila nova, japonska zamejitev TNM.

Pomemben prispevek k obravnavi bolnikov z jetrno cirozo in jetrnoceličnim rakom je v Sloveniji dala skupina, ki se ukvarja s presaditvami jeter, ki ob upoštevanju Milanskih meril za določitev bolnikov, primernih za presaditev (tumor pod 5 cm v premeru ali največ trije tumorji, manjši od 3 cm v premeru brez invazije v žile), uvršča bolnike z jetrnoceličnim rakom na program za zaenkrat najučinkovitejši način zdravljenja bolezni.

Zaradi organizacije oskrbe bolnikov z jetrnoceličnim rakom se v zadnjem obdobju kaže značilen premik prvega specifičnega zdravljenja v oba klinična centra, pri čemer pa ostaja še vedno preveč bolnikov brez zdravljenja (71 %).

V celotnem opazovanem obdobju je način zdravljenja pretežno kirurški; po letu 1996 se je zmanjšal odstotek kombiniranega zdravljenja s predoperativno kemoembolizacijo. Še vedno pa je nekaj bolnikov letno, ki pridejo do operacije jetrnoceličnega raka po zmanjševanju tumorja s transhepatično arterijsko kemoembolizacijo (TACE), pri kateri se v zadnjem obdobju uporabljata mikrosfere in doksorubicin namesto prejšnjega lipiodola in mitomicina. Porast drugih načinov zdravljenja v zadnjem opazovanem obdobju 2001–2005 gre na račun uveljavitve radiofrekvenčne ablacije kot intersticijske metode za uničevanje tumorskega tkiva, ki ga izvajamo lahko tudi perkutano pod nadzorom ultrazvoka in ima svoje posebne indikacije (recidiv bolezni, neoperabilnost tumorja).

Preživetje bolnikov z jetrnoceličnim rakom je še vedno majhno (triletno komaj dosega 10 % in petletno 5 % pri obeh spolih skupaj), kar gre zagotovo v veliki meri na račun velikega odstotka



Slika 5: *Petletno relativno preživetje bolnikov z jeternoceličnim karcinomom (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of hepatocellular carcinoma patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

CLINICAL COMMENTARY

Eldar M. Gadžijev

Although since 2002 the incidence rate of hepatocellular carcinoma has stopped increasing, we presume that it still has not reached the expected value associated with the anticipated high percentage of hepatitis-C infected persons. Presently, we may still observe the effects of the activity of gastroenterologists for early detection of hepatocellular cancer in patients with liver cirrhosis. Implementation of the doctrine, according to which no cytological or histopathological confirmation of cancer diagnosis is required in patients with cirrhosis, an US-imaged focal hepatic lesion and AFT (alpha-fetoprotein) values above 400, resulted in a considerably lower percentage of histologically confirmed disease in the period 2001–2005 as compared with the former periods.

Staging of liver disease and tumor stage according to Child-Pugh score or Okuda staging system has finally been adopted also in Slovenia. Surgeons, on the other hand, started using the new Japanese TNM staging system.

A relevant contribution towards the management of patients with liver cirrhosis and hepatocellular cancer in Slovenia was made by a group involved in liver transplantations: in accordance with the Milan criteria for determining suitable transplantation candidates (single tumor ≤ 5 cm in diameter or ≤ 3 tumors each ≤ 3 cm in diameter without vascular invasion) patients with hepatocellular carcinoma have been considered suitable for this, currently most effective method of treatment.

In order to provide organized care for patients with hepatocellular carcinoma, in the last period there has been a significant shift towards having the primary specific treatment performed in both university medical centers, but nevertheless, still too many patients are left without treatment (71%).

Throughout the observation period the prevailing treatment approach was surgery with a significant downward trend in the percentage of combined treatments with preoperative chemoembolization and subsequent surgery being noted after the year 1996. Still, there are a few patients yearly operated on for hepatocellular carcinoma after debulking treatment with transhepatic chemoembolization (TACE); in recent period, the latter method has been performed

nezdravljenih bolnikov. Zaskrbljujoče je, da se ta odstotek v opazovanih treh petletnih obdobjih ni zmanjšal in ostaja 71 %! Kljub uspešni akciji gastroenterologov pri odkrivanju zgodnejših primerov raka ob kontrolah bolnikov z jetrno cirozo pa je prosvetljenost prebivalstva še vedno preslaba in ob povečani incidenci verjetno tudi aktivnosti na primarni ravni niso ustrezne. Temu v prid govori tudi podatek o porazdelitvi po stadiju bolezni ob diagnozi, kjer je odstotek razširjene in razsejane bolezni še vedno enak ali večji od omejenega stadija predvsem pri ženskah, pri čemer se v opazovanih treh petletnih obdobjih razmerje ni bistveno spreminjalo. Še vedno visok odstotek neznanega stadija ob diagnozi pa kaže lahko tudi na premajhno natančnost ali vestnost pri obravnavi teh bolnikov.

Zaradi narave bolezni, ki ima osnovo v motenem delovanju jeter, je tudi petletno relativno preživetje bolnikov z omejeno boleznijo še majhno (9 %). Uspešnost kirurškega zdravljenja, ki prinaša lahko tudi 50-odstotno petletno preživetje, se zaradi premajhnega števila ustrezno zdravljenih bolnikov še ne kaže dovolj.

Izrazito slabše preživetje bolnikov, starih nad 50 let, ki so sicer v večini, morda lahko razložimo s trajanjem ciroze in bistveno bolj napredovalo jetrno boleznijo v tej starostni skupini. To se odraža na eni strani v večji incidenci v tem starostnem obdobju, na drugi strani pa v izrazito slabši napovedi izida, ker nanjo vpliva jetrna bolezen in ne tumor. Upoštevanja vredno pa je tudi dejstvo, da se jetrnocelični rak v necirotičnih jetrih (kljub temu, da je nekaj jetrne okvare praktično pri vsakem raku), ki je sicer redkejši, pojavlja pri mlajših bolnikih, pri katerih je potem tudi predvsem kirurško zdravljenje učinkovitejše.

Poleg uspešnega odkrivanja lahko pričakujemo v prihodnje tudi boljše rezultate ob uveljavljanju presaditve jeter pri zdravljenju jetrnoceličnega raka, pa tudi napredku laparoskopske kirurgije, pri kateri je poseg manj invaziven in imunsko manj kompromitirajoč. Poleg tega se bodo še nadalje uveljavljale ablacijske metode, predvsem tudi kot pomoč pri zadrževanju tumorske bolezni pri premostitvi do presaditve jeter.

Zdravljenje jetrnoceličnega raka ostaja izrazito multidisciplinarno in multimodalno, zato naj še naprej poteka le v terciarnih kliničnih ustanovah.

VIRI
Literature

Cottone M, Turri M, Caltagirone M, Parisi P, Orlando A, Fiorentino G, et al. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8-year prospective study by ultrasound and alphafetoprotein. J Hepatol 1994; 21: 1029–34.

Kudo M, Chung H, Osaki Y. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. J Gastroenterol 2003; 38: 207–15.

Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis.
N Engl J Med 1996; 334: 693–9.

Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg 2007; 245: 909–22.

using microspheres and doxorubicin instead of the previous lipiodol and mitomycin. The increase in other treatment approaches in the last observation period from 2001–2005 is attributable to the implementation of radiofrequency ablation as an interstitial method for destroying tumor tissue, which can be performed percutaneously under US guidance for special indications (recurrence, inoperable tumors).

The survival of patients with hepatocellular carcinoma is still low (3-year survival hardly reaches 10% while 5-year survival for both genders together amounts to 5%), which is certainly attributable mainly to the high proportion of untreated patients. It raises concern that throughout the three 5-year observation periods this percentage has not decreased and still persists at 71%! Despite the successful action by gastroenterologists to detect cancer at an early stage on follow-up examinations of patients with liver cirrhosis, the awareness of general population is still too low and the activities at the level of primary care also are inadequate. This observation is consistent with the data on the distribution of the disease by stage at diagnosis, where the proportion of regional and disseminated disease is still the same or even greater than the proportion of localized stage, particularly in females, the ratio remaining basically unchanged throughout the three 5-year observation periods. The high proportion of undefined stage at diagnosis may be indicative of an insufficient accuracy or conscientiousness in the treatment of these patients.

Owing to the nature of the disease, which originates from a liver disorder, the 5-year relative survival of patients with localized disease is also too low (9%). The effectiveness of surgical treatment, which may result in as high as 50% 5-year survival, still does not yield its full potential because the number of adequately treated patients is too scarce.

Markedly worse survival of patients above 50 years of age, which are in majority, could be explained by the duration of cirrhosis and significantly more advanced liver disease in this age group. On the one hand, this is reflected in a higher incidence in this age group and in a considerably worse prognosis on the other, since the prognosis is influenced by liver disease rather than by tumor. However, it is noteworthy to remember that hepatocellular cancer in a non-cirrhotic liver (although some liver damage is present in practically any cancer), albeit scarce, may occur in younger patients, in whom particularly surgical treatment turns out more effective.

Apart from efficient detection, better results in the future may be expected with wider use of liver transplantation in the treatment of hepatocellular carcinoma, as well as with advances in laparoscopic surgery, a procedure that is less invasive and has less immune system compromising effects. The use of ablation procedures will be continued too, particularly as an aid to control the tumor growth until liver transplantation.

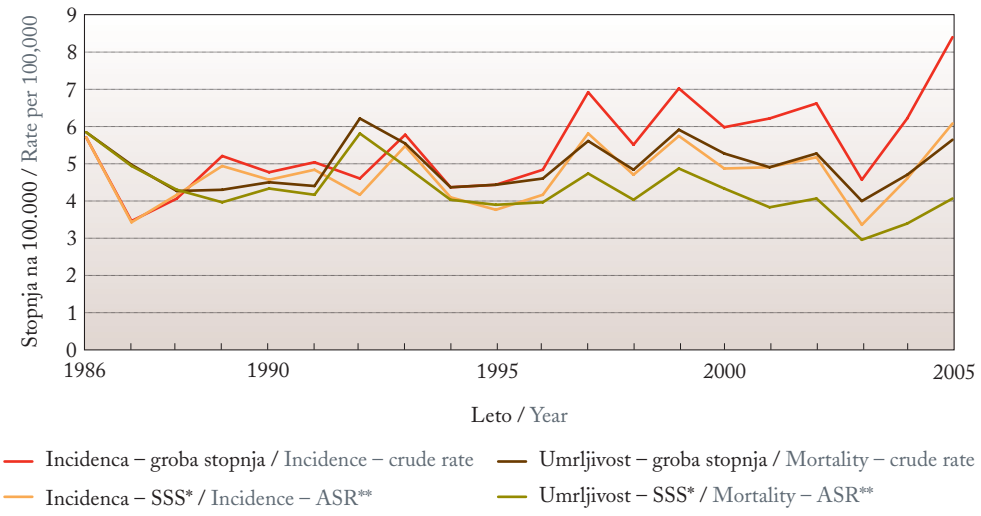
The treatment of hepatocellular carcinoma, which is distinctly multidisciplinary and multimodal, should remain the domain of the tertiary clinical institutions.

ŽOLČNIK IN ŽOLČNI VODI

MKB 10: C23, C24

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom žolčnika in žolčnih vodov zbolelo 1860 ljudi, od tega 683 moških in 1177 žensk. Kot je razvidno s Slike 1, se tako groba kot starostno standardizirana incidenčna stopnja od leta 1991 povečujeta; groba stopnja za 2,6 % povprečno letno, starostno standardizirana pa za 0,6 %. Umrljivostni stopnji se počasi zmanjšujeta, groba za 0,1 % povprečno letno, starostno standardizirana pa za 2,1 %.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja rakov žolčnika in žolčevodov, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of gallbladder and bill duct cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1722 primerov; 138 bolnikov (8 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

V prvem obdobju so več bolnikom odkrili tumor žolčnika (60 %), med tem ko se je v zadnjem obdobju razmerje med tumorji žolčnika in žolčnih vodov obrnilo v prid slednjih – med leti 2001–2005 je imelo 55 % bolnikov tumor žolčnih vodov.

Tabela 1: *Število bolnikov z raki žolčnika in žolčevodov po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of gallbladder and bill duct cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	165	6,7	61,2	32,1	318	5,0	58,5	36,5
1996–2000	221	5,9	68,3	25,8	379	3,2	53,0	43,8
2001–2005	251	6,8	63,3	29,9	388	2,3	44,1	53,6

GALLBLADDER AND BILE DUCTS

ICD 10: C23, C24

EPIDEMIOLOGY

In the period 1991–2005, a total of 1860 persons were diagnosed with cancer of the gallbladder and bile ducts, of these 683 males and 1177 females. As evident from Figure 1, since 1991 the crude and age standardized incidence rates have been increasing, the crude rate by 2.6% and the age-standardized by 0.6% annually on average. The mortality rates have been gradually decreasing, the crude rate by 0.1% and the age standardized by 2.1% annually on average.

The survival analysis included 1722 cases; 138 patients (8%) diagnosed only after death were not considered in the analysis. In the first period more patients were diagnosed with gallbladder cancer (60%), while in the last period this ratio changed in favor of bile ducts cancer; in the years 2001–2005 55% patients were diagnosed with the latter.

In the period 2001–2005, 62% of cancers were microscopically verified. In comparison with the period 1991–1995, the proportion of microscopically confirmed cancers has decreased by 12%. Among the microscopically confirmed cancers 77% were adenocarcinomas, 9% cystic, mucinous and serous carcinomas and 14% other carcinomas.

Age of the majority of patients at diagnosis ranged between 50 and 74 years. In the last period, approximately 60% of male and slightly less than a half of female patients belonged to this age group (Table 1). In the last period the proportion of females aged 75 years or older has increased to over 50%.

In all three time-periods, at the time of diagnosis, the majority of males were diagnosed with regional and females with disseminated disease; in the period 2001–2005 there were 42% males and 36% females (Table 2); in over 13% of patients stage at diagnosis was not determined.

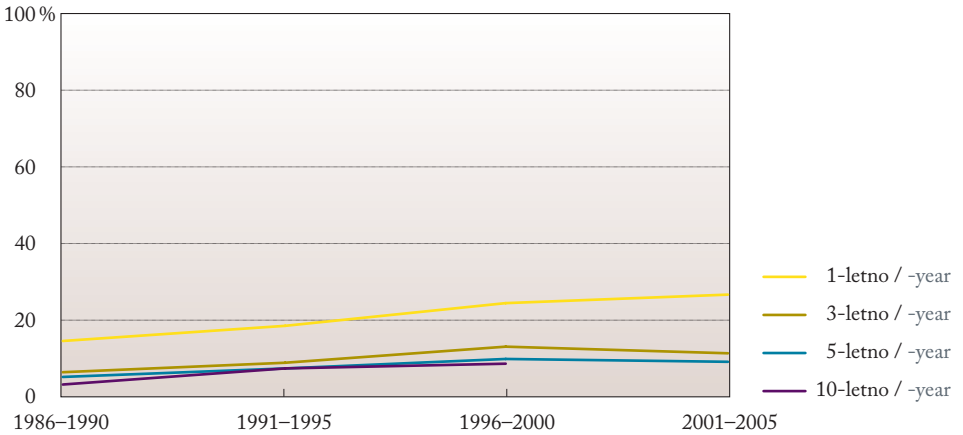
In the years 2001–2005, 62% of patients did not receive specific treatment. In comparison with the period 1991–1995, the proportion of untreated patients has decreased by 7%. Among the patients receiving specific treatment in the period 2001–2005, 85% were treated by surgery alone, 9% received additional chemotherapy, and 2% additional radiotherapy; 1% received radiotherapy and chemotherapy in addition to surgery while 2% were treated by radiotherapy alone.

In the period 2001–2005, 48% of the treated patients started their treatment in the UMC Ljubljana, 28% in the UMC Maribor, and the remaining 24% in practically all Slovenian general hospitals; except in the GH Slovenj Gradec and GH Nova Gorica, everywhere else they treated less than 10 patients.

Tabela 2: *Število bolnikov z raki žolčnika in žolčevodov po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of gallbladder and bill duct cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	165	21,8	33,9	30,9	13,3	318	16,0	33,6	38,4	11,9
1996–2000	221	20,8	38,0	25,8	15,4	379	14,0	34,8	34,8	16,4
2001–2005	251	12,7	42,2	31,5	13,5	388	15,5	35,3	36,1	13,1



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z raki žolčnika in žolčevodov po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of gallbladder and bill duct cancer patients by period of diagnosis.*

V obdobju 2001–2005 je bilo 62 % primerov raka mikroskopsko potrjenih. Delež mikroskopsko potrjenih se je v primerjavi z obdobjem 1991–1995 zmanjšal za 12 %. Med mikroskopsko potrjenimi je bilo 77 % adenokarcinomov, 9 % cističnih, mucinoznih in seroznih neoplazem, 14 % pa drugih karcinomov.

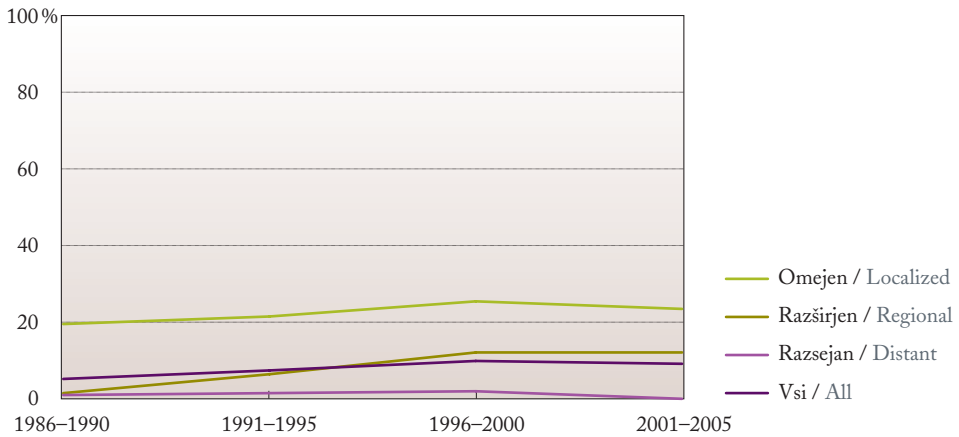
Največji delež zbolelih je ob diagnozi starih 50–74 let. Med moškimi je v tej starostni skupini približno 60 % zbolelih, med ženskami pa v zadnjem obdobju nekaj manj kot polovica (Tabela 1). Med ženskami se je v zadnjem obdobju delež starih 75 let in več povečal na več kot 50 %.

Tabela 3: *Opazovano in relativno preživetje bolnikov z raki žolčnika in žolčevodov po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of gallbladder and bill duct cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	23,0 (17,4–30,4)	10,9 (7,1–16,9)	6,7 (3,8–11,8)	14,8 (11,4–19,2)	6,0 (3,9–9,2)	5,0 (3,1–8,1)
1996–2000	32,1 (26,5–38,9)	17,2 (12,9–23,0)	10,9 (7,4–15,8)	18,2 (14,7–22,5)	7,7 (5,4–10,9)	5,8 (3,9–8,7)
2001–2005	31,9 (26,6–38,2)	11,2 (7,9–16,0)	8,8 (5,7–13,5)	20,9 (17,2–25,3)	8,4 (6,0–11,8)	5,2 (3,1–8,8)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	24,5 (16,6–32,4)	13,2 (6,0–20,4)	8,9 (2,1–15,8)	15,4 (10,8–20,1)	6,9 (3,1–10,6)	6,3 (2,4–10,1)
1996–2000	33,8 (26,7–41,0)	20,1 (13,3–26,8)	14,3 (7,7–20,8)	19,1 (14,6–23,7)	8,8 (5,1–12,5)	7,5 (3,7–11,2)
2001–2005	33,8 (27,1–40,5)	13,4 (7,7–19,1)	11,9 (5,5–18,4)	22,1 (17,3–26,8)	9,9 (6,0–13,9)	7,0 (2,2–11,8)



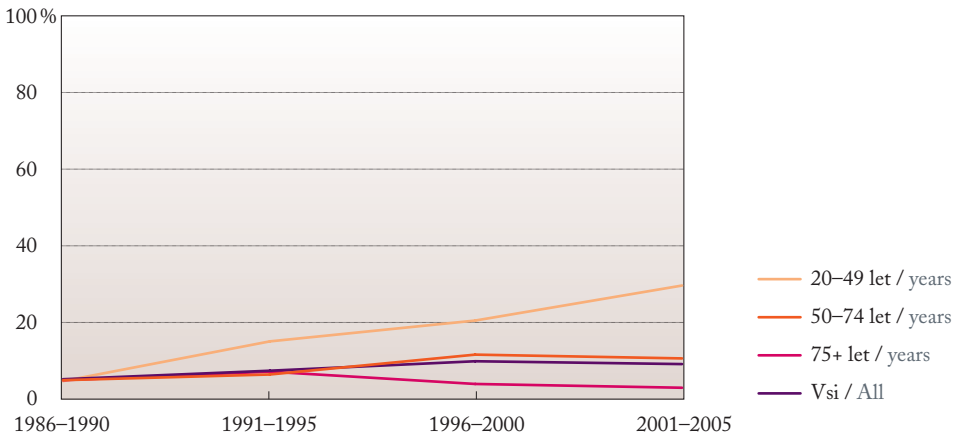
Slika 3: *Petletno relativno preživetje bolnikov z raki žolčnika in žolčevodov po stadiju in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of gallbladder and bill duct cancer patients by stage and period of diagnosis.*

5-year relative survival has been gradually increasing although even in the last period it was under 10% (Figure 2), being slightly higher in males (11%) than in females (7%) (Table 3). The survival in patients with localized stage is slightly higher than in patients with more advanced disease (Figure 3). The survival of patients younger than 50 years is slightly higher than the survival of older patients (Figure 4), however the number of these patients is the lowest.

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 9% (Figure 2); patients surviving the first year may expect to survive five years in 31%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, survival of Slovenian patients with gallbladder and bile ducts cancer is below (statistically not significant) the European average (Figure 5).



Slika 4: *Petletno relativno preživetje bolnikov z raki žolčnika in žolčevodov po starosti in obdobju postavitve diagnoze.*

Figure 4: *5-year relative survival of gallbladder and bill duct cancer patients by age and period of diagnosis.*

V vseh treh obdobjih je imelo največ moških ob diagnozi razširjeno bolezen, največ žensk pa razsejano; v obdobju 2001–2005 je bilo takih 42 % moških in 36 % žensk (Tabela 2); pri nekaj več kot 13 % bolnikov stadija ob diagnozi niso določili.

V letih 2001–2005 ni bilo specifično zdravljenih 62 % bolnikov. Delež nezdravljenih se je v primerjavi z obdobjem 1991–1995 zmanjšal za 7 %. Med specifično zdravljenimi je bilo v letih 2001–2005 85 % bolnikov samo operiranih, 9 % je prejelo še kemoterapijo, 2 % pa je bilo še obsevanih, 1 % je poleg operacije in radioterapije prejel še kemoterapijo; samo obsevana sta bila 2 % bolnikov.

V obdobju 2001–2005 je 48 % bolnikov, ki so bili zdravljeni, zdravljenje pričelo v UKC Ljubljana, 28 % v UKC Maribor, preostalih 24 % pa praktično v vseh slovenskih bolnišnicah; razen v SB Slovenj Gradec in SB Nova Gorica so povsod zdravili manj kot 10 bolnikov.

Petletno relativno preživetje se sicer postopno povečuje, je pa tudi v zadnjem obdobju manjše od 10 % (Slika 2); v zadnjem obdobju je malo večje pri moških (11 %) kot pri ženskah (7 %) (Tabela 3). Preživetje bolnikov z omejenim stadijem je nekoliko večje kot pri bolnikih z bolj napredovalo boleznijo (Slika 3). Preživetje mlajših od 50 let je nekoliko večje od tistega pri starejših (Slika 4), je pa teh bolnikov najmanj.

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 9 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 31-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom žolčnika in žolčnih vodov statistično neznačilno manjše od evropskega povprečja (Slika 5).

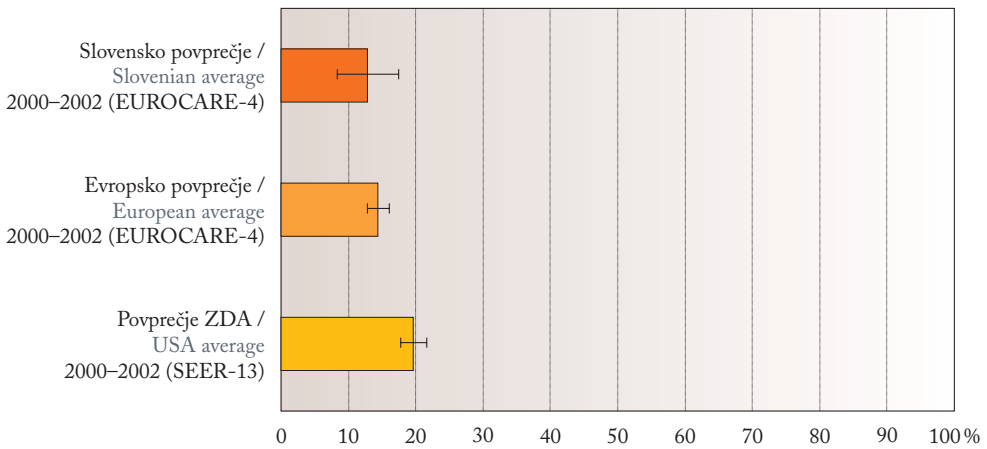
KLINIČNI KOMENTAR

Eldar M. Gadžijev

Ker sta rak žolčnika in rak žolčnih vodov dve različni entiteti, je komentiranje obeh patologij skupaj manj primerno in težko opredeljuje značilnosti posameznih bolezni. Simptomatika, odkrivanje in zdravljenje se namreč pri raku žolčnika razlikujejo od tistih pri raku žolčnih vodov. Poleg tega je kirurško zdravljenje raka žolčnih vodov odvisno od anatomskega mesta in je drugačno pri (glede na jetra) bližje ležečih tumorjih (Klatskinov tumor) kot pri bolj oddaljenih tumorjih. Ob tem je tudi oboperativna smrtnost, ki je pri nas presegala 5 %, pri nekaterih operacijah nezanemarljiva, pri operacijah zaradi raka žolčnika pa je manjša. Tam je operacija v osnovi manj zahtevna, predvsem pri nižjih stadijih bolezni. Pri raku žolčnika se uporablja klasifikacija TNM, pri raku žolčnih vodov pa poleg TNM kar nekaj kirurških klasifikacij (npr. Bismuth, Strassberg, nizozemska).

Pričujoča analiza kaže, da je v Sloveniji incidenca raka žolčnika in žolčnih vodov bolj ali manj enakomerna v opazovanih obdobjih z majhnimi nihanji, a vendar z izrazitejšim porastom v letu 2005. V svetu se incidenca raka žolčnika in žolčnih vodov še veča. Nastanek raka žolčnika je po eni strani povezan z dedno nagnjenostjo; pogostejši je pri ženskah, pri nenormalnem metabolizmu žolča z žolčnimi kamni in vnetjem, pri čemer pride do inaktivacije tumor supresorskega gena p53 in do nastanka raka. Po drugi strani (pretežno v Aziji) je rak žolčnika pogostejši pri prirojeni anomaliji, spojenem žolčnem in pankreatičnem vodu, kar omogoča refluks pankreatičnega soka v žolčnik in razvoj hiperplazije in raka ob mutaciji onkogena K-RAS. Nevarnostni dejavnik raka žolčnih vodov so še vnetne črevesne bolezni, anomalije žolčnih vodov in okužbe, predvsem s paraziti.

Odstotek mikroskopsko potrjenih primerov je sprejemljiv in se pričakovano manjša (v zadnjem petletnem obdobju na 62 %). Ob značilni klinični sliki oziroma izvidu morfoloških preiskav (ERC, MRI, EUZ) in značilno povečanem tumorskem označevalcu Ca 19-9 je diagnoza pri raku žolčnih vodov že brez mikroskopske potrditve jasna. Poleg tega pa je pridobitev materiala za



Slika 5: *Petletno relativno preživetje bolnikov z raki žolčnika in žolčevodov (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of gallbladder and bill duct cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

CLINICAL COMMENTARY

Eldar M. Gadžijev

Cancer of the gallbladder and cancer of the bile ducts being two different entities, commenting on both pathologies together is rather inconvenient, as it is difficult to point out their individual characteristics. Symptoms, diagnosis and treatment of gallbladder cancer differ from those of bile duct cancer. Furthermore, surgical treatment for bile duct cancers depends on their location and is different for tumors situated proximally to the liver (Klatskin's tumor) and for those situated distally. The perioperative lethality too – which in our case exceeded 5% – associated with certain surgical interventions is not negligible, while in surgeries for gallbladder cancer it is lower. The latter procedures are basically less demanding, particularly in patients with earlier stages of the disease. While the TNM classification is used for gallbladder cancer, in the case of bile duct cancer a number of other surgical classifications are used besides the TNM (Bismuth, Strassberg, Dutch).

A characteristic feature of the present analysis is more or less stable incidence of gallbladder and bile duct cancers throughout the observation periods, with minor shifts and a more prominent increase in the year 2005. Further increase in the incidence of gallbladder and bile duct cancer is observed worldwide. On the one hand, the development of gallbladder cancer is associated with hereditary predisposition: female gender, abnormal bile metabolism with gall stones and inflammation resulting in p53 tumor suppressor gene inactivation and the onset of cancer. On the other hand, (prevailingly in Asia) the onset of gallbladder cancer is associated with a congenital anomalous junction of the bile- and pancreatic ducts, which causes reflux of pancreatic juice into the gallbladder and the development of hyperplasia and cancer with K-RAS oncogene mutation. Risk factors for bile duct cancer are inflammatory intestinal diseases, bile duct anomalies and infections, particularly infestations with parasites.

The proportion of microscopically confirmed cases is within the expected limits and has been decreasing (in the last 5-year period to 62%). With typical clinical picture or morphological findings (ERC, MRI, EUS) and significantly elevated Ca 19-9 tumor marker the diagnosis of bile duct cancer is indisputable without microscopic confirmation. Moreover, in gallbladder cancer the bioptic sample taking is risky because it may cause leakage of bile into the abdomen and thus dissemination of the disease. However, in endoscopic examinations for suspected cancer

mikroskopsko preiskavo pri raku žolčnika tvegana, ker lahko povzroči zatekanje žolča v trebuh in razsoj bolezni. Iskanje malignih celic v žolču, predvsem pa krtačni odvzem celic iz endotela žolčevoda za citološko preiskavo, pa sta pri endoskopskih posegih ob sumu na raka žolčnega sistema vendarle smiselna.

Rak žolčnika danes pogosteje odkrijemo v začetnem stadiju, ko ga najdemo slučajno po operaciji zaradi žolčnih kamnov in ima zato boljšo napoved izida in preživetje. Napredovali rak žolčnika pa ima tudi, če je še kirurško odstranljiv, slabo napoved izida. Po drugi strani pa je zelo redko in težko odkriti raka žolčnih vodov v zgodnjem stadiju. Njegova rast v obliki tumorskih sprememb na preskok (t. i. skip lezij) in širjenje v steni žolčnih vodov s pogosto perivaskularno in perinevralno invazijo opredeljujejo invazivno rast in slabo napoved izida, čeprav redko metastazira in je tumor sam po sebi majhen. Temu ustrezni so rezultati analize, ki kažejo majhen odstotek omejene bolezni in velik odstotek razširjene in celo razsejane bolezni.

Zdravljenje je kirurško, kadar je le možno; kombinacija s kemoterapijo se uveljavlja v zadnjih letih tudi pri nas. Pri raku žolčnih vodov pride včasih v poštev le endoskopsko ali radiološko intervencijsko dreniranje oziroma postavitev opornice v žolčni vod.

Preživetje je majhno in se v opazovanih treh petletnih obdobjih ni povečalo, kar lahko kaže na slabše rezultate zdravljenja pri nas, ker je tudi v svetu, tako kot pri nas, le pri 10–20 % bolnikov bolezen omejena. V razvitih državah je petletno preživetje bolnikov z rakom žolčnika nekoliko večje: okrog 40 % pri tistih z omejenim stadijem, 15 % pri razširjeni bolezni in 10 % pri razsejani. Preživetje pri raku žolčnih vodov je odvisno ne le od stadija bolezni ampak tudi od mesta tumorja (proksimalen, distalen). Pri raku žolčnih vodov petletno preživetje opisujejo po stadijih TNM in se giblje med 8 % pri bolnikih s stadijem III in IV, prek 22 % pri bolnikih s stadijem II, 29 % pri bolnikih s stadijem I in 58 % pri bolnikih s stadijem 0. V prihodnje bi bilo treba za boljšo primerjavo s podatki iz literature ločiti obe bolezni; je pa res, da bi bilo verjetno potem primerov malo, zato pa tudi ocene manj zanesljive.

VIRI
Literature

Bartlett DL, Fong Y, Fortner JG, Brennan MF, Blumgart LH. Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg 1996; 224: 639–46.

Bartolasi L, Burgart LJ, Tsiotos GG, Luque-de Leon E, Sarr MG. Adenocarcinoma of the distal bile duct. A clinicopatologic outcome analysis after curative resection. Dig Surg 2000; 17: 36–41.

Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. Cancer 1992; 70: 1493–7.

Kloek JJ, Ten Kate FJ, Busch OR, Gouma DJ, VanGulik TM. Surgery for extrahepatic cholangiocarcinoma: predictors of survival. HPB 2008; 10: 190–5.

Nishio H, Nagino M, Oda K, Ebata T, Arai T, Nimura Y. TNM Classification for perihilar cholangiocarcinoma: comparison between 5th and 6th edition of the AJCC/UICC staging system. Langgenbecks Arch Surg 2005; 390: 319–27.

of the billiard system looking for the presence of malignant cells in bile, and particularly brush biopsy of the bile duct, seem reasonable.

Presently, gallbladder cancer is more frequently detected at an initial stage, as an incidental finding on surgery for gallstones, and is therefore associated with a better prognosis and survival. However, an advanced gallbladder cancer, even if operable, has a poor prognosis. On the other hand, bile duct cancer is very difficult to detect at an early stage. Its growth in the form of skip lesions (non-contiguous lesions) and spread into bile duct walls with frequent perivascular and perineural invasion are associated with invasive growth and a poor prognosis, regardless the fact that this cancer rarely metastasizes and that the tumor in itself is small. Accordingly, analysis results show a small percentage of localized disease and a proportionally greater percentage of regional and even disseminated disease.

The treatment of choice is surgery whenever feasible; in recent years a combination with chemotherapy has become more frequently used also in Slovenia. In bile duct cancer sometimes an endoscopic or radiological intervention drainage or bile duct stent placement is considered as the only option.

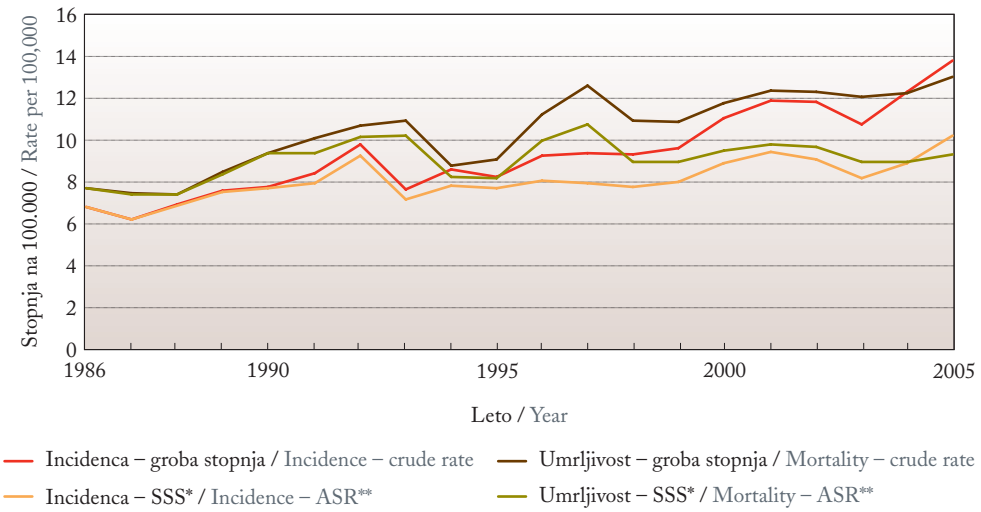
The survival is low and has not increased in the three 5-year observation periods, which may be indicative of our worse treatment outcomes, since in Slovenia, as elsewhere in the world, only 10–20% of patients will present with localized disease. In the developed countries, 5-year survival of patients with gallbladder cancer is slightly higher: approximately 40% in those with localized stage, 15% in regional stage and 10% in disseminated disease. The survival in bile duct cancer depends not only on stage of the disease but also on tumor site (proximal or distal). In bile duct cancer 5-year survival is described according to the TNM classification, ranging from 8% in patients with stages III and IV, through 22% in patients with stage II, 29% in those with stage I, to 58% in patients with stage 0. In order to facilitate comparison with the data from literature, in the future it would be necessary to analyze each of the two diseases separately, however, this may render the analysis results less reliable due to an insufficient number of cases.

TREBUŠNA SLINAVKA

MKB 10: C25

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom trebušne slinavke zbolelo 3323 ljudi, od tega 1582 moških in 1741 žensk. Kot je razvidno s Slike 1, je razmerje med grobima in starostno standardiziranima incidenčnima in umrljivostnima stopnjama manjše od 1 do leta 2003, kar razlagamo z manj natančnim opredeljevanjem vzrokov smrti in slabo napovedjo izida bolezni. Groba incidenčna stopnja se veča za povprečno 3,4 % letno, groba umrljivostna stopnja pa za povprečno 1,9 % letno; nekaj manj se veča starostno standardizirana incidenčna stopnja, medtem ko se umrljivostna stopnja manjša za povprečno 0,2 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka trebušne slinavke, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of pancreatic cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 3022 primerov; 301 bolnika (9,1 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti. Med vsemi bolniki jih 42 % ni imelo natančneje opredeljenega mesta nastanka malignoma, v zadnjem obdobju 38 %. Pri treh četrtinah z opredeljenim mestom je tumor nastal v glavi trebušne slinavke.

V obdobju 2001–2005 je bilo 54 % primerov raka mikroskopsko potrjenih. Delež mikroskopsko potrjenih se je v primerjavi z obdobjem 1991–1995 zmanjšal za 3 %. V vseh treh obdobjih je imelo največ bolnikov eno od vrst adenokarcinoma (81 %).

Tabela 1: *Število bolnikov z rakom trebušne slinavke po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of pancreatic cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	429	9,8	68,1	22,1	421	4,3	55,1	40,6
1996–2000	445	10,6	68,5	20,9	517	4,4	56,7	38,9
2001–2005	571	10,9	66,2	22,9	639	6,9	51,6	41,5

PANCREAS

ICD 10: C25

EPIDEMIOLOGY

In the period 1991–2005, a total of 3323 persons were diagnosed with cancer of the pancreas, of these 1582 males and 1741 females. As evident from Figure 1, until 2003 the ratio between crude and age standardized incidence and mortality rates had been less than 1, which can be explained by less accurate determination of the causes of death and poor prognosis of the disease, which has been improving very slowly. Thus crude incidence rate has been increasing by 3.4% and crude mortality rate by 1.9% annually on average; a lesser increase has been observed in the age-standardized incidence rate, while age standardized mortality rate is decreasing by 0.2% annually on average.

The survival analysis included 3022 cases; 301 patients (9.1%) diagnosed only after death were not considered in the analysis. Among all the patients, 42% did not have the site of malignoma more precisely defined, in the last period the proportion of such patients being 38%. In three fourths of patients with a defined site, the tumor originated in the pancreatic head.

In the period 2001–2005, 54% of cancers were microscopically verified. In comparison with the period 1991–1995 the proportion of microscopically confirmed cases has decreased by 3%. In all three time-periods, the majority of patients had one of types of adenocarcinoma (81%).

Age of the majority of patients at diagnosis ranged between 50–74 years. Approximately two thirds of male patients and slightly more than a half of female patients belonged to this age group. More than a third of females were diagnosed at the age of 75 years or older; slightly more males than females were diagnosed before 50 years of age (Table 1). The proportions in individual age groups did not change significantly with time.

In all three time-periods, the majority of patients were diagnosed with disseminated disease; in the period 2001–2005 there were 50% of males and 47% of females among such patients (Table 2). The proportion of localized stage has been decreasing in both genders, prevailingly on the account of regional and disseminated stages.

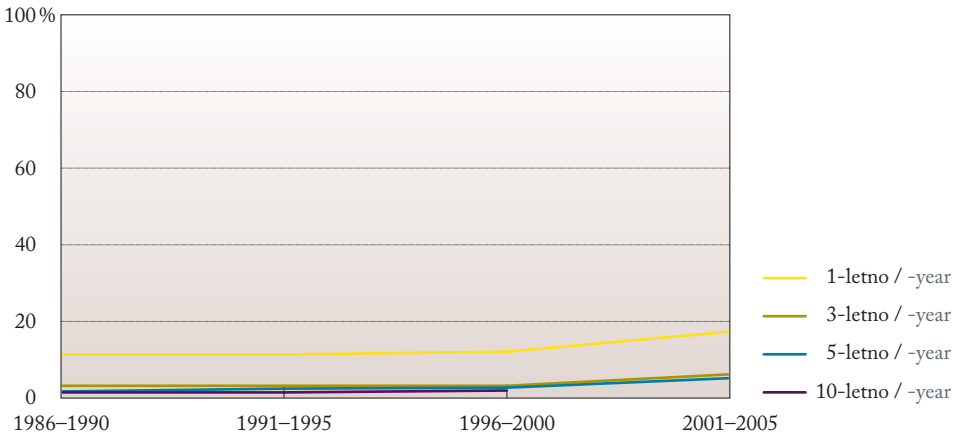
In the years 2001–2005, almost 70% of patients did not receive specific treatment. In comparison with the period 1991–1995 the percentage of untreated patients has decreased by 13%. Among the patients receiving specific treatment in the period 2001–2005, 58% were treated by surgery; in 42% this represented the only method of treatment, 16% also received chemotherapy; chemotherapy alone was used in 31% of the patients; 6% received radiotherapy in addition to chemotherapy or were only irradiated; the remaining 5% were treated by other combinations.

In the period 2001–2005, almost all patients started their treatment in one of the three leading Slovenian health institutions: 47% in the UMC Ljubljana, 32% at the IO Ljubljana, and 15% in the UMC Maribor.

Tabela 2: *Število bolnikov z rakom trebušne slinavke po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of pancreatic cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	429	15,6	26,3	41,0	17,0	421	11,2	30,4	41,3	17,1
1996–2000	445	9,4	29,2	49,2	12,1	517	12,6	31,7	40,8	14,9
2001–2005	571	6,5	34,3	50,4	8,8	639	8,3	33,6	47,4	10,6



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom trebušne slinavke po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of pancreatic cancer patients by period of diagnosis.*

Starost največjega deleža zbolelih je bila ob diagnozi od 50 do 74 let. Med moškimi je bilo v tej starostni skupini približno dve tretjini bolnikov, med ženskami pa nekaj več kot polovica. Več kot tretjina žensk je bila ob diagnozi starih 75 let in več, pred 50. letom pa je zbolelo nekaj več moških kot žensk (Tabela 1). Deleži v posameznih starostnih skupinah se s časom niso bistveno spreminjali.

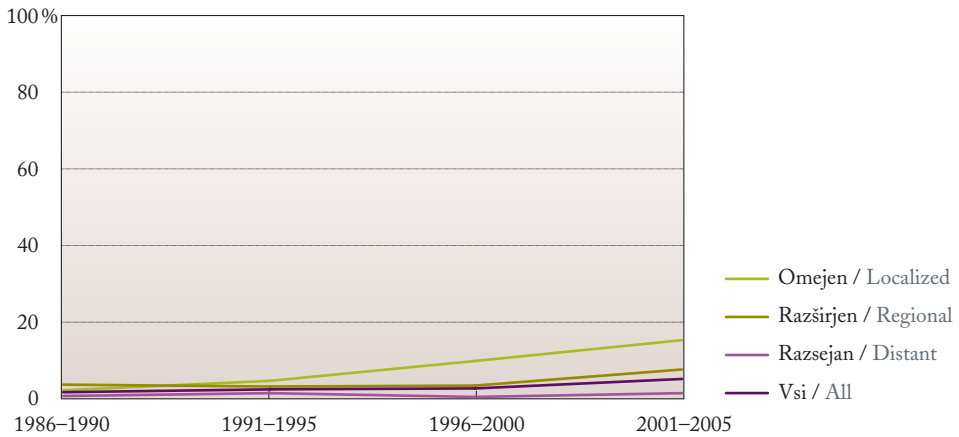
V vseh treh obdobjih je imelo največ bolnikov ob diagnozi razsejano bolezen; v obdobju 2001–2005 50 % moških in 47 % žensk (Tabela 2). Delež bolnikov z omejenim stadijem se zmanjšuje pri obeh spolih, tako na račun razširjenega kot razsejanega stadija.

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom trebušne slinavke po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of pancreatic cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	10,3 (7,8–13,6)	3,7 (2,3–6,0)	2,6 (1,4–4,6)	11,4 (8,7–14,9)	1,9 (1,0–3,8)	1,2 (0,5–2,8)
1996–2000	11,9 (9,3–15,3)	3,6 (2,2–5,8)	2,7 (1,5–4,7)	11,4 (9,0–14,5)	2,1 (1,2–3,8)	1,7 (0,9–3,3)
2001–2005	16,8 (14,0–20,2)	4,5 (3,1–6,7)	4,1 (2,7–6,2)	16,3 (13,7–19,4)	5,9 (4,3–8,0)	4,0 (2,7–6,1)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	10,8 (7,3–14,3)	4,3 (1,7–7,0)	3,3 (0,7–6,0)	12,0 (8,3–15,7)	2,2 (0,0–4,4)	1,6 (0,0–3,7)
1996–2000	12,5 (8,9–16,1)	4,1 (1,6–6,6)	3,4 (0,9–6,0)	12,0 (8,7–15,2)	2,4 (0,5–4,4)	2,2 (0,2–4,2)
2001–2005	17,6 (14,1–21,1)	5,2 (2,8–7,7)	5,2 (2,6–7,9)	17,0 (13,7–20,3)	6,8 (4,3–9,2)	5,1 (2,5–7,7)

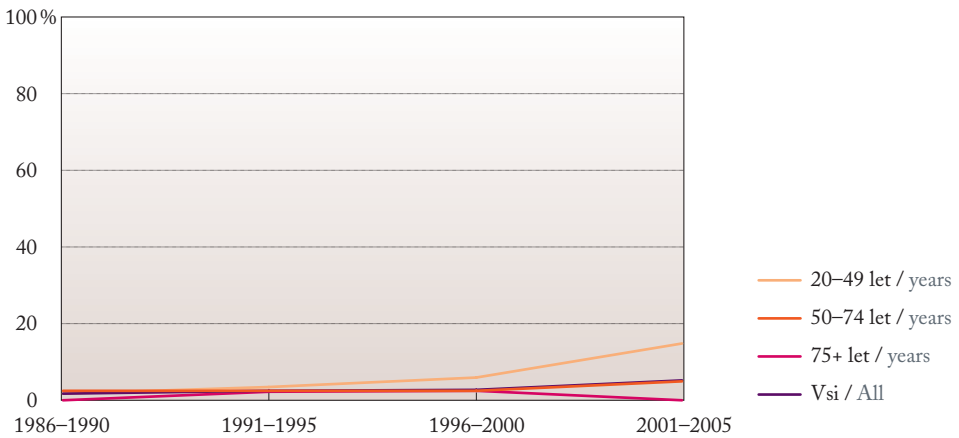


Slika 3: *Petletno relativno preživetje bolnikov z rakom trebušne slinavke po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of pancreas cancer patients by stage and period of diagnosis.*

The survival of patients with pancreatic cancer has been increasing very slowly; thus in 15 years, the 5-year relative survival increased only by 3% (Figure 2), slightly more in females (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage has exceeded 15%. However, the 5-year relative survival of patients with regional and disseminated stages is still lower than 10%. Age is a prognostic factor as well, since the worst relative survival is observed in patients aged 75 years or older, while the survival in those under 50 years of age is somewhat better, and has actually undergone the highest increase (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 5% (Figure 2); patients surviving the first year may expect to survive five years in 28%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, survival of Slovenian patients with pancreatic cancer is nearly equal to the European average (Figure 5).



Slika 4: *Petletno relativno preživetje bolnikov z rakom trebušne slinavke po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of pancreatic cancer patients by age and period of diagnosis.*

V letih 2001–2005 ni bilo specifično zdravljenih skoraj 70 % bolnikov. Delež nezdravljenih se je v primerjavi z obdobjem 1991–1995 zmanjšal za 13 %. Med specifično zdravljenimi je bilo v letih 2001–2005 58 % bolnikov operiranih; pri 42 % je bilo to edino zdravljenje, 16 % pa je prejelo še kemoterapijo; samo s kemoterapijo je bilo zdravljenih 31 % bolnikov; 6 % je poleg kemoterapije prejelo še radioterapijo ali pa so bili samo obsevani; preostalih 5 % so zdravili z drugimi kombinacijami.

V obdobju 2001–2005 so skoraj vsi bolniki, ki so bili zdravljeni, zdravljenje pričeli v eni od treh vodilnih slovenskih zdravstvenih ustanov: 47 % v UKC Ljubljana, 32 % na OI Ljubljana in 15 % v UKC Maribor.

Preživetje bolnikov z rakom trebušne slinavke se veča zelo počasi; v 15 letih se je petletno relativno preživetje povečalo le za 3 % (Slika 2), nekoliko bolj pri ženskah (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju preseglo 15 %. Petletno relativno preživetje bolnikov z razširjenim in razsejanim stadijem pa je še vedno manjše od 10 %. Napovedni dejavnik je tudi starost, saj je relativno preživetje najmanjše pri starih 75 let in več, nekoliko večje pa pri mlajših od 50 let, pri katerih se je s časom tudi najbolj povečalo (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 5 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 28-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je grobo petletno relativno preživetje slovenskih bolnikov z rakom trebušne slinavke (4,8 %) skoraj enako evropskemu povprečju (4,7 %).

KLINIČNI KOMENTAR

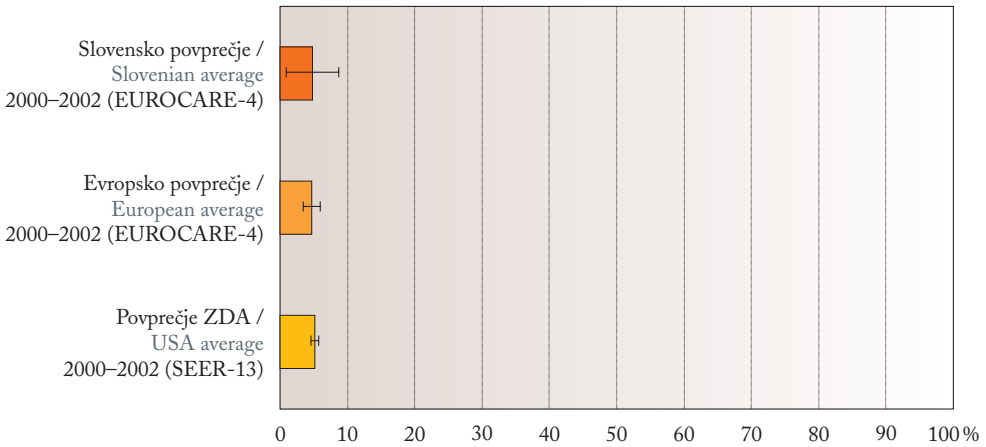
Mirko Omejc

Rak trebušne slinavke je zaradi svoje napadalnosti bolezen z veliko umrljivostjo. Klinično se kaže z obsežno perinevralno in retroperitonealno infiltracijo, invazijo žilja, lokalnim recidivom in zgodnjimi lokalnimi in oddaljenimi zasevki.

Raziskave v zadnjih letih so pripeljale do številnih novih vprašanj, a prinesle le malo odgovorov nanje. Veliko je novih spoznanj o tej bolezni, malo pa napredka v zdravljenju. Večina bolnikov ima v času diagnoze že razširjeno bolezen. Tudi velik del tistih z domnevno omejeno boleznijo umre zaradi raka trebušne slinavke. Kljub temu se je preživetje v zadnjem desetletju nekoliko izboljšalo.

V Sloveniji z večanjem incidence postopno prihaja do podobnih sprememb v odkrivanju in zdravljenju raka trebušne slinavke kot v svetu. Vzporedno z večanjem incidence se je večalo tudi število resekcij. Resekcija brez ostanka tumorja (R0) je najpomembnejši napovedni dejavnik. V zadnjem desetletju se je uveljavila tudi cefalična duodenopankreatektomija z ohranjenim pilorusom, ki bolnika manj poškoduje ob enakem preživetju kot klasična Whipplova operacija. Razširjena limfadenektomija ne izboljša preživetja v primerjavi s standardno operacijo.

Smrtnost in zapleti po operaciji so obratno sorazmerni s številom resekcij. V centrih z velikim številom operacij se je smrtnost v zadnjem desetletju zmanjšala pod 5 %, hkrati pa se je tudi preživetje bolnikov v teh centrih povečalo. V Sloveniji je bila v obdobju 1999–2000 smrtnost po resekciji glave trebušne slinavke velika, 16-odstotna. Po letu 2000 opažamo tudi v Sloveniji centralizacijo specifičnega zdravljenja na tri večje centre, ki se ukvarjajo z onkološko kirurgijo. Tu sta uveljavljena timski pristop in multimodalno zdravljenje. V tem obdobju se je zmanjšal delež bolnikov, zdravljenih le s kirurgijo, in povečal delež tistih, ki so bili še dodatno zdravljeni. Večanje preživetja je posebej izrazito v tem obdobju. Ob tem je zanimivo zmanjšanje deleža omejenega raka in povečanje deleža razširjenega in razsejanega raka v času diagnoze, kar govori predvsem v prid izboljšani diagnostiki v zadnjih letih. Novi diagnostični postopki omogočajo



Slika 5: *Petletno relativno preživetje bolnikov z rakom trebušne slinavke (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of pancreatic cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

CLINICAL COMMENTARY

Mirko Omejc

Because of its aggressiveness, pancreatic cancer is associated with a high mortality rate. Clinically it manifests itself with perineural and retroperitoneal infiltration, vascular invasion, local recurrence and early regional and distant metastases.

In recent years, research studies have opened a number of new questions, many of which remained unanswered. There are many new findings regarding this disease, though little progress has been achieved in terms of its treatment. The majority of patients will present with an advanced stage at diagnosis. Also a large proportion of those with supposedly localized disease will die from pancreatic cancer. Nevertheless, in the last decade the survival has undergone a slight improvement.

By increasing incidence, in Slovenia too – likewise elsewhere in the world – we witness changes in the diagnosis and treatment of pancreatic cancer. Along with the increasing incidence the number of resections has increased too. Radical (R0) resection is the most relevant prognostic factor. In the last decade, cephalic duodenopancreatectomy with pylorus preservation has gained in importance; this technique is less mutilating and associated with the same survival rate as the classical Whipple's procedure. In comparison with the standard surgical approach, the extended lymphadenectomy does not improve survival.

Postoperative lethality and complications are inversely proportional with the number of resections. In centers with a large number of surgeries performed, in the last decade the lethality rate has dropped under 5% while the survival of patients in those centers has improved. In the period 1999–2000, the cephalic pancreatectomy-related lethality in Slovenia was as high as 16%. After the year 2000, in Slovenia too we witness centralization of the specific treatment in three bigger centers engaged in oncological surgery with an established team approach and multimodality treatment. In that period, the proportion of patients treated with surgery alone has decreased while the proportion of those treated additionally with other modalities has increased. In the same period an increase in the survival is particularly apparent. Further to that, it is interesting to note a decrease in the proportion of localized cancer and an increase in the proportion of regional and disseminated disease at diagnosis, which is indicative of better diagnosis in recent

bolj natančno določitev stadija in s tem večanje števila bolnikov z razsejano boleznijo ob diagnozi. K povečanju števila bolnikov z razširjeno in razsejano boleznijo je prispevalo tudi izboljšanje tehničnih in diagnostičnih zmogljivosti, ki omogočajo varne in točne preiskave tudi pri težjih bolnikih z zlatenico.

Pri mlajših bolnikih z omejenim rakom je izboljšanje preživetja najbolj izrazito. Starejši bolniki so zaradi pridruženih bolezni manj primerni za obsežen operativni poseg in dodatno zdravljenje, zato se tu preživetje le malo spreminja. Pri bolnikih z razširjenim ali razsejanim tumorjem in obstrukcijsko zlatenico je pogosto mogoče napraviti le paliativen poseg.

Povečanje preživetja v zadnjem 5-letnem obdobju gre predvsem na račun večje točnosti določitve bolezenskega stadija, boljše izbire bolnikov za operacijo, manjše zgodnje pooperacijske smrtnosti in dodatnega onkološkega zdravljenja, kar je posledica timskega pristopa k obravnavi bolnikov z rakom trebušne slinavke. Še vedno pa ostaja velik del bolnikov, pri katerih do specifičnega zdravljenja sploh ni prišlo.

VIRI
Literature

Bachmann J, Michalski CW, Martignoni ME, Büchler MW, Friess H. Pancreatic resection for pancreatic cancer. HPB 2006; 8: 346–51.

Friess H, Kleef J, Büchler M. Pancreatic cancer. Guest editorial. HPB 2006; 8: 323.

Merchant N, Berlin J. Past and future of pancreas cancer: are we ready to move forward together? J Clin Oncol 2008; 26: 3478–80.

Omejc M. Rak trebušne slinavke v Sloveniji. Anketa kirurških oddelkov za leti 1999–2000. In: Pleskovič A, ed. Kirurgija trebušne slinavke. Ljubljana: Kirurške klinike KC, 2002: 135–9.

years. New diagnostic procedures and improvements facilitate a more accurate staging and thus also a higher yield of patients with disseminated disease at diagnosis. The higher number of patients with disseminated disease is also attributable to the improved technical and diagnostic facilities, which enable safe and accurate examinations in severe patients with jaundice.

The improvement in survival is most apparent in younger patients with localized cancer. Owing to concomitant diseases, older patients are less suitable for extensive surgical procedures and adjuvant therapy, and therefore their survival does not change much. In patients with regional or disseminated tumor and obstructive icterus a palliative intervention is frequently the only option.

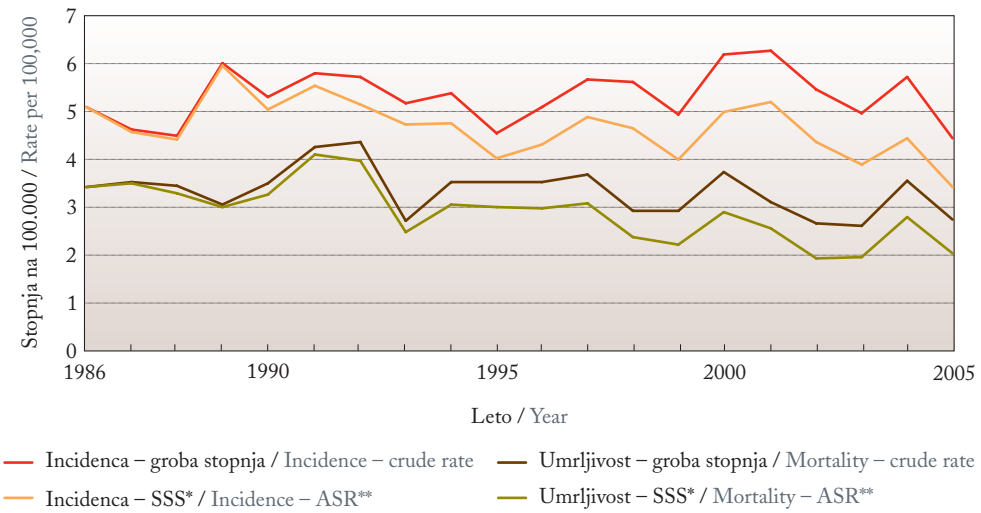
Improved survival observed in the last 5-year period is prevailingly due to greater accuracy of staging, better selection of patients suitable for surgery, lower early postoperative lethality and additional oncological treatment, which is all a result of team approach to the treatment of patients with pancreatic cancer. However, there are still a large proportion of patients left without any specific treatment.

GRLO

MKB 10: C32

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom grla zbolelo 1640 ljudi, od tega 1482 moških in 158 žensk. Kot je razvidno s Slike 1, se tako grobe kot starostno standardizirane incidenčne in umrljivostne stopnje od leta 1991 zmanjšujejo. Groba incidenčna stopnja se zmanjšuje povprečno za 0,3 % letno, groba umrljivostna stopnja pa povprečno za 2,2 % letno. Starostno standardizirani stopnji se manjšata še nekoliko hitreje, saj v zadnjih letih zboli več starejših bolnikov (Tabela 1).



Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka grla, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of laryngeal cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1610 primerov; 29 bolnikov (1,8 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, enega, mlajšega od 20 let, pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. Med vsemi bolniki, ki smo jih vključili v analizo, jih je imelo 78 % opredeljeno natančnejše mesto nastanka tumorja v grlu: 54 % med njimi je imelo tumor glasilk, 37 % tumor supraglotisa, okrog 1 % tumor subglotisa in grlnega hrustanca, 7 % pa je imelo ob diagnozi tako razširjen tumor, da natančnejšega mesta ni bilo mogoče opredeliti.

Manj kot 1 % bolnikov v vsakem obdobju ni imelo mikroskopsko potrjene bolezni. Praktično vsi mikroskopsko potrjeni tumorji (95 %) so bili ploščatocelični karcinomi.

Tabela 1: *Število bolnikov z rakom grla po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of laryngeal cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	484	17,4	76,2	6,4	46	21,7	69,6	8,7
1996–2000	493	17,6	73,6	8,7	51	13,7	72,5	13,7
2001–2005	479	14,4	74,5	11,1	57	22,8	54,4	22,8

LARYNX

ICD 10: C32

EPIDEMIOLOGY

In the period 1991–2005, a total of 1640 persons were diagnosed with cancer of the larynx, of these 1482 males and 158 females. As evident from Figure 1, since 1991 crude as well as age-standardized incidence and mortality rates have been decreasing. The estimated annual percentage decrease in crude incidence rate was 0.3%, while in crude mortality rate it was 2.2%. The age-standardized rates have been decreasing even more rapidly as in the recent years the number of patients diagnosed at an advanced age is increasing (Table 1).

The survival analysis included 1610 cases; 29 patients (1.8%) diagnosed only after death, were not considered in the analysis, one patient under 20 years of age is presented in the chapter on the survival of children and adolescents. Among all the patients included in the analysis, 78% had the site of tumor origin in the larynx more precisely defined: thus 54% had tumor of the vocal cords, 37% of the supraglottis, approximately 1% of the subglottis and laryngeal cartilage, while in 7% tumor at the time of diagnosis was so advanced that the exact site of origin could not be precisely defined.

Approximately 1% of patients in each time period did not have microscopically confirmed disease. Practically all microscopically confirmed tumors were planocellular carcinomas (95%).

The greatest proportion of patients was between 50 and 74 years of age at diagnosis. In both genders, the proportion of those aged 75 years or older has been increasing with time while the proportion of male patients under 50 years of age has undergone a slight decrease; in females however it did not change much (Table 1).

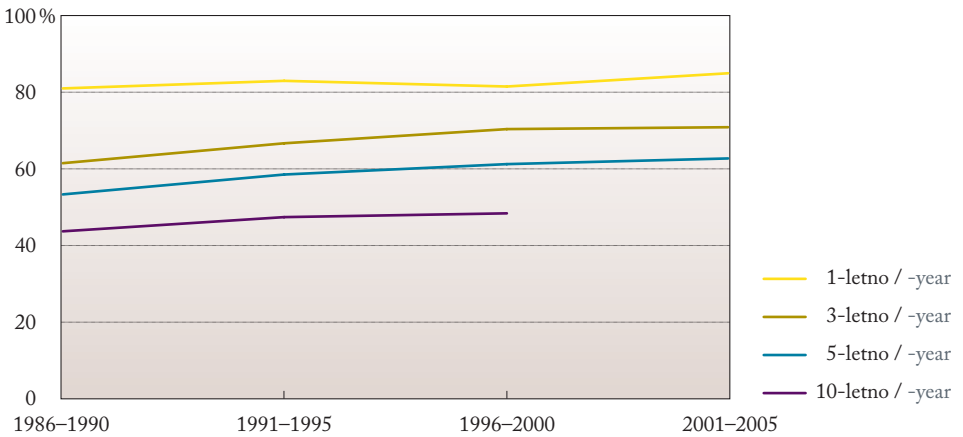
Almost all patients had the disease diagnosed at localized or regional stage. The proportions of disseminated and undefined stages are negligible (Table 2). In the years 2001–2005 more than a half of males and approximately a third of females had the disease diagnosed at a localized stage. In males, the ratio between stages remained roughly equal throughout the observation period while in females a decrease in the percentage of patients with localized stage was noted in the recent period.

In the period 2001–2005, 5% of patients did not receive specific treatment. In the observed 15-year period the proportion of untreated patients has remained almost unchanged. Among the patients receiving specific treatment in the period 2001–2005, 40% were irradiated, 38% had irradiation combined with surgery while 11% underwent surgery alone. Twelve percents of patients also received chemotherapy besides standard treatment with irradiation and/or surgery. The proportions of individual treatment modalities did not change significantly with time.

In the period 2001–2005, practically all treated patients started their treatment in one of the three leading Slovenian health institutions: 53% at the IO Ljubljana, 30% in the UMC Ljubljana and 15% in the UMC Maribor. A few patients started their treatment in general hospitals in Celje, Murska Sobota and Novo mesto.

Tabela 2: *Število bolnikov z rakom grla po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*
Table 2: *Number of laryngeal cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	484	49,4	48,1	1,4	1,0	46	63,0	34,8	0,0	2,2
1996–2000	493	58,2	40,4	0,8	0,6	51	56,9	43,1	0,0	0,0
2001–2005	479	51,4	47,4	0,8	0,4	57	33,3	61,4	3,5	1,8



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom grla po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of laryngeal cancer patients by period of diagnosis.*

Starost največjega deleža zbolelih je bila ob diagnozi med 50–74 let. Delež starih 75 let in več se pri obeh spolih s časom veča, medtem ko se delež mlajših od 50 let pri moških nekoliko manjša, pri ženskah pa ostaja nespremenjen (Tabela 1).

Skoraj vsem bolnikom je bila bolezen odkrita v omejenem ali razširjenem stadiju. Deleži razsejanih in neopredeljenih stadijev so zanemarljivi (Tabela 2). V letih 2001–2005 je bila bolezen odkrita v omejenem stadiju pri več kot polovici moških in pri približno tretjini žensk. Razmerja med stadiji pri moških ostajajo ves čas opazovanja približno enaka, pri ženskah pa se je v zadnjem obdobju zmanjšal delež bolnic z omejenim stadijem.

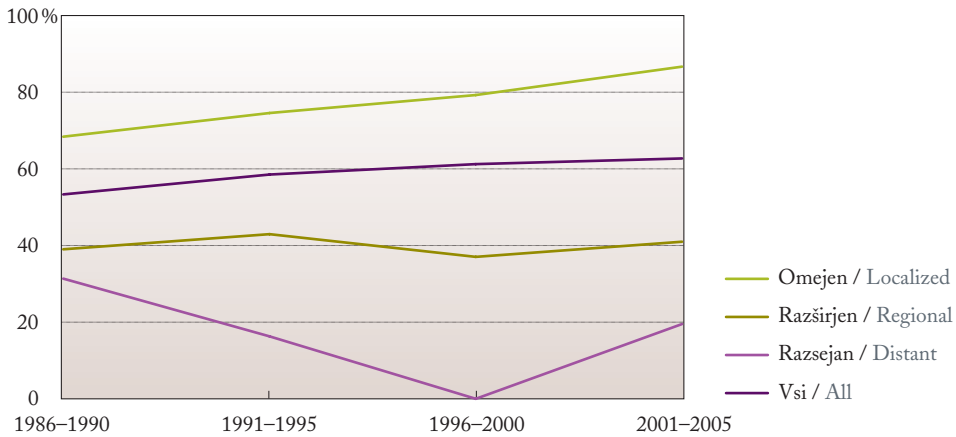
V obdobju 2001–2005 ni bilo specifično zdravljenih 5 % bolnikov. Delež nezdravljenih bolnikov ostaja v opazovanem 15-letnem obdobju skoraj enak. Med specifično zdravljenimi bolniki

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom grla po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of laryngeal cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	81,0 (77,6–84,6)	60,3 (56,1–64,9)	49,2 (44,9–53,8)	76,1 (64,7–89,5)	69,6 (57,5–84,2)	60,9 (48,3–76,7)
1996–2000	78,1 (74,5–81,8)	63,1 (59,0–67,5)	50,9 (46,7–55,5)	88,2 (79,8–97,5)	72,5 (61,3–85,9)	62,7 (50,8–77,5)
2001–2005	83,3 (80,0–86,7)	65,4 (61,2–69,8)	53,9 (49,2–59,0)	75,4 (65,1–87,5)	59,3 (47,7–73,7)	51,0 (38,7–67,2)

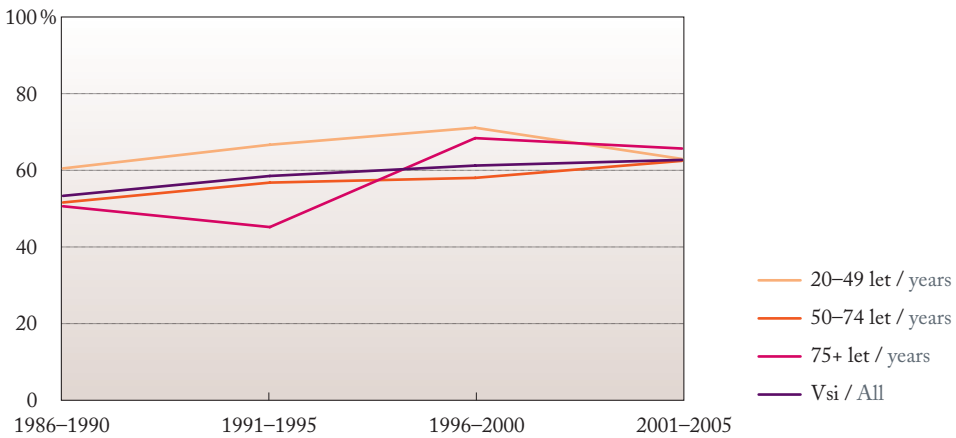
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	83,4 (79,7–87,1)	66,1 (61,1–71,0)	57,4 (52,0–62,9)	77,5 (63,9–91,1)	73,7 (58,2–89,3)	67,2 (49,7–84,7)
1996–2000	80,6 (76,7–84,4)	69,5 (64,7–74,4)	60,2 (54,7–65,6)	90,0 (80,5–99,5)	77,2 (63,0–91,4)	69,8 (53,3–86,2)
2001–2005	85,7 (82,2–89,2)	72,0 (67,1–76,8)	63,7 (57,6–69,7)	76,5 (64,3–88,8)	62,4 (47,2–77,5)	55,8 (38,0–73,6)



Slika 3: *Petletno relativno preživetje bolnikov z rakom grla po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of laryngeal cancer patients by stage and period of diagnosis.*

The relative survival of patients with laryngeal cancers has been moderately increasing; in 15 years, it increased by 5% (Figure 2). In comparison with females, the 5-year relative survival of males is slightly better (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage was 87%, while in those with regional stage at diagnosis it was 41%. Due to a small number of patients with disseminated disease, the evaluation of their survival is unreliable. In recent years, a considerable improvement in the survival was observed in patients with localized disease, whereas no significant improvement was noted in those with regional and disseminated disease. The survival of patients in our analysis did not depend on age at diagnosis (Figure 4).

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 63% (Figure 2); patients surviving the first year may expect to survive five years in 74%. In comparison with the rest of cancer patients, those with cancers of the head/neck will more frequently develop a second primary cancer. Patients in whom larynx was the only primary cancer site had 70% 5-year relative survival rate.



Slika 4: *Petletno relativno preživetje bolnikov z rakom grla po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of laryngeal cancer patients by age and period of diagnosis.*

je bilo v letih 2001–2005 40 % obsevanih, 38 % je bilo poleg obsevanja še operiranih, 11 % pa je bilo samo operiranih. Poleg klasičnega zdravljenja z obsevanjem in/ali operacijo je 12 % bolnikov prejelo še kemoterapijo. Deleži posameznih načinov zdravljenja se s časom niso bistveno spreminjali.

V obdobju 2001–2005 so skoraj vsi bolniki, ki so bili zdravljeni, pričeli zdravljenje v eni od treh vodilnih slovenskih zdravstvenih ustanov: 53 % na OI Ljubljana, 30 % v UKC Ljubljana in 15 % v UKC Maribor. Nekaj bolnikov se je začelo z zdraviti še v SB Celje, SB Murska Sobota in SB Novo mesto.

Petletno relativno preživetje bolnikov z rakom grla se zmerno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 5 % (Slika 2). Petletno relativno preživetje moških je v primerjavi z ženskami nekoliko boljše (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3. Petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju 87 %, medtem ko je pri bolnikih z razširjenim stadijem bolezni ob diagnozi 41 %. Bolnikov v razsejanem stadiju je malo, tako da je ocenjevanje njihovega preživetja nezanesljivo. V zadnjih letih se je precej izboljšalo preživetje bolnikov z omejenim stadijem bolezni, medtem ko pri bolnikih z razširjeno in razsejano boleznijo ni bistvenega napredka. Preživetje bolnikov, vključenih v našo analizo, ni bilo odvisno od starosti ob ugotovitvi bolezni (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 63 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 74-odstotno petletno relativno preživetje. Pogosteje kot drugi bolniki z rakom zbolijo bolniki z rakom na področju glave in vratu še za drugim primarnim rakom. Bolniki z rakom grla kot edinim rakom so imeli petletno relativno preživetje 70 %.

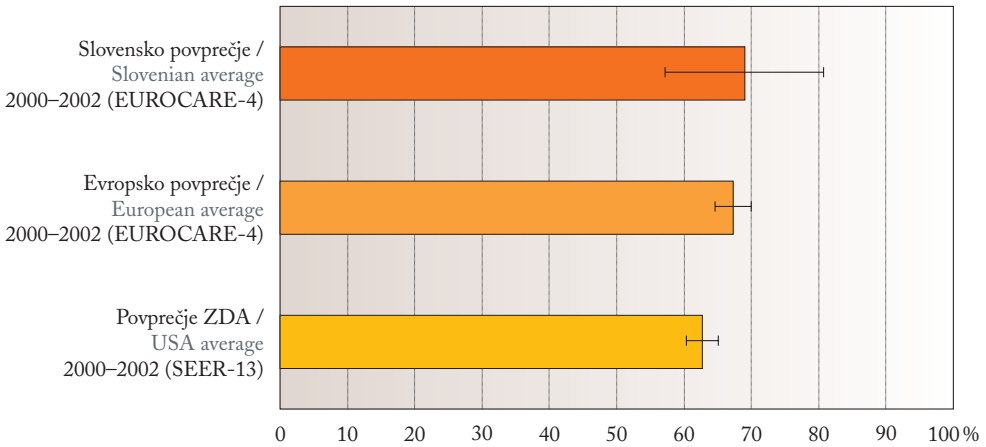
Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je grobo petletno relativno preživetje slovenskih bolnikov z rakom grla statistično neznačilno večje od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

Lojze Šmid
Primož Strojan
Branko Zakotnik

Visok delež histološko opredeljene bolezni ne preseneča, saj je mikroskopska potrditev bolezni pred pričetkom zdravljenja že desetletja ena temeljnih zahtev multidisciplinarnega tima strokovnjakov, ki v Sloveniji obravnavajo to vrsto raka. Čeprav je v zadnjem petletnem obdobju pri bolnicah opaziti manj primerov z omejeno obliko bolezni (na račun razširjene oblike), ta »premik« zaradi sorazmerno majhnega števila bolnic (okoli 10 % vseh bolnikov z rakom grla) ne vpliva pomembneje na porazdelitev stadijev bolezni ob diagnozi. Razmerje med omejenim in razširjenim stadijem tako ostaja skozi celotno 15-letno obdobje stabilno in znaša približno 50 % : 50 %. Obstoječe razmerje potrjuje spoznanje, kako pomembna je za posameznika barva glasu, kajti sprememba v barvi je pri raku grla običajno prvi znanilec bolezenskega dogajanja v tem delu dihalne poti.

Preživetje bolnikov z rakom grla se je ves čas, iz obdobja v obdobje, večalo, stopnja umrljivosti pa ustrezno nižala. Žal pa se opazovano izboljšanje kaže izključno pri bolnikih z omejeno obliko bolezni, kar se pripisuje napredku v kirurgiji in radioterapiji (izboljšanje postopkov načrtovanja in priprave bolnikov na obsevanje, uvedba naprednejših obsevalnih tehnik). V skupini z razširjeno obliko bolezni, ki je (bila) tarčna skupina za sodobnejše kombinirane načine zdravljenja, v prvi vrsti radiokemoterapije, ki se je v 90. letih preteklega stoletja uveljavila kot zlati standard v zdravljenju lokalno in področno napredovalih rakov glave in vratu, se preživetje bolnikov ni izboljšalo. Vzrok velja iskati v spoznanju, da je bil delež naših bolnikov, zdravljenih s kombinacijo obsevanja in kemoterapije (po operaciji ali brez) sorazmerno majhen oziroma vsekakor manjši kot v primeru drugih rakov področja glave in vratu. Tudi za vpliv prognostično ugodnejših tumorjev, nastalih kot posledica okužbe s HPV, domnevamo, da je v slovenski populaciji bolnikov manjši kot v zahodnih državah; žal sta prevladujoča dejavnika tveganja raka grla čezmerno pitje alikoholnih pijač in kajenje.



Slika 5: *Petletno relativno preživetje bolnikov z rakom grla (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of laryngeal cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the crude 5-year relative survival of Slovenian patients with laryngeal cancer is above (statistically not significant) the European average (Figure 5).

CLINICAL COMMENTARY

Lojze Šmid
Primož Strojan
Branko Zakotnik

The high proportion of histologically verified/confirmed disease is not surprising, since for decades microscopical confirmation of the disease prior to the beginning of therapy has been one of the fundamental requirements of the multidisciplinary team of experts dealing with this type of cancer in Slovenia. Although in the last 5-year period fewer cases with localized disease were observed in women (on the account of regional disease), owing to a relatively small number of female patients (approximately 10% of all laryngeal cancer patients) this shift does not exert a significant influence on stage-distribution at diagnosis. Thus, the ratio between localized and regional stage remains stable throughout the 15-year observation period, being 50% vs. 50%. The present finding confirms the relevance of individual's voice color, which, when changed, is generally the first indicator of a pathological process in that part of the respiratory tract.

The survival of laryngeal cancer patients has been steadily improving with every next observation period, and accordingly their mortality rates have been decreasing. Unfortunately, the observed improvement has been limited exclusively to the patients with localized disease, which should be attributed to the advances in surgery and radiotherapy (improved irradiation planning and patient preparation procedures and the implementation of more advanced irradiation techniques). No improvement in the survival was noted in the group with regional disease representing the target group for more advanced combined treatment modalities, in particular radiochemotherapy, which made the gold standard in the treatment of localized and regionally advanced head and neck cancers. The reason should be sought in the fact that the proportion of our patients treated with a combination of irradiation and chemotherapy (with or without previous surgery) was relatively low or in any case lower than in other head and neck cancers. We assume that the proportion of prognosticaly favurable tumors caused by HPV infection in Slovenian population is smaller than in western Europe; unfortunately, the prevailing risk factors for laryngeal cancer in Slovenia are alcohol abuse and tobacco smoking.

(Ne)uspehov pri zdravljenju bolnikov z razsejano obliko bolezni ob diagnozi v različnih obdobjih zaradi maloštevilnosti teh bolnikov ni možno vrednotiti. Vsekakor pa drži, da je učinkovitost zdravljenja, ki je na voljo (predvsem kemoterapija), pri razsejanem raku grla večja kot pri drugih, prav tako razsejanih rakih zgornjega dela prebavne cevi in dihalnih poti.

Primerjava uspešnosti zdravljenja med posameznimi starostnimi skupinami ni bila možna, ker je bila večina bolnikov z rakom grla v srednji starostni skupini (med 50–74 let).

VIRI
Literature

Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008; 100: 261–9.

Lešničar H, Šmid L, Zakotnik B. Early glottic cancer: the influence of primary treatment on voice preservation. Int J Radiat Oncol Biol Phys 1996; 36: 1025–32.

Strojan P, Karner K, Šmid L, Šoba E, Fajdiga I, Jančar B, et al. Concomitant chemoradiotherapy with mitomycin C and cisplatin in advanced unresectable carcinoma of the head and neck: Phase I–II clinical study. Int J Radiat Oncol Biol Phys 2008; 72: 365–72.

Šmid L, Lešničar H, Zakotnik B, Šoba E, Budihna M, Furlan L, et al. Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer-preliminary report. Int J Radiat Oncol Biol Phys 1995; 32: 769–75.

Šmid L, Budihna M, Zakotnik B, Šoba E, Strojan P, Fajdiga I, et al. Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma. Int J Radiat Oncol Biol Phys 2003; 56: 1055–62.

Zakotnik B, Šmid L, Budihna M, Lešničar H, Šoba E, Furlan L, et al. Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. Int J Radiat Oncol Biol Phys 1998; 41: 1121–7.

Zakotnik B, Budihna M, Šmid L, Šoba E, Strojan P, Fajdiga I, et al. Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin. Int J Radiat Oncol Biol Phys 2007; 67: 685–90.

Owing to a small number of patients with disseminated disease at diagnosis it is not possible to evaluate their treatment success or failure during different observation periods. It is true, however, that in laryngeal cancer the effectiveness of the available therapy (in particular chemotherapy) is greater than in other also disseminated cancers of the upper gastrointestinal and respiratory tract.

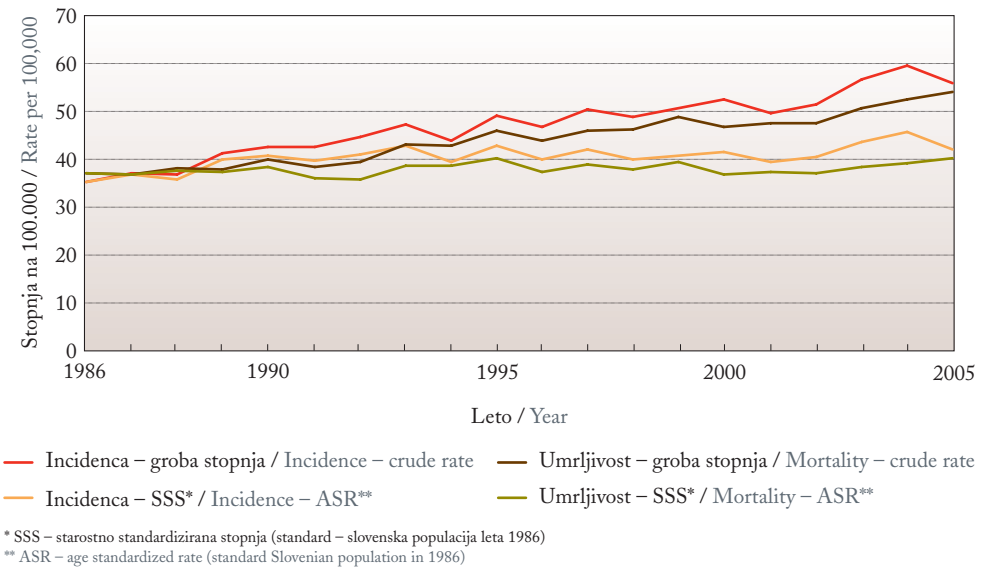
The fact that the majority of laryngeal cancer patients belonged to the middle-age group (between 50 to 74 years) rendered a comparison of treatment success between different age groups unfeasible.

PLJUČA

MKB 10: C33, C34

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za pljučnim rakom zbolelo 15.647 ljudi, 12.377 moških in 3270 žensk. Kot je razvidno s Slike 1, sta se v opazovanem obdobju večali groba incidenčna in umrljivostna stopnja, povprečno za 2,0 % letno. Večino tega povečanja lahko pripišemo staranju prebivalstva, saj sta obe starostno standardizirani stopnji vsa leta praktično konstantni. Starostno standardizirane stopnje po spolu pa kažejo drugačno sliko pri moških in ženskah: pri prvih se obe zmanjšujeta od sredine devetdesetih let, pri drugih pa večata, kar je posledica različnih kadilskih navad med spoloma.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja pljučnega raka, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of lung cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 14.921 primerov; 722 bolnikov (4,6 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 4 mlajše od 20 let pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. 85 bolnikov je imelo tumor na sapniku, ostali tumorji pa so vzniknili v sapnicah in pljučih.

Odstotek mikroskopsko potrjenih primerov je v vseh treh obdobjih enak: 93 %. Med mikroskopsko potrjenimi je imelo v 15-letnem obdobju 34 % bolnikov ploščatocelični karcinom, 25 % adenokarcinom, 18 % drobnocelični karcinom in 16 % karcinome drugih vrst. Delež adeno-

Tabela 1: *Število bolnikov s pljučnim rakom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of lung cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	3782	9,5	79,3	11,2	753	10,6	72,0	17,4
1996–2000	3943	9,9	76,7	13,3	990	13,8	66,6	19,6
2001–2005	4104	7,1	75,1	17,8	1349	11,6	62,6	25,9

LUNG

ICD 10: C33, C34

EPIDEMIOLOGY

In the period 1991–2005, a total of 15,647 persons were diagnosed with lung cancer, of these 12,377 males and 3270 females. As evident from Figure 1, in the observation period the estimated annual percentage increase in crude incidence and mortality rate was 2.0%. This increase can be attributed mainly to population ageing, since both age-standardized rates have remained practically stable throughout the observation period. Age-standardized rates by gender reveal differences between males and females: in the former, both rates have been decreasing since the middle of the 90's, while in the latter they have been increasing as a result of differences in smoking habits between genders.

The survival analysis included 14,921 cases; 722 patients (4.6%) diagnosed only after death were not considered in the analysis, four patients under 20 years of age are presented in the chapter on the survival of children and adolescents. 85 patients had tumor of trachea, the rest of tumors originated in the bronchus and lung.

The percentage of microscopically confirmed disease remained the same (93%) in all three observation periods. In the 15-year observation period, among the microscopically confirmed cases, planocellular carcinoma was found in 34% of patients, adenocarcinoma in 25%, small-cell carcinoma in 18% and other types of carcinoma in 16% of patients. The proportion of adenocarcinoma has been increasing all the time; in the last period this histological type represented already 30% of all lung cancers; in comparison with the period 1991–1995, in the period 2001–2005 the number of patients with adenocarcinoma almost doubled. The number of patients with planocellular carcinoma has remained all the time unchanged while the proportion of these patients among all lung cancers has been decreasing; the proportion of small-cell carcinomas has remained almost the same throughout the observation period.

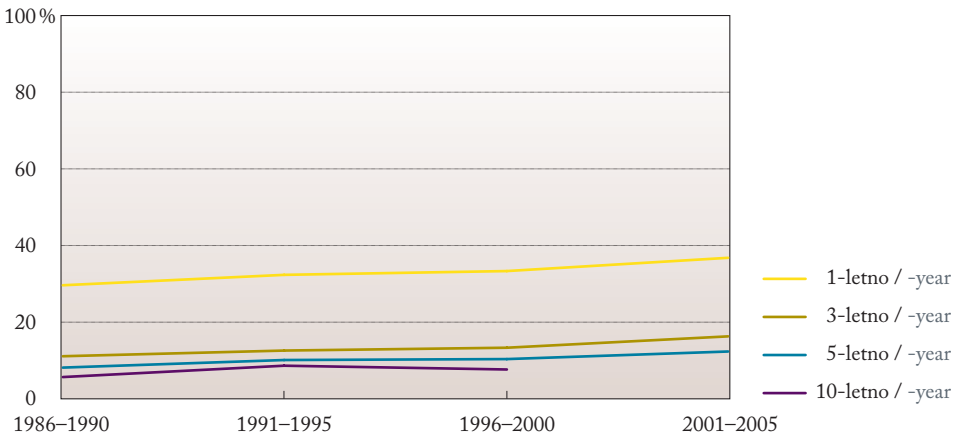
More than two thirds of patients of both genders were aged between 50 and 74 years at the time of diagnosis; less than 10% were diagnosed before 50 years of age (Table 1). Proportions in these two age groups have not been changing significantly with time, however, the proportion of those aged 75 years or older has been increasing in both genders, thus in the last period almost a quarter of female patients were aged 75 years or older.

Most patients present with disseminated disease at diagnosis. The proportion of these patients has been increasing throughout the observation period, in the last period exceeding 40%. In particular, the proportion of patients with localized disease has been decreasing on the account of a higher proportion of those with disseminated disease; the proportion of patients with undefined stage has remained all the time approximately 4% (Table 2).

In the years 2001–2005, 32% of patients did not receive specific treatment. The proportion of untreated patients was decreasing throughout the study period; among those diagnosed in the period 1991–1995 there were 39% of patients without specific treatment. The untreated patients

Tabela 2: *Število bolnikov s pljučnim rakom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*
Table 2: *Number of lung cancer patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	3782	27,5	37,1	30,9	4,5	753	26,0	31,1	35,7	7,2
1996–2000	3943	24,5	39,5	32,9	3,0	990	22,4	33,0	40,2	4,3
2001–2005	4104	16,6	38,9	41,0	3,5	1349	17,5	36,2	42,8	3,6



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov s pljučnim rakom po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of lung cancer patients by period of diagnosis.*

karcinoma se ves čas povečuje. V zadnjem obdobju je ta histološka vrsta predstavljala že 30 % vseh primerov pljučnega raka, število bolnikov s pljučnim adenokarcinomom pa se je v obdobju 2001–2005 glede na obdobje 1991–1995 skoraj podvojilo. Število bolnikov s ploščatoceličnim karcinomom ostaja ves čas enako, znižuje pa se delež teh bolnikov med vsemi primeri pljučnega raka; delež drobnoceličnih karcinomov ostaja ves čas opazovanja skoraj enak.

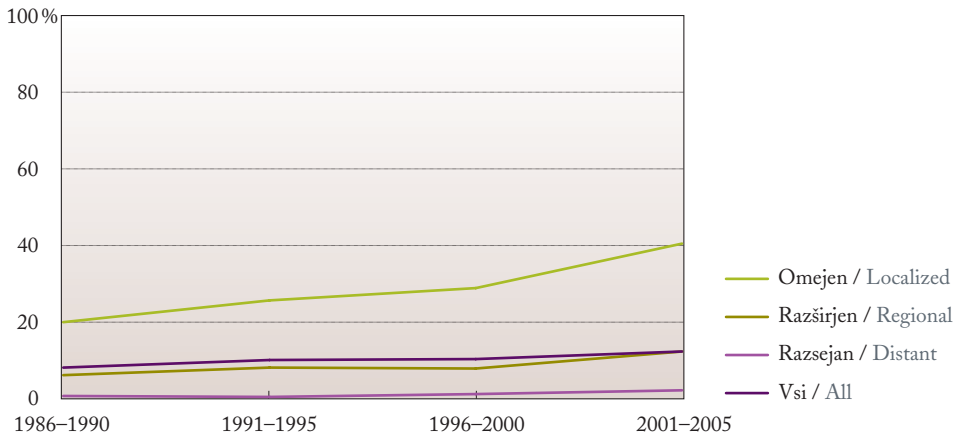
Več kot dve tretjini bolnikov in bolnic je bilo ob diagnozi starih med 50 in 74 let, manj kot 10 % jih je zbolelo pred 50. letom starosti (Tabela 1). Deleži v teh dveh starostnih skupinah se s časom niso bistveno spreminjali, pri obeh spolih pa se povečuje delež starih 75 let in več; v zadnjem obdobju je bila že četrtina bolnic, starih 75 let in več.

Tabela 3: *Opazovano in relativno preživetje bolnikov s pljučnim rakom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of lung cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	31,2 (29,8–32,7)	10,9 (9,9–11,9)	8,0 (7,2–8,9)	31,2 (28,1–34,7)	13,8 (11,6–16,5)	10,4 (8,4–12,8)
1996–2000	31,5 (30,1–33,0)	11,8 (10,8–12,8)	8,3 (7,5–9,2)	34,3 (31,5–37,4)	12,6 (10,7–14,9)	9,3 (7,6–11,3)
2001–2005	34,1 (32,7–35,6)	13,7 (12,7–14,8)	9,6 (8,6–10,7)	39,3 (36,8–42,0)	16,6 (14,7–18,7)	11,6 (9,9–13,7)

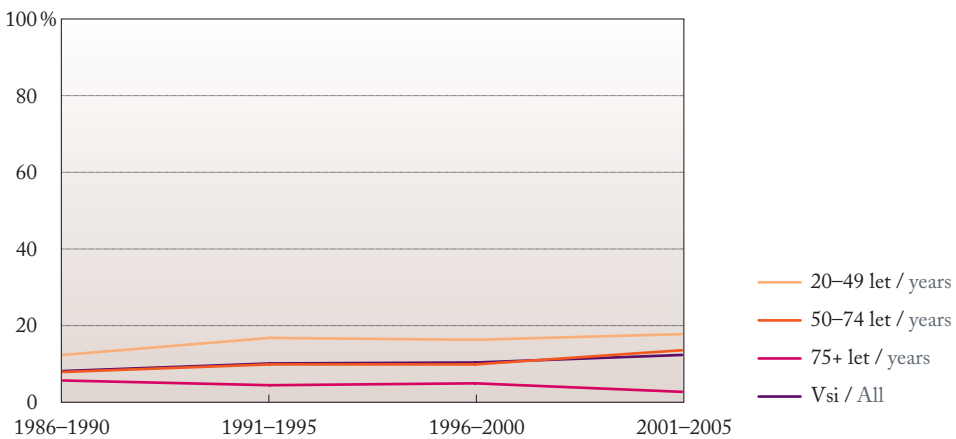
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	32,4 (30,8–34,0)	12,2 (11,0–13,4)	9,8 (8,7–10,9)	32,1 (28,5–35,7)	15,0 (12,1–18,0)	12,0 (9,2–14,8)
1996–2000	32,7 (31,2–34,2)	13,2 (12,1–14,4)	10,2 (9,0–11,3)	35,2 (32,1–38,4)	13,7 (11,2–16,1)	10,7 (8,4–13,0)
2001–2005	35,5 (33,9–37,0)	15,6 (14,3–16,8)	12,0 (10,7–13,3)	40,3 (37,6–43,1)	18,0 (15,7–20,3)	13,5 (11,1–15,9)



Slika 3: *Petletno relativno preživetje bolnikov s pljučnim rakom po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of lung cancer patients by stage and period of diagnosis.*

do not differ significantly from those with specific treatment in terms of stage or age at diagnosis. Among the patients receiving specific treatment in the period 2001–2005, the majority (31%) were treated by radiotherapy alone, 27% received chemotherapy in addition to irradiation while 15% were treated by chemotherapy alone. Within their primary treatment 25% of patients underwent surgery, half of them also receiving chemotherapy and/or radiotherapy. Compared to the period 1991–1995, the proportion of patients treated either by radiotherapy or surgery alone or with a combination of radiotherapy and surgery as single-modality treatment has decreased. Contrary to that, there is an increasing number of patients in whom standard radiotherapy and/or surgery has been combined with chemotherapy.

In the period 2001–2005, 61% of patients started their treatment at the IO Ljubljana, 19% in the UMC Ljubljana and 10% respectively in the UMC Maribor and at Hospital Golnik. Individual patients started their treatment in general hospitals of Murska Sobota, Topolšica and Izola.



Slika 4: *Petletno relativno preživetje bolnikov s pljučnim rakom po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of lung cancer patients by age and period of diagnosis.*

Največ bolnikov ima ob diagnozi razsejano bolezen. Delež teh bolnikov se je ves čas opazovanja povečeval. V zadnjem obdobju je presegel 40 %. Na račun večjega deleža bolnikov z razsejanim stadijem se je zmanjševal predvsem delež bolnikov z omejenim stadijem; delež bolnikov brez znanega stadija ostaja ves čas približno 4 % (Tabela 2).

V letih 2001–2005 se ni specifično zdravilo 32 % bolnikov. Delež nezdravljenih bolnikov se je v celotnem obdobju analize zmanjševal; med bolniki, zbolelimi v obdobju 1991–1995, jih ni bilo specifično zdravljenih 39 %. Skupina nezdravljenih se ne razlikuje bistveno glede na stadij ali starost ob diagnozi od specifično zdravljenih bolnikov. Med specifično zdravljenimi je bilo v letih 2001–2005 največ bolnikov (31 %) samo obsevanih, pri 27 % je bila radioterapiji dodana še kemoterapija, 15 % jih je bilo zdravljenih le s kemoterapijo. V sklopu prvega zdravljenja je bilo operiranih 25 % bolnikov, polovici med njimi je bila dodana še kemoterapija in/ali obsevanje. V primerjavi z obdobjem 1991–1995 se je zmanjšal delež bolnikov, ki so bili samo obsevani, samo operirani ali pa obsevani in operirani. Nasprotno pa se veča število bolnikov, pri katerih je bila klasičnemu zdravljenju z obsevanjem in/ali operacijo dodana še kemoterapija.

V obdobju 2001–2005 se je 61 % bolnikov pričelo zdraviti na OI Ljubljana, 19 % v UKC Ljubljana, po 10 % pa v UKC Maribor in Bolnišnici Golnik. Posamezne bolnike so pričeli zdraviti še v splošnih bolnišnicah v Murski Soboti, Topolšici in Izoli.

Petletno relativno preživetje bolnikov s pljučnim rakom se je v 15 letih povečalo za 2,2 % (Slika 2), približno enako pri obeh spolih (Tabela 3). Relativno dobro je preživetje bolnikov z omejeno boleznijo ob diagnozi: v obdobju 1991–1995 je bilo 26 %, v zadnjem obdobju pa se je povečalo na 41 %. Večje je tudi petletno relativno preživetje bolnikov z razširjenim stadijem, medtem ko se preživetje bolnikov z razsejanim stadijem bistveno ne spreminja in je še vedno majhno (Slika 3). Napovedni dejavnik je tudi starost, saj je bilo petletno relativno preživetje bolnikov, ki so v letih 2001–2005 zboleli pred 50. letom starosti, 18 %, tistih, ki so zboleli stari 75 let in več, pa manjše od 5 % (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 12 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 33-odstotno petletno relativno preživetje.

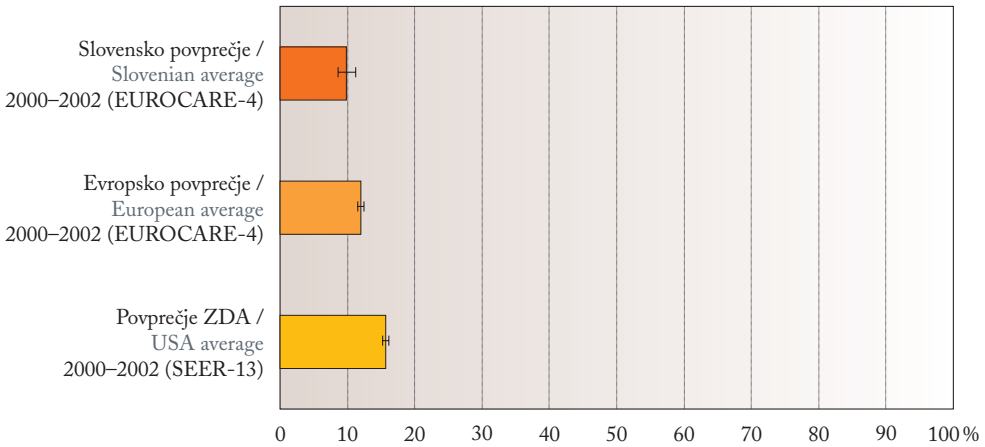
Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov s pljučnim rakom statistično značilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

Andrej Debeljak

Petletno relativno preživetje bolnikov s pljučnim rakom kaže rastoči trend, zamejitev raka je natančnejša, eksplorativnih torakotomij je manj. Izboljšanje preživetja ni posledica zgodnejšega odkrivanja bolezni, pač pa boljše diagnostične in terapevtske oskrbe bolnikov s pljučnim rakom v zadnjih desetletjih. Za obravnavo bolnikov s pljučnim rakom skrbijo timski konziliji po slovenskih smernicah.

Za prikaz tumorja, povečanih bezgavk in zasevkov v oddaljene organe se uporablja računalniška tomografija prsnih organov, glave in zgornjega trebuha. Vse pogostejša je tudi uporaba preiskav PET CT. Na osnovi slikovnih preiskav se pri bronhoskopiji uporablja bronhialna biopsija, bronhoskopska pljučna biopsija, vodena z rentgensko ali ultrazvočno presvetljavo. Bezgavke v mediastinumu so dostopne s pomočjo endobronhialne in ezofagealne ultrazvočne preiskave. Za bezgavke v lateralni loži aorto-pljučnega okna in ob aorti ascendens pa so še vedno potrebni kirurški diagnostični posegi: prednja mediastinotomija (hiloskopija), VATS ali torakotomija. VATS se uporablja pri neopredeljenih okroglih spremembah, ki bi lahko bile periferni pljučni rak. Kadar diagnostična bronhoskopija ni uspela potrditi diagnoze, se uporablja transtorakalna igelna biopsija, ne le z rentgensko ali ultrazvočno presvetljavo, temveč tudi z natančnejšo računalniško tomografijo.



Slika 5: *Petletno relativno preživetje bolnikov s pljučnim rakom (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of lung cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

In 15 years, the 5-year relative survival of patients with lung cancer increased by 2.2% (Figure 2), the rates being comparable in both genders (Table 3). The survival of patients with localized disease at diagnosis is relatively favorable: in the period 1991–1995 their rate was 26%, whereas in the last period it increased to 41%. A higher 5-year relative survival is also observed in patients with regional stage, while no significant improvement has been noted in those with disseminated disease, which still remains low (Figure 3). Age is a prognostic factor as well, since in the period 2001–2005, the 5-year relative survival of patients less than 50 years of age at diagnosis was 18%, while the rate in those aged 75 years or older was under 5% (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 12% (Figure 2); patients surviving the first year may expect to survive five years in 33%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of lung cancer patients in Slovenia is significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Andrej Debeljak

The 5-year relative survival of patients with lung cancer shows an increasing trend, staging of the disease is more accurate and there are fewer explorative thoracotomies performed. Rather than being a consequence of earlier diagnosis, the improved survival in the last decades is attributable to a better diagnostic and therapeutic approach to patients with lung cancer. Lung cancer patients are treated by multidisciplinary teams according to the national guidelines.

The primary tumor, enlarged lymph nodes and metastases to distant organs are imaged by means of computer tomography of the thoracic organs, head and upper abdomen. The use of PET and CT examinations is becoming more frequent too. Based on imaging methods, bronchoscopy is performed by means of bronchial biopsy and either X-ray- or US-guided bronchoscopic lung biopsy. Mediastinal lymph nodes are accessible by endobronchial and esophageal ultrasonography. However, surgical diagnostic procedures, such as anterior mediastinotomy (hiloscopy), VATS or thoracotomy, are still required for the examination of lymph nodes in the lateral part of the aortopulmonary window and along the ascending aorta. VATS is used in undefined round lesions, which might be interpreted as peripheral lung cancer. When diagnosis fails to

Slovenski kirurgi so v zadnjih letih uporabljali predvsem lobektomije, manj pulmektomije, raje rokavaste lobektomije. Izjemoma, ob slabi pljučni funkciji ali visoki starosti, so bile uporabljene omejene resekcije. Za pljučne resekcije so pričeli uporabljati tudi VATS. Ob vsaki resekciji so delali limfadenektomijo bezgavk v mediastinumu.

Radioterapija se uporablja vse bolj usmerjeno na tumor, zgodaj, v kombinaciji s kemoterapijo. Omejene tumorje, pri katerih kirurško zdravljenje ni bilo možno zaradi spremljajočih bolezni ali starosti, so radioterapevti zdravili z obsevanjem ali RFA pod nadzorom računalniške tomografije.

Največji premiki so se zgodili pri citostatskemu zdravljenju; vse bolj se različne načine zdravljenja kombinira. Citostatike dobivajo tudi bolniki z nižjimi stadiji. Uvajajo se novejši citostatiki: gemcitabin, docetaksel, pemetreksed ter tarčna zdravila, kot so zaviralci tirozin kinaze (npr. gefitinib, erlotinib) in zaviralci neoangiogeneze (npr. bevacizumab). Pri nedrobnoceličnem raku 3. in 4. stadija se je poleg najboljšega podpornega zdravljenja pričela uporabljati paliativna citostatska kemoterapija.

Vse večji poudarek se tudi v Sloveniji daje paliativnemu zdravljenju, ki omogoči bolnikom bolj kakovostno življenje. Pri centralnih tumorjih se uporablja simptomatsko odstranjevanje tumorskega tkiva iz bronhijev in vstavljanje stentov. Poleg protibolečinskega zdravljenja je vse pomembnejša skrb za bolnike na domu ob sodelovanju bolnika in svojcev pri procesu zdravljenja. Pri tem so pomembne pomoč patronažne službe, laična pomoč, psihološka podpora, pa tudi skrb za ustrezno prehrano.

Za ugotavljanje zgodnjih oblik pljučnega raka, pri katerih so uspehi zdravljenja boljši, bo v prihodnje treba pregledovati bolj ogrožene skupine prebivalstva s spiralno računalniško tomografijo z nizkim sevanjem.

VIRI
Literature

Debeljak A, Triller N, Kecelj P, Pompe-Kirn V, Rott T, Osolnik K, et al. Smernice za internistično obravnavo bolnika s pljučnim rakom. Uradno stališče Združenja pulmologov Slovenije, sprejeto na letni konferenci decembra 2001. Zdrav Vestn 2001; 70: 751–70.

Zwitter M, ed. Smernice za diagnostiko in zdravljenje bolnikov z rakom pljuč. Ljubljana: Onkološki inštitut Ljubljana; 2006.

KLINIČNI KOMENTAR
Janez Eržen

Dandanes se skoraj vsa klinična in znanstvenoraziskovalna poročila in dela, ki govorijo o pljučnem raku, začnejo z ugotovitvijo, da je to bolezen, zaradi katere po vsem svetu umira največ ljudi, posebno v razvitem delu. Zadnje desetletje na novo vsako leto zboli v Sloveniji za pljučnim rakom okrog 1000 ljudi, med njimi okrog 800 moških. Tudi pri nas, tako kot v razvitih zahodnih državah, se zbolevnost za pljučnim rakom veča pri ženskah hitreje kot pri moških. Število zbolelih žensk v zadnjem opazovanem obdobju se je v primerjavi s prvim skoraj podvojilo. Malo, le nekaj nad 10 % ljudi, ki zbolijo za pljučnim rakom, ne bo umrlo zaradi te bolezni. Na splošno velja, da je skupno petletno preživetje pri vseh epitelijskih malignih tumorjih okrog 50 % in da ima pljučni rak med vsemi najslabšo napoved izida. Pri približno polovici bolnikov, ki so bili radikalno operirani zaradi pljučnega raka, se namreč po dveh letih rak ponovi, le 10–14 % bolnikov s pljučnim rakom preživi pet let.

Preživetje bolnikov s pljučnim rakom se je zadnjih 40 let le malo povečalo. Preživetje je najbolj odvisno od stadija bolezni ob diagnozi in začetku zdravljenja. Bolniki, operirani na našem kliničnem oddelku s stadijem IA in IB, so imeli petletno preživetje 66 %, s stadijem IIA in IIB 37 %, s stadijem IIIA 22 % in s stadijem IIIB manj kot 10 %. Klinična ocena, na podlagi katere se odločamo o vrsti in načinu zdravljenja, je pogosto napačna, večkrat podcenjena kot obratno.

be confirmed by bronchoscopy, transthoracal needle biopsy guided not only by x-ray or US imaging but also by more accurate computer tomography is used.

In recent years, surgeons in Slovenia have been using prevailingly lobectomies while pulmectomies were used less frequently, preference being given to sleeve lobectomies. Exceptionally, in the case of poor pulmonary function or an advanced age, limited resections have been used. VATS for pulmonary resections started to be used too. Each resection included lymphadenectomy of the mediastinal lymph nodes.

Radiotherapy is increasingly more frequently targeted at the primary tumor, and used at an early stage in combination with chemotherapy. Where surgical treatment was not feasible due to concomitant diseases or an advanced age, localized tumors were treated by irradiation or CT-guided RFA.

The greatest advances were made in the area of treatment with cytotoxic drugs by combining different therapeutic modalities. Chemotherapy is also administered to the patients with earlier stages of the disease. New cytotoxic drugs are being introduced: gemcytabine, docetaxel, pemetrexed and target drugs such as tyrosine kinase inhibitors (e. g. gefitinib, erlotinib) and neoangiogenesis inhibitors (e. g. bevacizumab). In non-small cell cancer of stages III and IV, palliative chemotherapy has been used in addition to the best supportive therapy.

In Slovenia too, an increasingly important role is ascribed to palliative therapy, which can improve the quality of patients' life. In centrally situated tumors the treatment consists of symptomatic tumor tissue removal from the bronchi and stent placement. Besides pain-control therapy, care outside the hospital setting in cooperation with patients and their families is gaining in importance. In this respect, the assistance offered by community nursing care, lay caregivers, psychological support as well as care for an adequate diet are considered important.

In order to detect lung cancer at its early stages associated with a more favorable treatment outcome, in the future screening of high risk population should be carried out using low-dose spiral computer tomography.

CLINICAL COMMENTARY

Janez Eržen

Nowadays practically all clinical and scientific reports and articles on lung cancer start with the fact that lung cancer is a disease associated with the highest mortality rates worldwide, particularly in the developed parts. In the last decade, every year approximately a thousand people will be diagnosed with lung cancer in Slovenia, approximately 800 of these being males. As in other developed countries, in Slovenia the lung cancer incidence in females has been increasing more rapidly than in males too. In comparison with the first observation period, the number of women diagnosed in the last observation period is almost two-fold higher. Only few (slightly above 10%) people with lung cancer will not die of the disease. It is generally believed that overall 5-year survival rate in all epithelial malignomas is around 50%, among them lung cancer being the one with the worst prognosis. Thus, in approximately a half of the patients who have undergone radical surgery for lung cancer, the disease will recur within two years, and only 10–14% of them will survive five years.

In the last 40 years, the survival of patients with lung cancer has slightly increased. Survival largely depends on the stage of the disease at diagnosis and on the beginning of treatment. Patients with stage IA and IB treated at our department had a 66% 5-year survival rate, while those with stage IIA and IIB 37%, with stage IIIA 22% and with stage IIIB less than 10%. Clinical assessment, which serves as a basis for choosing the treatment modality, is often incorrect and underestimated rather than the opposite. The first weak link is the reliability of stage assessment, which is still considered to be the most reliable prognostic factor. There the possibility

Prva šibka točka je zanesljivost ocene stadija, ki še vedno velja za najzanesljivejši napovedni dejavnik. Pri tem je možnost napake večplastna. Prične se s podcenjenostjo kliničnega stadija, ker imajo vse klinične in slikovne preiskave (RTG, CT, UZ, MRI, PET, scintigrafija kosti itd.) omejeno zmogljivost občutljivosti, specifičnosti in natančnosti pri zamejevanju bolezni. Pri načrtovanju najbolj ustreznega zdravljenja bolnikov s pljučnim rakom upoštevamo določene klinično-patološke napovedne dejavnike, od katerih sta za zdaj najpomembnejša stadij bolezni in bolnikova zmogljivost, ki pa pri posameznem bolniku ne moreta zanesljivo napovedati poteka bolezni. Verjetnost zmote je velika in nastane pri tretjini bolnikov.

Možnosti za zmanjšanje umrljivosti zaradi pljučnega raka so zato omejene na optimalno zdravljenje, ki naj bo prilagojeno posameznemu bolniku. Ponovitev raka se mnogo pogosteje pokaže z oddaljenimi zasevki kot z lokalno širitvijo. Kljub temu ostaja znatno področje skritega, saj še vedno tretjina ali več bolnikov po radikalni operaciji z najugodnejšim stadijem IA umre v petih letih po operaciji.

VIRI
Literature

Black RJ, Bray F, Ferlay J, Parkin DJ. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997; 33: 1075–107.

Baldini EH, Strauss GM. Women and lung cancer. Waiting to exhale. Chest 1997; 112 Suppl 4: 229–3.

Gawrychowski J, Lackowska B, Gabriel A. Prognosis of the surgical treatment of patients with non-small cell lung cancer (NSCLC) – relation to DNA ploidy. Eur J Cardiothorac Surg 2003; 23: 870–77.

Litvinov SV, Velders MP, Bakker HA, Fleuren GJ, Warnaar SO. EpCAM: a human epithelial antigen is a homophilic cell-cell adhesion molecule. J Cell Biol 1994; 125: 437–46.

Pearson GF. Non-small cell lung cancer. Role of surgery for stages I–III. Chest 1999; 116 Suppl 6: 500–03.

Poleri C, Morero JL, Nieva B, Vazquez MF, Rodriguez C, de Titto E, et al. Risk of recurrence in patients with surgically resected stage I non-small cell lung carcinoma: histpathologic and immunohistochemical analysis. Chest 2003; 123: 1858–67.

Rice D, Kim HW, Sabichi A, Lippman S, Lee JJ, Williams B, et al. The risk of second primary tumors after resection of stage I non-small cell lung cancer. Anal Thorac Surg 2003; 76: 1001–8.

KLINIČNI KOMENTAR
Matjaž Zwitter

Pljučni rak spreminja svojo podobo. V sorazmerno kratkem obdobju petnajstih let vidimo strmo naraščanje incidence pljučnega raka pri ženskah, ki sledijo slabemu zgledu moških ne le pri kajenju, pač pa tudi pri boleznih, ki jih tobak pospešuje. Očiten je tudi izrazit porast deleža žlezne oblike pljučnega raka, pa hkrati upad ploščatoceličnega karcinoma, morda kot posledica kajenja »lahkih« cigaret, ki jih globlje inhaliramo. Tretja sprememba pa je premik na bolje pri preživetju: dobra dva odstotka več preživelih in to ne le v okviru posamezne bolnišnice, pač pa v okviru cele države. To, na prvi pogled skromno izboljšanje preživetja, je pomembno prav zaradi dejstva, da so v tej statistiki zajeti tudi mnogi bolniki v zelo šibkem splošnem stanju in s hudo napredovalo boleznijo, ki jim nismo mogli veliko pomagati niti pred petnajstimi leti in tudi danes ne. Pri bolnikih z zgodnjimi stadiji bolezni (predstavljeni kot omejen in razširjen stadij) pa je izboljšanje preživetja še bistveno večje.

Krivulje o boljšem preživetju bolnikov s pljučnim rakom so spodbuda, da smo na pravi poti. Podatki kažejo, da se stadiji bolezni niso spremenili. Boljše preživetje torej lahko pripišemo uspešnejšemu zdravljenju. Kirurgija ni več šablonska, pač pa prilagojena vsakemu posameznemu bolniku. Zdravljenje z obsevanjem je z novo opremo in novim znanjem bistveno natančnejše, z manj neželenimi sopojavi in z večjimi izgledi za lokalno ozdravitev tumorja. Slovenija se je tudi na tem področju v zadnjih letih približala mednarodnim standardom. Velik premik pa je tudi pri sistemskem zdravljenju, ki je danes osnovno zdravljenje ne le pri drobnoceličnem raku, pač pa tudi pri ostalih vrstah pljučnega raka.

Podatki o preživetju bolnikov s pljučnim rakom nam kažejo, kam naj v bodoče usmerimo svojo pozornost. V tem kratkem komentarju naj omenim štiri pomembne naloge. Prva izhaja iz

of error is multifold. It starts with the underestimation of clinical stage, since all the available clinical and imaging examinations (X-ray, CT, US, MRI, PET, bone scintigraphy, etc.) have limited sensitivity, specificity and accuracy with respect to their disease staging potential. In planning the most suitable treatment for lung cancer patients certain clinical-pathological prognostic factors are taken into account, among these stage of the disease and patient's performance status being the most important, although they are unable to predict reliably the course of disease in an individual patient. The possibility of error is considerable and occurs in one third of the patients.

Therefore, the possibilities for reducing mortality due to lung cancer are limited to an optimal treatment, which should be tailored to the individual patient. Rather than with local spread, cancer recurrence much more frequently presents itself with distant metastases. Nevertheless, a large area still remains obscure, since over a third of patients with the most favorable IA stage, having radical surgery, still die within five years from surgical treatment.

CLINICAL COMMENTARY

Matjaž Zwitter

Lung cancer is changing its features. In a relatively brief period of fifteen years we may witness a steep increase in the incidence of lung cancer in women, who follow the negative example of men not only in smoking habits but also in the diseases caused by tobacco. Furthermore, there is an obvious increase in the proportion of adenocarcinoma with a simultaneous decrease in planocellular carcinoma, possibly as a result of »light« cigarettes smoking associated with deeper inhalation. The third change is a shift towards better survival: there are over two more percents of survivors, and that not only at the level of an individual hospital but also at the level of the whole state. This, at a first glance modest improvement of survival, is important in view of the fact this statistics also includes a large number of patients with very poor general condition and highly advanced disease, whose prospects for treatment were rather limited fifteen years ago and are currently not much better either. In patients with early stages (localized and regionally advanced) the survival is even better.

The improved survival curves of lung cancer patients are encouraging and should be regarded as a proof that we are on the right way. The data show that stages of the disease have not changed. Therefore, better survival can be attributed to more effective treatment. Surgery, rather than being standardized, is tailored to every individual patient. Thanks to new equipment and advanced knowledge, radiotherapy has become significantly more accurate, with fewer adverse effects and better chances for a local tumor cure. In this area, Slovenia has approached the international standards in the recent years. A great advance has also been achieved in systemic therapy, which nowadays represents the basic treatment not only for small-cell carcinoma but also for other types of lung cancer.

The data on lung cancer patients' survival point out, where to concentrate our future activities. In this brief comment, let me point out four important tasks. The first results from the finding that stage distribution is changing: the proportion of patients with an early, operable lung cancer is not increasing but rather the opposite. A more favorable stage distribution will not happen *per se*. Instead, we need a systematic approach to early lung cancer detection in high risk groups, such as e. g. those with cured head and neck cancers, along with the committed work of all those that can help to reduce the presently intolerable long interval from first symptoms to diagnosis of lung cancer. The second task would be to implement the advances in lung cancer treatment at the national level. Although this publication does not present the survival curves for individual regions of Slovenia, a detailed review of the data from the Cancer Registry of Slovenia reveals that the north-eastern Slovenia is lagging behind, the survival of patients in this region in the past decade being no better than in the 90's. This should not be understood as a criticism but rather as an encouragement for a detailed analysis and development

opažanja, da se ne spreminja razporeditev po stadijih: delež bolnikov z zgodnjim, operabilnim pljučnim rakom se ne veča, prej nasprotno. Ugodnejša razporeditev po stadijih ne bo prišla sama od sebe. Potrebujemo torej sistematičen pristop pri zgodnjem odkrivanju pljučnega raka pri zelo ogroženih skupinah bolnikov, na primer tistih z ozdravljenim rakom glave in vratu, ter resno delo vseh, ki lahko prispevajo k skrajšanju danes nedopustno dolgega intervala med prvimi simptomi in diagnozo pljučnega raka. Druga naloga je, da napredek pri zdravljenju pljučnega raka prenesemo na vso državo. Ta knjiga sicer ne prinaša krivulj preživetja po posameznih regijah Slovenije, podroben pregled podatkov RRS pa nam razkrije, da severovzhodna Slovenija zaostaja in da je preživetje pri njih v zadnjem desetletju enako slabo kot v devetdesetih letih. To naj ne bo kritika, pač pa spodbuda k natančni analizi in oblikovanju smernic za bodoče delo. Tretja naloga izhaja iz zaskrbljujočega poslabšanja preživetja pri starejših bolnikih. Je morda res, da več starejšim bolnikom v šibkem splošnem stanju, ki bi poprej ostali brez natančne opredelitve narave njihove bolezni, postavimo pravo diagnozo? So ti bolniki zapostavljeni v diagnostiki in zdravljenju, ali pa so morda zdravljeni preveč agresivno? Tudi tu bo potrebna natančna analiza, ki naj pokaže na vzrok in hkrati ponudi navodila za bodoče delo. Četrta zelo pomembna naloga pa je, da vztrajamo pri zastavljeni protikadilski politiki, ki že kaže uspehe pri moških, potrebno pa jo bo nadgraditi za populacijo žensk in mladih.

VIRI
Literature

Zielinski C, Zwitter M. Consensus on medical treatment of non-small-cell lung cancer – update 2004. Lung cancer 2005; 50: 129–37.

Zwitter M, Kovač V, Smrdel U, Strojan P. Gemcitabine, cisplatin and hyperfractionated accelerated radiotherapy for locally advanced non-small cell lung cancer. J Thorac Oncol 2006; 1: 662–6.

Zwitter M. Nove podobe pljučnega raka. Onkologija 2000; 4: 69–73.

Zwitter M. Comments on treatment strategy for locally advanced non-small cell lung cancer. Lung cancer 2002; 38: S33–5.

Zwitter M, Čufer T, Wein W. Gemcitabine and vincristine: an effective outpatient regimen with low myelotoxicity for stage IV non-smallcell lung cancer. Neoplasma 2001; 48: 200–2.

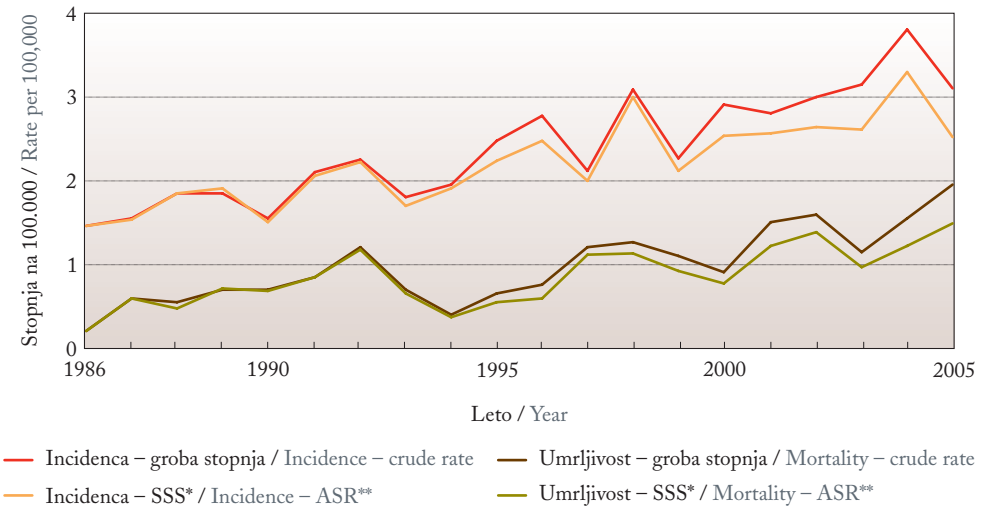
of guidelines for future work. The third task relates to worse survival of the elderly patients. Could it be that more elderly patients with poor general condition, who would previously be left without exact assessment of the nature of their disease, are nowadays diagnosed correctly? Are those patients deprivileged in terms of diagnosis and treatment or are they perhaps treated too aggressively? This calls for a detailed analysis that should point out the true reasons, at the same time providing guidelines for work in the future. Last but not least, the fourth task is to stick with the set anti-smoking policy, which has already yielded positive results in males and needs to be upgraded for the population of females and youth.

MEHKA TKIVA

MKB 10: C38.0, C47–C49

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za malignimi tumorji mehkih tkiv zbolelo 816 ljudi, od tega 384 moških in 432 žensk. Kot je razvidno s Slike 1, se tako grobe kot starostno standardizirane incidenčne in umrljivostne stopnje od leta 1991 večajo. Groba incidenčna stopnja se veča povprečno za 4,0 % letno, groba umrljivostna stopnja pa povprečno za 6,7 % letno. Rast obeh starostno standardiziranih mer je nekoliko manjša: starostno standardizirana incidenca se veča za 2,8 %, umrljivost pa za 5,2 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka mehkih tkiv, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of soft tissue cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 725 primerov; 17 primerov (2,1 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 74 mlajših od 20 let pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. V obdobju 2001–2005 sta 2 od 302 bolnikov imela malignom osrčnika, 5 % je imelo malignom perifernih živcev in avtonomnega živčevja, 29 % malignom potrebušnice ali retroperitoneja, 66 % pa malignom vezivnega in mehkega tkiva na raznih telesnih mestih, največ (46 %) na spodnjem udu (vključno s kolkom).

V zadnjem obdobju je bilo mikroskopsko potrjenih 98 % primerov. Delež mikroskopsko potrjenih primerov je približno enak v vseh obdobjih opazovanja. Daleč največjo histološko skupino

Tabela 1: *Število bolnikov z rakom mehkih tkiv po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of soft tissue cancer patients by sex and period of diagnosis with their proportions by age.*

Obdobje / Period	Moški / Males				Ženske / Females			
	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	88	38,6	50,0	11,4	102	27,5	59,8	12,7
1996–2000	102	46,1	42,2	11,8	131	29,8	49,6	20,6
2001–2005	148	33,1	53,4	13,5	154	26,6	51,9	21,4

SOFT TISSUE

ICD 10: C38.0, C47–C49

EPIDEMIOLOGY

In the period 1991–2005, a total of 816 persons were diagnosed with malignant soft tissue tumors, of these 384 males and 432 females. As evident from Figure 1, since 1991 crude as well as age-standardized incidence and mortality rates have been increasing. Thus crude incidence rate has been increasing by 4.0% and crude mortality rate by 6.7% annually on average. The increase in both age-standardized rates is lower: age-standardized incidence rate is increasing by 2.8% and mortality rate by 5.2% annually on average.

The survival analysis included 725 cases; 17 cases (2.1%) diagnosed only after death, were not considered in the analysis; 74 patients under 20 years of age are presented in the chapter on the survival of children and adolescents. In the period 2001–2005, 2 of 302 patients had malignoma of the pericardium, 5% had malignoma of the peripheral nerves and autonomous nerves, 29% malignomas of the peritoneum or the retroperitoneum while 66% had malignomas of the connective and soft tissue in different parts of the body, most frequently (46%) in the lower limb (including the hip).

In the last period, 98% of cancers were microscopically verified. The proportion of microscopically confirmed cases was basically the same throughout the observation period. Sarcomas represent by far the largest histological group of soft tissue tumors (78% of all soft tissue tumors), germ-cell tumors represent 6% while carcinomas and nerve sheath tumors are represented by 5% each. Other defined histological types represented less than 2% of cases, while in 3% of tumors histological type was not precisely defined. Approximately one fourth of sarcomas were leiomyosarcomas, 20% liposarcomas, 16% fibrohistiocytic sarcomas, 8% synovial sarcomas and 7% fibrosarcomas; 17% of all sarcomas remained undefined. The proportions of all defined sarcomas, except for fibrohistocytic ones, have been increasing with time while the proportion of undefined sarcomas and other soft tissue tumors exhibits a downward trend.

More than half of patients are diagnosed at an age between 50 and 74 years, approximately one third are under 50 years of age, and the rest are aged 75 years or older (Table 1). The proportion of the oldest patients has been increasing all the time, mainly on the account of a smaller proportion of patients younger than 50 years.

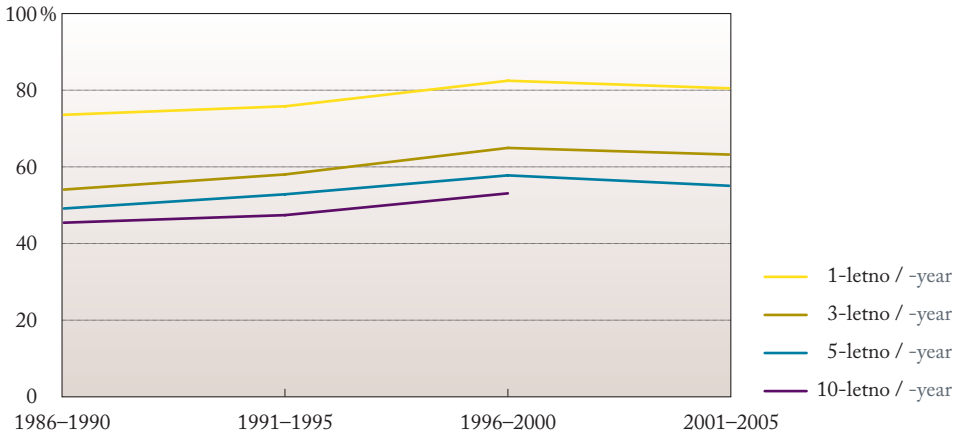
In the period 2001–2005, almost half of the patients had disease diagnosed at a regional stage (Table 2). Along with the increasing proportion of regional disease, the proportion of localized disease has been decreasing throughout the observation period. In the last period, only one third of patients were diagnosed with localized disease; particularly in males, the percentage of patients with unknown stage is very high (10%).

In the period 2001–2005, 7% of patients did not receive specific treatment. The proportion of untreated patients has not changed significantly throughout the observation period. In the

Tabela 2: *Število bolnikov z rakom mehkih tkiv po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of soft tissue cancer patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	88	46,6	33,0	12,5	8,0	102	55,9	24,5	14,7	4,9
1996–2000	102	48,0	36,3	10,8	4,9	131	48,1	35,9	11,5	4,6
2001–2005	148	33,8	42,6	14,2	9,5	154	35,1	46,1	16,9	1,9



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom mehkih tkiv po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of soft tissue cancer patients by period of diagnosis.*

med tumorji mehkih tkiv predstavljajo sarkomi (78 % vseh tumorjev mehkih tkiv), 6 % je tumorjev kličnih celic, po 5 % pa karcinomov in tumorjev živčnih ovojnic. Drugih opredeljenih histoloških vrst je bilo 2 %, 3 % tumorjev pa ni imelo natančno opredeljene histološke vrste. Med sarkomi jih je približno četrtina leiomiosarkomov, 20 % liposarkomov, 16 % fibrohistocitnih sarkomov, 8 % sinovijskih sarkomov in 7 % fibrosarkomov. Neopredeljenih je bilo 17 % med vsemi sarkomi. Deleži vseh opredeljenih sarkomov z izjemo fibrohistocitnih se z leti povečujejo, zmanjšuje pa se delež neopredeljenih sarkomov in delež drugih tumorjev mehkih tkiv.

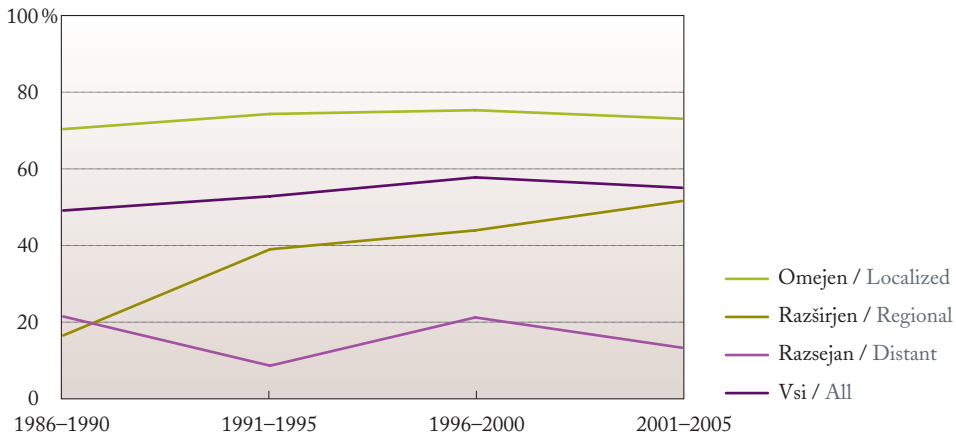
Več kot polovica bolnikov je ob diagnozi stara od 50 do 74 let, približno tretjina je mlajših od 50 let, ostali pa so stari 75 let in več (Tabela 1). Delež najstarejših se ves čas veča, večinoma na račun manjšega deleža bolnikov, mlajših od 50 let.

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom mehkih tkiv po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of soft tissue cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	72,7 (64,0–82,7)	48,9 (39,5–60,5)	44,3 (35,1–56,0)	74,5 (66,5–83,5)	56,9 (48,0–67,3)	47,1 (38,3–57,8)
1996–2000	76,5 (68,7–85,2)	57,8 (49,0–68,3)	51,0 (42,1–61,7)	83,2 (77,0–89,9)	61,8 (54,0–70,7)	50,4 (42,5–59,7)
2001–2005	79,1 (72,8–85,9)	57,7 (50,2–66,3)	49,3 (41,3–58,9)	77,9 (71,6–84,8)	58,6 (51,3–67,0)	46,0 (37,8–55,9)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	75,3 (65,0–85,6)	53,6 (40,8–66,4)	52,5 (38,6–66,3)	76,3 (67,2–85,5)	60,6 (49,5–71,8)	53,0 (40,9–65,1)
1996–2000	78,5 (69,6–87,5)	62,6 (51,4–73,9)	58,3 (46,1–70,5)	85,4 (78,5–92,2)	66,7 (57,1–76,3)	57,3 (46,7–68,0)
2001–2005	81,6 (74,5–88,6)	63,5 (54,0–72,9)	58,3 (47,0–69,6)	79,6 (72,6–86,6)	62,7 (53,7–71,7)	51,8 (40,6–63,0)

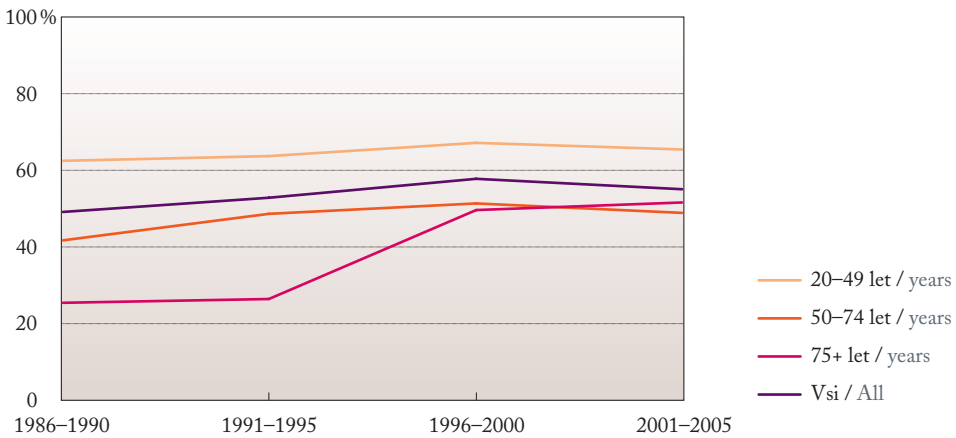


Slika 3: *Petletno relativno preživetje bolnikov z rakom mehkih tkiv po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of soft tissue cancer patients by stage and period of diagnosis.*

period 2001–2005, 93% of patients with specific treatment underwent surgery. In over a half of them this was the only treatment modality, 19% were also irradiated, and 16% received chemotherapy in addition to surgery while 11% were treated by surgery, irradiation and chemotherapy. In comparison with the earlier periods, the proportion of patients treated by chemotherapy and the proportion of those treated by surgery alone have been increasing.

In the period 2001–2005, almost a half of patients started their treatment at the IO Ljubljana, 17% in the UMC Ljubljana and 10% in the UMC Maribor. Individual patients started their treatment in nine Slovenian general hospitals. Practically all patients (92%), irrespective of the hospital of their initial treatment, were in the course of their primary treatment referred to the IO Ljubljana.

Compared to the first period (1991–1995), in the last one the survival of patients with soft tissue malignomas has actually increased; in 15 years, the 5-year relative survival increased by 2% (Figure 2); while in males it increased by 6%, in females the survival rate in the last period slightly decreased (Table 3). The relevance of stage at diagnosis is shown in Figure 3. The



Slika 4: *Petletno relativno preživetje bolnikov z rakom mehkih tkiv po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of soft tissue cancer patients by age and period of diagnosis.*

V obdobju 2001–2005 je bila pri skoraj polovici bolnikov bolezen odkrita v razširjenem stadiju (Tabela 2). Z večanjem deleža razširjene bolezni se ves čas opazovanja manjša delež bolnikov z boleznijo, odkrito v omejenem stadiju. V zadnjem obdobju je bila le še tretjina bolnikov odkritih z omejeno boleznijo; predvsem pri moških pa je velik odstotek bolnikov brez opredeljenega stadija ob diagnozi (10 %).

V obdobju 2001–2005 ni bilo specifično zdravljenih 7 % bolnikov. Delež nezdravljenih bolnikov se skozi vse obdobje analize ni bistveno spreminjal. Med specifično zdravljenimi je bilo v letih 2001–2005 93 % bolnikov operiranih. Pri dobri polovici je bil to edini način zdravljenja, 19 % je bilo še obsevanih, 16 % pa je poleg operacije prejelo še kemoterapijo; 11 % je bilo zdravljenih z operacijo, obsevanjem in kemoterapijo. V primerjavi z začetnimi obdobji se veča delež bolnikov, ki so prejeli kemoterapijo, in delež tistih, ki so bili samo operirani.

Skoraj polovica bolnikov je v obdobju 2001–2005 začela z zdravljenem na OI Ljubljana, 17 % v UKC Ljubljana ter 10 % v UKC Maribor. Posamezne bolnike so pričeli zdraviti še v devetih slovenskih splošnih bolnišnicah. Skoraj vsi bolniki (92 %), ne glede na bolnišnico pričetka zdravljenja, pa so bili v okviru prvega zdravljenja obravnavani na OI Ljubljana.

Relativno preživetje bolnikov z rakom mehkih tkiv se je v zadnjem obdobju v primerjavi s prvim (1991–1995) nekoliko povečalo; v 15 letih se je petletno relativno preživetje povečalo za 2 % (Slika 2), pri moških se je povečalo za 6 %, pri ženskah pa se je v zadnjem obdobju celo nekoliko zmanjšalo (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je ves čas opazovanja približno 75 %. Preživetje bolnikov z razširjenim stadijem se z leti veča; zboleli v letih 2001–2005 so imeli petletno relativno preživetje 52 %. Bolniki z razsejanim stadijem ob diagnozi imajo 13-odstotno petletno relativno preživetje. Napovedni dejavnik je tudi starost, saj imajo mlajši od 50 let za približno 15 % večje preživetje od bolnikov, ki zbolijo po 50. letu starosti (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 55 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 68-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov s tumorji mehkih tkiv statistično neznačilno večje od evropskega povprečja (Slika 5).

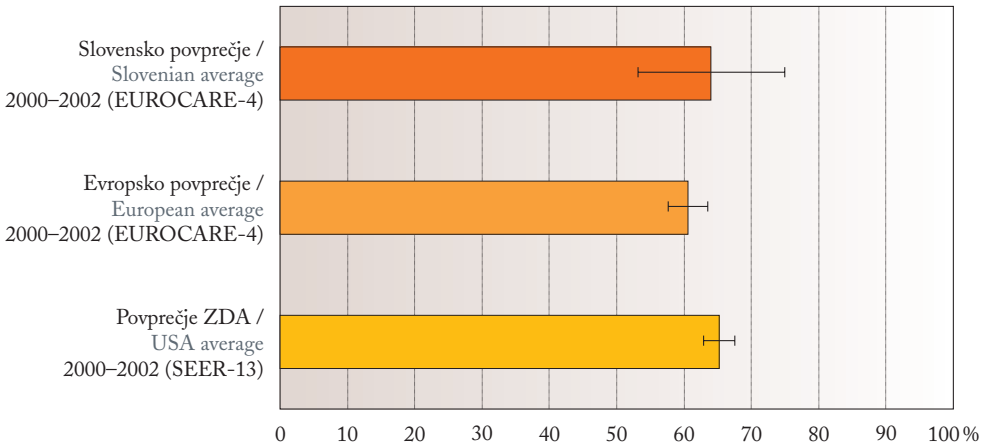
KLINIČNI KOMENTAR

Branko Zakotnik

Večina malignomov mehkih tkiv (83 %) so sarkomi. Ker so ostali malignomi v tej skupini redki, princip njihovega zdravljenja pa drugačen kot pri sarkomih, omejujem svoj komentar le na sarkome.

Incidenca sarkomov mehkih tkiv se je v 20 letih povečala (Slika 1), vendar je to kljub temu še vedno redka bolezen, saj lahko pričakujemo, da bo letno zbolelo 70 do 80 bolnikov. Smiselno bi torej bilo, da bi se ti bolniki pričeli zdraviti v Sloveniji na enem mestu, kjer so na razpolago vse moderne diagnostične možnosti (CT, MRI), usposobljeni citolog in patolog, onkološki kirurg, radioterapevt in internist onkolog, ki kot člani multidisciplinarnega konzilija načrtujejo in izvedejo prvo zdravljenje pri tej redki bolezni. Takšna so vsa mednarodna in slovenska priporočila. Podatki pa kažejo, da se je odstotek bolnikov, ki so prvič obravnavani na OI Ljubljana, ki je edina ustanova, ki ima trenutno zagotovljene primerne pogoje za kakovostno zdravljenje, zmanjšal s 50 % v obdobju 1991–1995 na 47 % v obdobju 2001–2005. Pričakovali bi, da se bo, glede na objavljena priporočila, ta odstotek večal.

Razloga za povečevanje incidence ni moč ugotoviti. Vsekakor ne gre na račun staranja prebivalstva, saj je razlika med grobo in starostno standardizirano incidenčno stopnjo minimalna. Morda gre na račun boljše dostopnosti do diagnostičnih možnosti v Sloveniji (UZ, CT, MRI)



Slika 5: *Petletno relativno preživetje bolnikov z rakom mehkih tkiv (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of soft tissue cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

5-year relative survival of patients with localized stage has been approximately 75% throughout the observation period. The survival of patients with regional disease has been increasing with time, in those diagnosed between the years 2001–2005, 5-year relative survival rate was 52%. Patients with disseminated disease at diagnosis have 13% 5-year relative survival. Age is a prognostic factor as well, since patients younger than 50 years have around 15% higher survival than those diagnosed after 50 years of age (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 55% (Figure 2); patients surviving the first year may expect to survive five years in 68%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of patients with soft tissue tumors in Slovenia is above (statistically not significant) the European average (Figure 5).

CLINICAL COMMENTARY

Branko Zakotnik

Sarcomas (including nerve sheath tumors) represent the majority of soft tissue malignancies (83%). Other malignomas in this group are rare and the approach to their treatment is different than in sarcomas, therefore my comment is limited only to sarcomas.

In 20 years, the incidence of soft tissue sarcomas has increased (Figure 1), however the disease is still rare since it may be expected that 70 to 80 patients will be diagnosed with it annually. Therefore, it would be reasonable that these patients would start their treatment in Slovenia in one and the same place, where all the up-to-date diagnostic facilities (CT, MR), skilled cytologists and pathologists, oncological surgeons, radiotherapists and medical oncologists are available; the latter, as members of a multidisciplinary team, plan and carry out the primary treatment in this rare disease. This is consistent with all international and national recommendations. The data however show that the proportion of patients initially treated at the IO Ljubljana, which is the only institution with suitable conditions for quality treatment, has decreased from 50% in the period 1991–1995 to 47% in the period 2001–2005. Considering the published recommendations, it would be expected that this percentage should be increasing.

in/ali zaradi vpliva karcinogenov okolja. Vendar bi glede na majhno število bolnikov, ki letno zboli v Sloveniji, te vplive pri naših bolnikih težko raziskali.

Kako si lahko razlagamo, da ugotovimo vedno več bolnikov z razširjeno boleznijo, medtem ko ostaja petletno relativno preživetje enako dobro v primerjavi z evropskimi državami, celo nad evropskim povprečjem? Z leti ugotavljamo manj bolnikov z omejenim stadijem in več z razširjenim (Tabela 2). Na določitev stadija najbolj vpliva dostopnost sodobnejše natančnejše diagnostike (CT, MRI), ki se je v Sloveniji v zadnjem obdobju izboljšala in s katero ugotavljamo selitev stadija navzgor. Z natančnejšo diagnostiko pa sta lahko boljša tudi načrtovanje zdravljenja in s tem njegov izid. Na račun obeh teh dejavnikov smo pri bolnikih z razširjenim stadijem dosegli statistično pomembno povečanje relativnega preživetja s 17 % v obdobju 1986–1990 na 52 % v obdobju 2001–2005. Pri omejenem stadiju ostaja petletno relativno preživetje ves čas opazovanja enako, večje od 70 % (Slika 2). Na osnovi tega je težko zanesljivo ugotoviti, ali gre samo za selitev stadija navzgor na račun boljše diagnostike ali pa dejansko bolniki pridejo do sicer bolje načrtovanega zdravljenja, vendar kasneje, v bolj napredovalem stadiju.

Kljub vsem priporočilom, da je pri malignomih mehkih tkiv najpomembnejše prvo zdravljenje v primerno usposobljenem centru z odločitvami glede zdravljenja na multidisciplinarnem konziliju, prvo zdravljenje na OI Ljubljana prične le polovica bolnikov. Poleg te polovice bolnikov zdravimo (s ponovno operacijo in/ali obsevanjem in/ali kemoterapijo) tudi tiste, pri katerih so prvo zdravljenje opravili drugje, a ni bilo opravljeno po smernicah za zdravljenje tumorjev mehkih tkiv. Ker je za končni izid najpomembnejše pravilno prvo zdravljenje, bi lahko slovenske rezultate zdravljenja bolnikov s tumorji mehkih tkiv še izboljšali, če bi zdravljenje izvajali pri večini bolnikov v skladu z mednarodnimi in slovenskimi smernicami za zdravljenje sarkomov mehkih tkiv.

VIRI
Literature

Brennan M, Singer S, Maki R, O'Sullivan B. Sarcomas of the soft tissues and bone. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005: 1581–631.

Casali PG, Jost L, Sleijfer S, Verweij J, Blay JY. Soft tissue sarcomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology 2008; 19 Suppl 2: ii89–ii93.

Eržen D. Pomen prvega kirurškega posega pri bolnikih s sarkomi. Onkologija 2007; 1: 49–52.

Eržen D, Novak J, Spiler M, Senčar M. Aggressive surgical treatment of retroperitoneal sarcoma: long-term experience of a single institution. Surg Technol Int 2007; 16: 97–106.

Nacional Cancer Institute: Adult Soft Tissue Sarcoma Treatment. Dosegljivo na: http://www.cancer.gov/cancertopics/pdq/treatment/adult-soft-tissue-sarcoma/HealthProfessional/.

Novak J. Kirurgija malignih tumorjev mehkih tkiv. In: Smrkolj V, ed. Kirurgija. Ljubljana: Sledi; 1995: 500–8.

Onkološki Inštitut Ljubljana. Smernice za zdravljenje sarkomov, RSK za onkologijo, 2008.

The exact reason for an increase in the incidence is not known, but it is certainly not attributable to population ageing, as the difference between the crude and age-standardized incidence rates is minimal. Perhaps it could also be attributed to a better accessibility of diagnostic facilities in Slovenia (US, CT, MR) and/or due to the influence of environmental carcinogens. However, considering the small number of patients diagnosed in Slovenia annually, it would be difficult to investigate these influences in our patients.

How can we explain that ever more patients are diagnosed with regional disease, while the 5-year relative survival remains just as good in comparison with other European countries, in fact even above the European average? Recently, we find fewer patients with localized stage and more with regionally advanced disease (Table 2). Staging is mainly influenced by the accessibility of modern and more accurate diagnostic procedures (CT, MRI), that is followed by an upward stage migration; in the last period, these diagnostic options have improved in Slovenia. More accurate diagnosis can further improve treatment planning and thus also the outcome of treatment. Both these factors contributed to a statistically significant increase in the relative survival of patients with regional stage, from 17% in the period 1986–1990 to 52% in the period 2001–2005. Five-year relative survival in localized stage has remained the same throughout the observation period and exceeds 70% (Figure 2). Based on the above data it is difficult to establish with certainty whether the upward stage migration results from better diagnosis or the patients are diagnosed with more advanced stage, but receive better treatment.

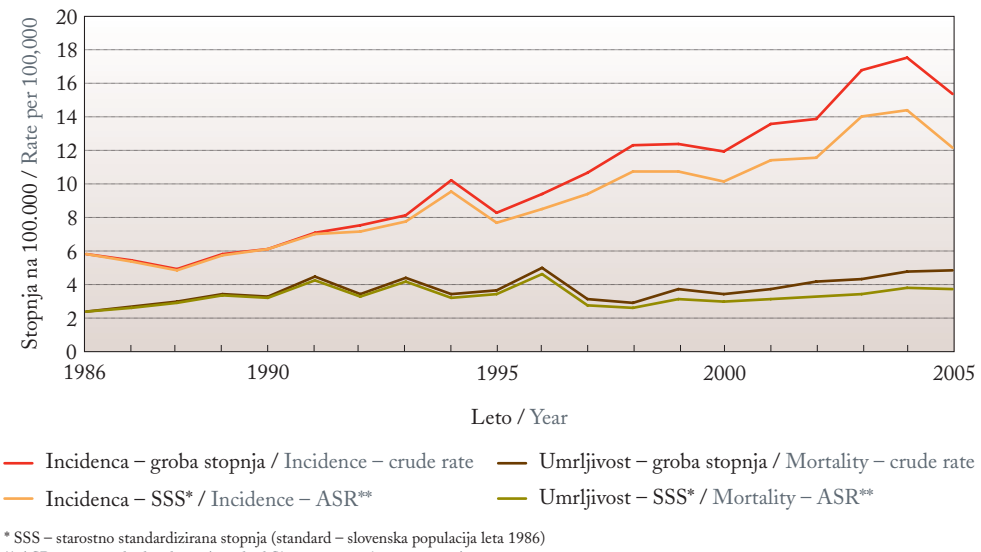
Despite all the recommendations claiming that in soft tissue malignomas it is of essential importance that patients start their primary treatment in an adequately equipped center, where the decision about treatment is accepted by a multidisciplinary team counsel, only half of the patients start their treatment at the IO Ljubljana. Apart from this half of the patients, at IO Ljubljana we perform also reoperations and/or irradiation and/or chemotherapy in those who had their primary treatment started elsewhere, however, not in accordance with the guidelines for soft tissue tumor treatment. Since the final outcome crucially depends on the correct choice of primary treatment, the results of soft tissue tumor treatment in Slovenia could be further improved by treatment of the majority of patients according to the international and national guidelines for the treatment of soft tissue sarcomas.

KOŽA, MELANOM

MKB 10: C43

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za kožnim melanomom zbolelo 3508 ljudi, od tega 1608 moških in 1900 žensk. Kot je razvidno s Slike 1, se časovna trenda grobe in starostno standardizirane incidenčne stopnje od leta 1991 večata, groba stopnja se veča bolj od standardizirane, povprečno za 6,4 % letno. Umrljivostni stopnji se med letoma 1991 in 2005 nista bistveno spreminjali.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja malignega melanoma, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of malignant melanoma, Slovenia 1986–2005.*

V analizo preživetja je vključenih 3463 primerov; 20 bolnikov (0,6 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 25 mlajših od 20 let pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. V obdobju 2001–2005 so vsi primeri (1526) imeli opredeljen del telesa, kjer je melanom nastal: pri moških najpogosteje na trupu (58 %), sledili so zgornji ud (13 %), spodnji ud (12 %), lobanja (7 %) in obraz (6 %), na vseh drugih mestih je bilo 4 % melanomov. Pri ženskah je melanom najpogosteje nastal na koži spodnjega uda (33 %), sledili so trup (29 %), zgornji ud (18 %), obraz (11 %), koža lobanje (4 %); na vse drugih mestih jih je bilo 4 %.

Tabela 1: *Število bolnikov z malignim melanomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of malignant melanoma patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	360	36,4	52,2	11,4	459	39,9	49,2	10,9
1996–2000	527	34,9	54,3	10,8	591	35,2	49,1	15,7
2001–2005	704	28,6	58,7	12,8	822	34,1	45,9	20,1

SKIN, MELANOMA

MKB 10: C43

EPIDEMIOLOGY

In the period 1991–2005, a total of 3508 persons were diagnosed with skin melanoma, of these 1608 males and 1900 females. As evident from Figure 1, since 1991 the crude and age standardized incidence rates have been increasing, the crude rate more than the age-standardized one, by 6.4% annually on average. In the years 1991–2005, both mortality rates did not change much.

The survival analysis included 3463 cases; 20 patients (0.6%) diagnosed only after death, were not considered in the analysis, 25 patients under 20 years of age are presented in the chapter on the survival of children and adolescents. In the period 2001–2005, the site of melanoma origin was determined in all cases (1526): in males the most frequent site was the trunk (58), followed by upper limbs (13%) lower limbs (12%), skull (7%) and face (6%); other sites were found in 4% of cases. In females, the most frequent site was skin of the lower limb (33%), followed by the skin of trunk (29%), upper limb (18%), face (11%), skin of the skull (4%); all other sites represented 4% of cases.

Tumors of all patients included in the analysis were microscopically confirmed; in the first two periods, in almost a half of the cases histological type was not exactly defined, in the last period in 32% (494 cases); among the defined ones (1032), 44% were superficially growing melanomas and 33% nodular melanomas, 6% melanomas of lentigo maligna type and 2% acral lentiginous melanomas; all other histological types represented 15%.

Approximately half of patients are diagnosed at an age between 50–74 years, a majority of the remaining ones before 50 years of age, while less than 20% of patients are aged 75 years or older at the time of diagnosis (Table 1). Except for the greater proportion of females in the oldest age group, the proportions of patients in individual age groups did not change significantly with time.

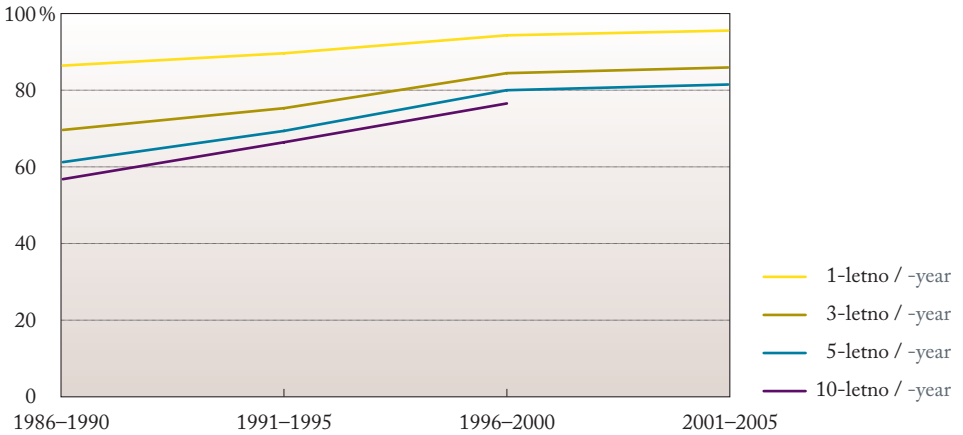
In all three time-periods, the majority of patients were diagnosed with localized disease; in the period 2001–2005 there were 76% such male and 81% female patients. The proportions of individual stages did not change significantly with time (Table 2). According to the simplified staging used by cancer registries and thus also by the CRS, the category of localized melanoma already includes tumors which have different prognosis with respect to the depth of invasion, tumor thickness and possible ulceration. The data collected by the CRS also include information on the depth of invasion by Clark, and on tumor thickness by Breslow. In 15 years, the average tumor thickness has decreased from 3.37 mm in the years 1991–1995 (measured in 73% cases, i. e. in 599 of 819 cases) to 2.59 mm (thickness determined in 90% of cases, i. e. in 1370 of 1526 cases).

In the years 2001–2005, 1.3% of patients did not receive specific treatment. The proportion of untreated patients was gradually decreasing throughout the time of analysis; among those

Tabela 2: *Število bolnikov z malignim melanomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of malignant melanoma patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	360	74,2	17,8	4,7	3,3	459	79,5	12,4	3,9	4,1
1996–2000	527	79,7	15,0	3,2	2,1	591	81,4	14,2	2,9	1,5
2001–2005	704	76,3	16,5	4,3	3,0	822	80,5	13,3	3,0	3,2



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z malignim melanomom po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of malignant melanoma patients by period of diagnosis.*

Vsi tumorji bolnikov, vključenih v analizo, so bili mikroskopsko potrjeni; v prvih dveh obdobjih pri skoraj polovici histološka vrsta ni bila natančneje opredeljena, v zadnjem pri 32 % (494); med opredeljenimi (1032) je bilo 44 % površinsko rastočih melanomov in 33 % nodularnih melanomov, 6 % melanomov lentigo maligna in 2 % akralnih lentigioznih melanomov; vseh ostalih histoloških vrst je bilo 15 %.

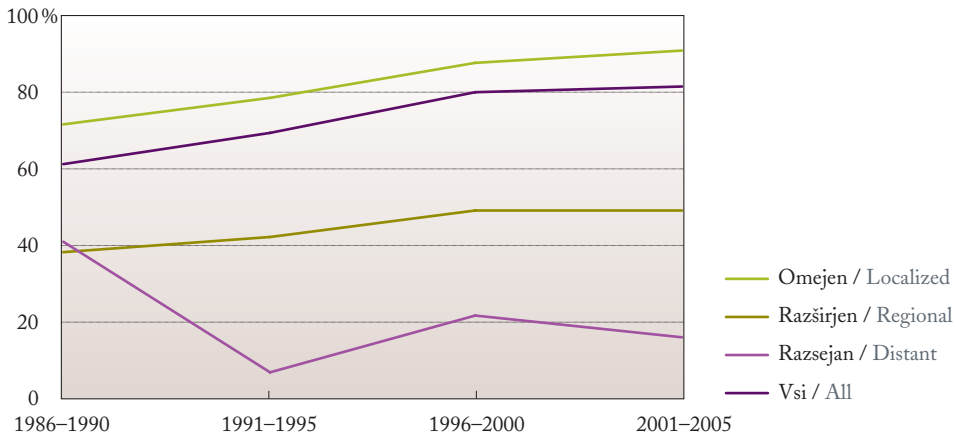
Približno polovica bolnikov zboli v starosti 50–74 let, večina ostalih do 50. leta, manj kot 20 % bolnikov pa je ob postavitvi diagnoze starih 75 let in več (Tabela 1). Razen večjega deleža najstarejših žensk, se deleži v posameznih starostnih skupinah s časom niso bistveno spreminjali.

Tabela 3: *Opazovano in relativno preživetje bolnikov z malignim melanomom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of malignant melanoma patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	83,6 (79,9–87,5)	63,3 (58,5–68,5)	54,7 (49,8–60,1)	90,4 (87,8–93,1)	75,4 (71,5–79,4)	66,9 (62,7–71,3)
1996–2000	91,8 (89,5–94,2)	75,5 (71,9–79,3)	65,5 (61,5–69,7)	92,2 (90,1–94,4)	81,0 (78,0–84,3)	74,8 (71,4–78,4)
2001–2005	91,6 (89,6–93,7)	77,3 (74,2–80,5)	67,0 (63,2–70,9)	94,3 (92,7–95,9)	80,8 (78,1–83,6)	74,0 (70,8–77,4)

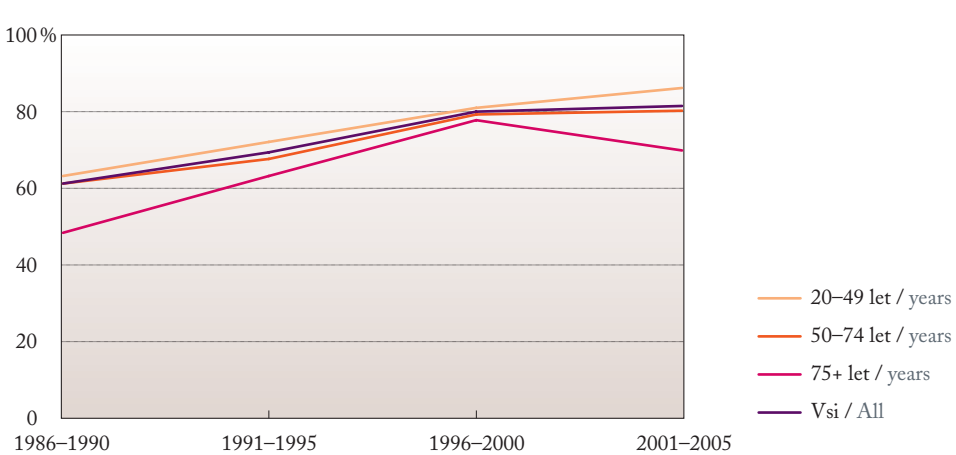
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	86,1 (82,1–90,1)	69,4 (63,7–75,0)	63,8 (57,5–70,1)	92,1 (89,3–94,9)	79,7 (75,4–84,0)	73,3 (68,4–78,2)
1996–2000	94,5 (92,0–96,9)	82,4 (78,3–86,5)	75,9 (71,1–80,8)	94,2 (92,0–96,4)	86,3 (82,9–89,8)	83,3 (79,3–87,3)
2001–2005	94,6 (92,5–96,7)	85,2 (81,7–88,7)	79,2 (74,5–83,9)	96,4 (94,7–98,0)	86,5 (83,6–89,5)	83,2 (79,4–87,0)



Slika 3: *Petletno relativno preživetje bolnikov z malignim melanomom po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of malignant melanoma patients by stage and period of diagnosis.*

diagnosed in the period 1991–1995 there were 2.4% of patients without specific treatment. Almost all patients among the specifically treated in the period 2001–2005 underwent surgery; only 7 patients with highly advanced disease at diagnosis were not treated by surgery. In near to 80% of patients primary treatment consisted of surgery alone, 7% of surgically treated patients received interferon and the remaining ones additionally received irradiation combined with or without interferon. Compared to the previous periods, in the period 2001–1995 the proportion of patients receiving interferon in addition to surgery has decreased significantly. In the years 1991–1995, 26% of patients were treated with a combination of surgery and interferon.

In the period 2001–2005, 36% started their treatment in the UMC Ljubljana, 12% each in the UMC Maribor and at the IO Ljubljana, 9% in the GH Celje and 7% in the GH Novo mesto. Between 1–3% of patients were treated in general hospitals of Jesenice, Nova Gorica, Slovenj Gradec, Murska Sobota and Izola. Nine percent of patients started their treatment in private clinics.



Slika 4: *Petletno relativno preživetje bolnikov z malignim melanomom po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of malignant melanoma patients by age and period of diagnosis.*

V vseh treh obdobjih je imelo največ bolnikov ob diagnozi omejeno bolezen; v obdobju 2001–2005 je bilo pri moških takih bolnikov 76 %, pri ženskah pa 81 %. Deleži posameznih stadijev se s časom niso bistveno spreminjali (Tabela 2). Poenostavljena opredelitev stadijev, kot jo uporabljajo registri raka, tudi slovenski, pri kožnem melanomu že v omejenem stadiju združuje tumorje, ki imajo glede na globino invazije, debelino tumorja in morebitno ulceracijo različno napoved izida. V RRS zbiramo tudi podatke o globini invazije po Clarku in o debelini tumorja po Breslowu. V 15 letih se je povprečna debelina tumorjev zmanjšala s 3,37 mm v letih 1991–1995 (opredeljena pri 73 % primerov, to je pri 599 primerih od 819) na 2,59 mm (debelina opredeljena pri 90 % primerov, to je pri 1370 primerih od 1526).

V letih 2001–2005 ni bilo specifično zdravljenih 1,3 % bolnikov. Delež nezdravljenih bolnikov se je v obdobjih analize počasi zmanjševal; med bolniki, zbolelimi v obdobju 1991–1995, ni bilo specifično zdravljenih 2,4 %. Med specifično zdravljenimi bolniki so bili v letih 2001–2005 skoraj vsi operirani; brez kirurškega zdravljenja je ostalo 7 bolnikov z močno napredovalo boleznijo ob diagnozi. Pri skoraj 80 % je bilo prvo zdravljenje zaključeno z operacijo, 7 % operiranih je prejelo interferon, ostali pa so bili še obsevani in so prejeli interferon ali pa ne. V primerjavi s prejšnjima obdobjema se je v letih 2001–2005 bistveno zmanjšal delež bolnikov, ki so bili poleg operacije zdravljeni še z interferonom. V letih 1991–1995 je bilo s kombinacijo kirurgije in interferona zdravljenih 26 % bolnikov.

V obdobju 2001–2005 je 36 % bolnikov pričelo zdravljenje v UKC Ljubljana, po 12 % v UKC Maribor in na OI Ljubljana, 9 % v SB Celje in 7 % v SB Novo mesto. Med 3 in 1 % bolnikov se je zdravilo v splošnih bolnišnicah na Jesenicah, v Novi Gorici, Slovenj Gradcu, Murski Soboti in Izoli. V zasebnih ordinacijah se je pričelo zdraviti 9 % bolnikov.

Relativno preživetje bolnikov s kožnim melanomom se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 12 % (Slika 2), pri moških nekaj več kot pri ženskah (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju preseglo 90 %. Petletno relativno preživetje bolnikov z razširjenim stadijem se približuje 50 %, bolnikov z razsejanim stadijem pa je malo, tako da je ocenjevanje preživetja precej nezanesljivo. Napovedni dejavnik je tudi starost, saj je relativno preživetje najslabše pri starih 75 let in več, preživetje zbolelih med 50. in 75. letom pa ves čas opazovanja rahlo zaostaja za relativnim preživetjem zbolelih pred 50. letom (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 81 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 85-odstotno petletno relativno preživetje.

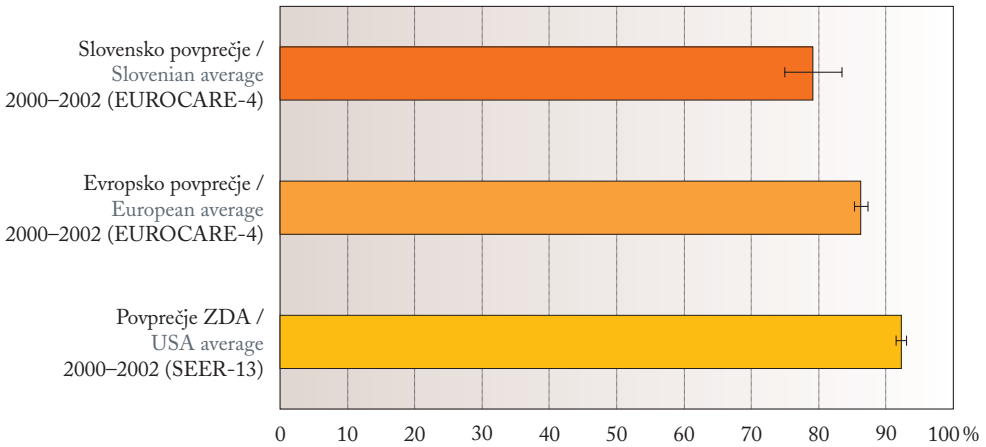
Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov s kožnim melanomom statistično značilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

Marko Hočevar

Preživetje bolnikov z melanomom ostaja še naprej v največji meri odvisno od stadija bolezni ob postavitvi diagnoze. Stadij ob postavitvi diagnoze je pri melanomu še bolj kot pri drugih rakih zrcalo ozaveščenosti prebivalstva, saj se melanom kaže kot kožna sprememba in je s tem dostopna prostemu očesu vsakega izmed nas. Glede na izboljšano relativno petletno preživetje v zadnjih 15 letih bi lahko sklepali, da je zaradi večje ozaveščenosti prebivalstva prišlo do postavitve diagnoze že v zgodnejšem stadiju in s tem do izboljšanega preživetja. To kažejo tudi podatki o manjši povprečni debelini tumorja

Rezultati porazdelitve bolnikov po stadijih v različnih obdobjih zadnjih 15 let so premalo natančni, da bi lahko to zanesljivo potrdili. Velika večina bolnikov (> 75 %) ima namreč ob postavitvi



Slika 5: *Petletno relativno preživetje bolnikov z malignim melanomom (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of malignant melanoma patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

The relative survival rate of patients with skin melanoma has been gradually increasing: in 15 years, the 5-year relative survival increased by 12% (Figure 2), in males slightly more than in females (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage has exceeded 90%. The 5-year relative survival of patients with regional stage is near to 50%, whereas patients with disseminated disease are so scarce that the evaluation of their survival is unreliable. Age is a prognostic factor as well, since the relative survival is the lowest in patients aged 75 years or older, while the survival of those diagnosed between 50–74 years of age was lagging behind the relative survival of the patients diagnosed before the age of 50 throughout the observation period (Figure 4).

The five-year relative survival of all patients diagnosed in the period 2001–2005 was 81% (Figure 2); patients surviving the first year may expect to survive five years in 85%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of patients with skin melanoma in Slovenia is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Marko Hočevar

The survival of melanoma patients still depends to the greatest extent on the stage of the disease at diagnosis. In melanoma, more than in any other cancer, stage at diagnosis reflects the level of public awareness, since melanoma occurs in form of a skin change that every one of us can see with bare eye. Considering the improved 5-year survival in the last 15 years, we might presume that greater public awareness resulted in the diagnosis being established at an earlier stage, thus facilitating better survival. This is consistent with the data on smaller average tumor thickness.

However, the results of patient distribution by stage in different observation periods in the last 15 years are insufficiently accurate to confirm this hypothesis. Namely, throughout the 15-year observation period, a vast majority of patients (> 75%) presented with localized stage at diagnosis. In the last 15 years the percentage of patients with regional disease at diagnosis has not changed either (approximately 15–20%). Patients with localized stage at diagnosis, which are

diagnoze vse 15-letno obdobje omejeni stadij bolezni. Tudi odstotek bolnikov z razširjenim stadijem bolezni ob postavitvi diagnoze se v zadnjih 15 letih ni spremenil (približno 15–20 %). Bolniki z omejenim stadijem bolezni ob postavitvi diagnoze, ki so najštevilčnejši, so glede preživetja zelo heterogena skupina. Preživetje je odvisno predvsem od debeline primarnega melanoma in morebitne ulceracije tumorja. Vseh podatkov sicer nimamo na voljo, kaže pa, da se povprečna debelina melanomov v Sloveniji ne znižuje tako, kot bi si želeli. Povprečna debelina ob postavitvi diagnoze je nad 2 mm in je še vedno bistveno večja kot v državah z najboljšim preživetjem, v Avstraliji, na Švedskem in Škotskem (bolniki s povprečno debelino pod 1 mm imajo petletno preživetje nad 90 %). Razlog boljšega preživetja je zato potrebno iskati še drugje.

Drug razlog za izboljšano preživetje bolnikov z melanomom bi lahko bila uvedba novih načinov zdravljenja. V zadnjih 30 letih pri zdravljenju melanoma ni bistvenega napredka. Osnovno zdravljenje je še naprej preprosta radikalna ekscizija primarnega melanoma. Adjuvantno zdravljenje je še naprej večinoma samo v sklopu kliničnih študij, čeprav so nekatere države, med njimi tudi Slovenija, uvrstile zdravljenje z interferonom v svoja klinična priporočila. Podobno je pri bolnikih z razširjenim stadijem ob postavitvi diagnoze. Tudi tu ostaja odstotek teh bolnikov v zadnjih 15 letih nespremenjen. Prav tako ostaja nespremenjen način zdravljenja – radikalna disekcija področnih bezgavk. Tudi v tej skupini bolnikov opažamo skoraj 10-odstotno izboljšanje petletnega preživetja.

Razlog za boljše preživetje bolnikov z melanomom v zadnjih 15 letih je zato verjetno v spremenjeni biologiji (naravnem poteku) samega melanoma. Kot se je pokazalo v multivariatni analizi, ki smo jo opravili na OI Ljubljana, in v kateri smo upoštevali obdobje diagnoze in debelino primarnega melanoma, je obdobje, v katerem so bolniki zboleli, najpomembnejša neodvisna spremenljivka. Bolniki z melanomom, debelim 4 mm, imajo danes takšno napoved izida, kot so jo imeli pred 20 leti bolniki z melanomom, debelim 1 mm. Večina razlogov za tako spremenjen naravni potek melanoma s časom še ni znana. Vse več podatkov pa kaže, da gre pri melanomu za hetereogeno skupino bolezni z različno patogenezo – različno spremenjenim genskim zapisom, ki je odvisen predvsem od tega, kje na telesu se melanom razvije. Razlog je verjetno različna izpostavljenost (intermitentna ali kronična) različnih delov telesa UV žarkom.

Glede na to, da je povprečna debelina melanoma v Sloveniji še vedno precej večja kot v najbolj razvitih državah, pa imamo veliko priložnost, da z boljšim ozaveščanjem prebivalstva dodatno izboljšamo preživetje bolnikov s kožnim melanomom.

VIRI
Literature

Lasithiotakis KG, Leiter U, Eigentler T, Breuninger H, Metzler G, Meier F, et al. Improvement of overall survival of patients with cutaneous melanoma in Germany, 1976–2001: which factors contributed? Cancer 2007; 109: 1174–82.

Perič B, Žgajnar J, Bešić N, Hočevar M. Changing biology of cutaneous melanoma. Melanoma Res 2008; 18: 225–9.

KLINIČNI KOMENTAR
Janja Ocvirk

Preživetje bolnikov z rakom je odvisno od stadija bolezni ob postavitvi diagnoze in načina zdravljenja. Pri melanomu nimamo presejalnega programa, tako da je veliko odvisno od ozaveščenosti prebivalstva, za katero je bilo v Sloveniji v letih, ki jih obravnava publikacija, storjenega malo. Veliko več pa so za osveščanje prinesla zadnja leta. Diagnoza je v večini primerov mogoča že s pregledom kože, zaradi česar je velikega pomena samopregledovanje in poznavanje enostavnega sistema diagnosticiranja (sistem ABCDE iz angleških besed, ki v slovenščini pomenijo: A – asimetrija, B – rob, C – barva, D – premer (diameter) in E – evolucija in elevacija). V državah z boljšo ozaveščenostjo in poznavanjem tega sistema si 80–90 % bolnikov samih postavi diagnozo oz. pridejo k zdravniku v začetni fazi bolezni.

most numerous, represent in terms of their survival a very heterogeneous group. The survival primarily depends on the thickness of primary melanoma and possible tumor ulceration. Although not all the data are available, it seems that the average melanoma thickness in Slovenia is not decreasing as anticipated. The average thickness at diagnosis exceeds 2 mm and is still significantly greater than in countries with the best survival, i. e. in Australia, Sweden and Scotland (patients with average thickness less than 1mm have 90% 5-year survival). Therefore the cause of better survival should also be sought elsewhere.

Another reason for better survival of melanoma patients might be attributable to the implementation of new treatment modalities. In the last 30 years, no significant progress has been achieved in the area of melanoma treatment. The basic therapy still consists of a simple radical excision of the primary melanoma. Adjuvant therapy is still carried out mainly in the framework of clinical studies, although certain countries, among them also Slovenia, have included interferon-based treatment into their clinical recommendations. The situation in patients with regional disease at diagnosis is similar. In the last 15 years, their proportion too has remained unchanged. The mode of treatment – radical regional lymph node dissection – has remained unchanged too. In this group of patients too we observe an almost 10% improvement in the 5-year survival.

The reason for better survival of melanoma patients in the last 15 years should probably be sought in a changed biology (natural course) of melanoma itself. As shown by the results of a multivariate analysis carried out at the IO Ljubljana, where the time at diagnosis and primary melanoma thickness were considered, the period of patients' diagnosis turned out to be the most relevant independent variable. Today the prognosis in patients with melanoma thickness of 4 mm is comparable with the prognosis in patients with melanoma thickness of 1mm 20 years ago. Most reasons for the changed natural course of melanoma with time have not been explained yet. However, there is growing evidence in favor of the belief that melanoma represents a heterogeneous group of diseases with varying pathogenesis – differently changed genetic code, primarily depending on the site of melanoma origin. The reason probably lies in different exposure (intermittent or chronic) of various body parts to UV rays.

In view of the fact that the average thickness of melanoma in Slovenia is still greater than in the most developed countries, we have an ample opportunity to further improve the survival of patients with skin melanoma by raising public awareness.

CLINICAL COMMENTARY

Janja Ocvirk

Survival of cancer patients depends on the stage of the disease at diagnosis and the mode of treatment. No screening program being available for melanoma, a lot depends on public awareness, though not much has been done in this respect in the years covered by this report. In recent years, however, the situation as regards awareness rising has improved considerably. In most cases the diagnosis is possible already on the basis of skin examination, which points out the importance of self-examination; it is also important to know the simple system of diagnosis (ABCDE system meaning: A – asymmetry, B – border, C – color, D – diameter and E – elevation). In the countries with greater awareness and knowledge of this system, 80–90% of patients will make their own diagnosis or see the doctor at an early stage of the disease.

The incidence of melanoma is increasing, which could be ascribed to the environmental influences as well as to a changed lifestyle and longer lifespan, which also explains a higher number of the elderly among melanoma patients.

In recent years we changed the approach to melanoma patients, introduced the sentinel node biopsy, which facilitates more accurate staging of the disease and thus treatment already at the presence of micrometastases in the lymph nodes, resulting in a longer survival of patients with

Incidenca melanoma se veča, kar bi lahko pripisali vplivu okolja in spremenjenemu načinu življenja, pa tudi daljši življenjski dobi, zaradi česar je med bolniki z melanomom tudi več starejših.

V zadnjih letih smo spremenili obravnavo bolnikov z melanomom, uvedli smo biopsijo varovalne bezgavke, ki omogoča natančnejšo določitev stadija bolezni in s tem zdravljenje že ob prisotnosti mikrozasevkov v bezgavkah, kar vodi v podaljšanje preživetja bolnikov s to boleznijo. Uveden je bil tudi nov sistem določanja stadijev melanoma; poleg biopsije varovalne bezgavke omogoča bolj natančno odbiro bolnikov tudi za sistemsko adjuvantno zdravljenje, ki je bilo uvedeno v zadnjem petletju in je vplivalo na podaljšanje preživetja bolnikov z lokalno razširjeno boleznijo.

Relativno 1-, 3-, 5- in 10-letno preživetje bolnikov se veča v vseh opazovanih obdobjih, še posebej bolnikov z omejeno in razširjeno boleznijo zaradi uvedbe novih načinov zdravljenja: biopsije varovalne bezgavke in sistemskega adjuvantnega zdravljenja, žal pa ostaja preživetje bolnikov z razsejano boleznijo še vedno slabo, pri teh bolnikih tako v Sloveniji kakor v svetu še nimamo na voljo učinkovitega zdravljenja.

Z vse večjo ozaveščenostjo prebivalstva, ob izboljšanih načinih zdravljenja in seveda njegovem izvajanju ter ob multidisciplinarni obravnavi bolnika lahko pričakujemo, da se bo preživetje tudi v nadaljnjih letih še izboljševalo.

VIRI
Literature

Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001; 19: 3635–48.

Ocvirk J. Dopolnilno sistemsko zdravljenje melanoma. In: Ocvirk J, Snoj M, Strojan P, eds. Šola o melanomu. Radiol Oncol 2007; 41: S43–S45.

this disease. The newly introduced system of melanoma staging facilitates, apart from sentinel node biopsy, a more accurate selection of patients for systemic adjuvant therapy introduced in the last 5-year period and influencing a longer survival of patients with locally advanced disease.

The relative 1-, 3-, 5- and 10-year survival of patients has been increasing in all the observed periods, particularly in patients with localized and regional disease as a result of new treatment methods: sentinel lymph node biopsy and adjuvant systemic therapy. Unfortunately, however, the survival of patients with disseminated disease is still poor; there is no effective treatment method available for these patients either in Slovenia or elsewhere in the world.

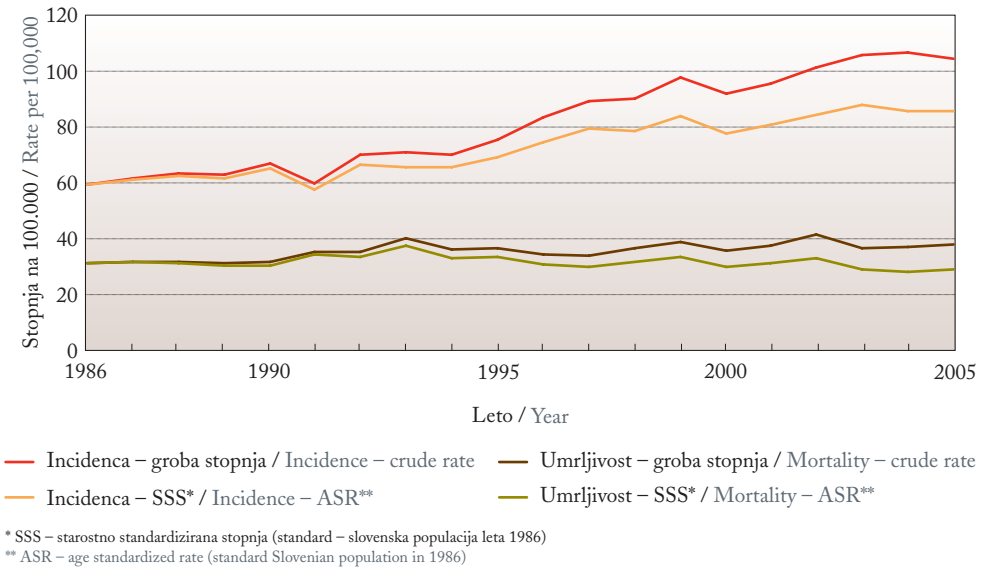
Ever greater public awareness, improved treatment methods and their implementation as well as the multidisciplinary treatment approach to these patients are expected to contribute to a further increase in the survival in the future.

DOJKA

MKB 10: C50

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom dojk zbolelo 13.756 ljudi, 13.635 žensk in 121 moških. Kot je razvidno s Slike 1, ki prikazuje podatke le za ženske, sta se v opazovanem obdobju povečevali groba in starostno standardizirana incidenčna stopnja; bolj do leta 1998 (5,8 % oz. 4,6 % povprečno letno) kot kasneje (2,2 % oz. 1,4 % povprečno letno). Umrljivostna stopnja se zmanjšuje od leta 1991, bolj starostno standardizirana (1,3 % povprečno letno) kot groba (0,4 % povprečno letno).



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka dojk, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of breast cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 13.411 bolnic; 224 (1,6 %) jih nismo upoštevali, ker jim je bila diagnoza postavljena po smrti. Izključili smo tudi 121 moških, tako da se vsi rezultati nanašajo samo na ženske. V obdobju 2001–2005 je imelo 3241 bolnic (od 5236) natančneje opredeljeno mesto vznika tumorja v dojki. V 35 % je bil to zgornji zunanji kvadrant, tumorjev ostalih treh kvadrantov je bilo manj kot po 8 %, v dva kvadranta ali več je segalo 36 % tumorjev, manj kot po 1 % pa so zavzemali tumorji bradavice in pazdušnega predela dojke.

Odstotek mikroskopsko potrjenih primerov se je povečal s 96 % v letih 1991–1995 na 98 % v letih 2001–2005. V vseh treh obdobjih so prevladovali karcinomi, druge histološke vrste so

Tabela 1: *Število bolnic z rakom dojk po obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of breast cancer patients by period of diagnosis with their proportions by age.*

	Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	3552	25,9	59,1	15,0
1996–2000	4623	24,2	59,6	16,1
2001–2005	5236	22,3	59,0	18,7

BREAST

ICD 10: C50

EPIDEMIOLOGY

In the period 1991–2005, a total of 13,756 persons were diagnosed with breast cancer, of these 13,635 females and 121 males. As evident from Figure 1, which is shown the female data only, in the study period the crude and age-standardized incidence rates have been increasing, more so till 1998 (by 5.8% and 4.6% annually on average) than later on (by 2.2% and 1.4% annually on average). Since 1991, the mortality rates have been decreasing, the age-standardized more than the crude rates (1.3% vs. 0.4% annually on average).

The survival analysis included 13,411 patients; 224 patients (1.6%) diagnosed only after death were not considered in the analysis. There were 121 males excluded as well, so that the results apply to women. In the period 2001–2005, 3241 patients (out of total 5236) had the site of tumor origin in the breast more precisely defined. Thus, in 35% of cases tumor was situated in the upper outer quadrant, sites in the remaining three quadrants were present in less than 8% each, 36% of tumors involved two or more quadrants, while tumors of the nipple and axillary area of the breast occurred in less than 1% each.

The percentage of microscopically confirmed cases increased from 96% in the years 1991–1995 to 98% in the years 2001–2005. With respect to histological type, carcinomas were prevailing while other histological types were rare; in the last period there were 8 cases of sarcoma and 4 cases of fibroepithelial malignomas (malignant phyloid tumors).

Compared to the first period, in the last one, the proportion of younger patients (20–49 years) was lower by 4%, the proportion of those at an age between 50–74 years has not changed significantly while the proportion of patients aged 75 years or older has increased by 4% (Table 1).

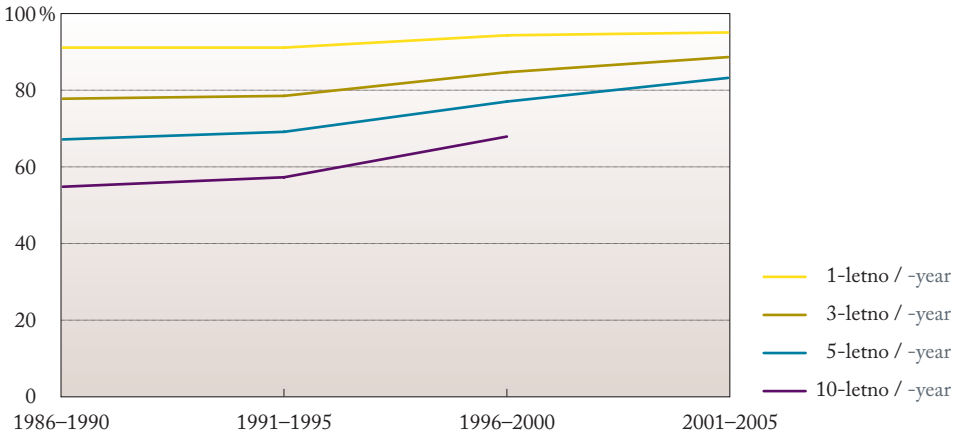
The proportion of patients with localized disease has gradually increased, in the last period the proportion of newly diagnosed cases with localized stage being 50%, i. e. 7% more than in the first period (Table 2).

In all three time-periods, most patients received specific treatment, 5050 (96%) in the period 2001–2005. In the period 2001–2005, 10% were treated only locally, by surgery and/or radiotherapy, (12% less than in the period 1991–1995); 8% underwent surgery alone (vs. 14% in the past), while 2% had radiotherapy either with or without surgery (vs. 8% in the past). In comparison with the first period, in the last one the greatest increase (16%) was observed in the proportion of patients who received adjuvant hormonal therapy: In the period 2001–2005, there were 39% such patients (21% underwent surgery alone and 18% also received radiotherapy) vs. 23% in the period 1991–1995 (13% had surgery alone while 10% also received irradiation). In the period 2001–2005, 26% of patients received chemotherapy besides adjuvant hormonal therapy, the rate being comparable with the one in the first period (26.0%); in this group, as compared to the first period, the proportion of those treated by surgery alone has increased by 2% only (on the account of adjuvant irradiation), from previous 5% to 7%. Seventeen per-

Tabela 2: *Število bolnic z rakom dojk po obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of breast cancer patients by period of diagnosis with their proportions by stage.*

	Ženske / Females				
Obdobje / Period	število / number (%)	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown
1991–1995	3552	42,6	45,9	10,2	1,4
1996–2000	4623	46,9	42,0	9,7	1,4
2001–2005	5236	50,0	41,1	8,0	0,9



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnic z rakom dojk po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of breast cancer patients by period of diagnosis.*

izjemno redke; v zadnjem obdobju je bilo 8 primerov sarkomov in 4 primeri fibroepitelijskih malignomov (malignih filodnih tumorjev).

V zadnjem obdobju je bilo 4 % manj mlajših bolnic (20–49 let) kot v prvem, odstotek bolnic v starosti 50–74 let se ni bistveno spreminjal, za 4 % pa se je povečal odstotek starih 75 let in več (Tabela 1).

Odstotek bolnic z omejeno boleznijo se je postopno večal, v zadnjem obdobju je bilo z omejeno boleznijo odkritih 50 % novih primerov, 7 % več kot v prvem (Tabela 2).

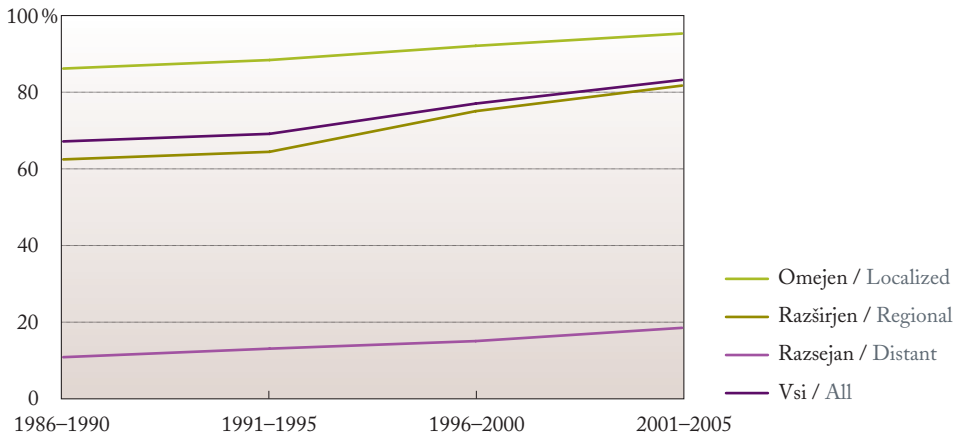
V obdobju 2001–2005 je bilo zdravljenih samo lokalno, z operacijo in/ali obsevanjem, 10 % bolnic (za 12 % manj kot v letih 1991–1995); samo operiranih je bilo 8 % bolnic (prej 14 %), obsevanih (poleg operacije ali brez nje) pa 2 % (prej 8 %). V primerjavi s prvim obdobjem se

Tabela 3: *Opazovano in relativno preživetje bolnic z rakom dojk po obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of breast cancer patients by period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	89,1 (88,1–90,1)	73,0 (71,5–74,4)	61,1 (59,5–62,7)
1996–2000	92,3 (91,5–93,0)	79,3 (78,2–80,5)	68,7 (67,4–70,1)
2001–2005	93,1 (92,4–93,8)	83,1 (82,0–84,1)	74,2 (72,9–75,6)

	Relativno preživetje / Relative survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	91,2 (90,1–92,2)	78,4 (76,8–80,0)	69,0 (67,2–70,9)
1996–2000	94,3 (93,5–95,1)	84,7 (83,5–86,0)	77,0 (75,5–78,5)
2001–2005	95,1 (94,4–95,8)	88,7 (87,6–89,8)	83,3 (81,8–84,8)

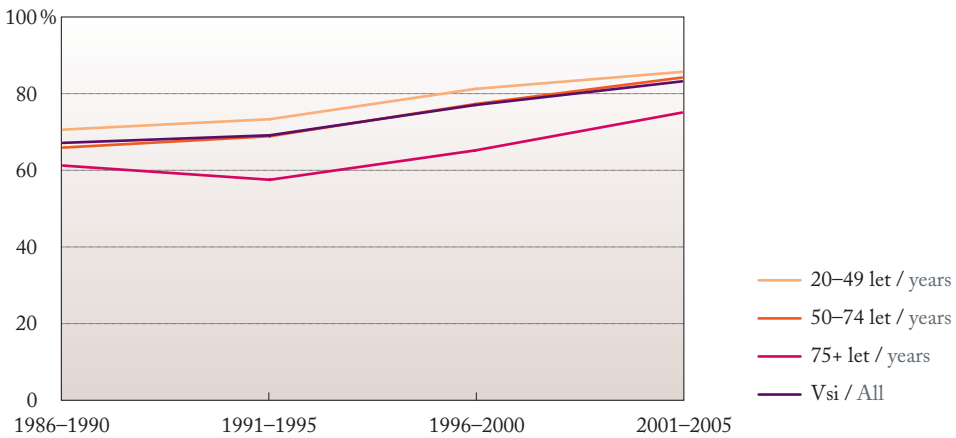


Slika 3: *Petletno relativno preživetje bolnic z rakom dojk po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of breast cancer patients by stage and period of diagnosis.*

cents of patients received only adjuvant chemotherapy (4% less than in the first period); 7% underwent surgery alone while 10% also received radiotherapy (in the first period out of 21% of patients receiving chemotherapy 10% underwent surgery alone and 11% also received radiotherapy). In all three time-periods nearly 9% of patients were not treated locally but only systemically, with chemotherapy, hormones or a combination of both.

In the last period 58% of patients started their treatment at the IO Ljubljana (the percentage being comparable with those in the previous periods), 18% in the UMC Maribor, 9% in the GH Nova Gorica, 8% in the GH Celje, and 3% in the GH Slovenj Gradec and GH Novo mesto respectively. Ten or less patients started their treatment in UMC Ljubljana and GH in Murska Sobota, Izola, Trbovlje, and Jesenice and in the hospitals for gynecology and obstetrics in Postojna and Kranj.

The relative survival of patients has been gradually increasing, particularly in the last period; in 15 years, the 5-year relative survival increased by 14% (Figure 2; Table 3). The relevance of stage at diagnosis is shown in Figure 3. Compared to the period 1991–1995, in the last period



Slika 4: *Petletno relativno preživetje bolnic z rakom dojk po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of breast cancer patients by age and period of diagnosis.*

je v zadnjem najbolj, za 16 %, povečal delež bolnic, ki so prejele dopolnilno hormonsko zdravljenje: v letih 2001–2005 je bilo takih 39 % (21 % samo operiranih in 18 % dodatno obsevanih), v letih 1991–1995 pa 23 % (13 % samo operiranih, 10 % še obsevanih). V letih 2001–2005 je 26 % bolnic poleg hormonskega dopolnilnega zdravljenja prejelo še kemoterapijo; ta delež je skoraj enak kot v prvem obdobju (26 %); v tej skupini se je v primerjavi s prvim obdobjem le za 2 % povečal delež samo operiranih (na račun dodatnega obsevanja), s 5 % na 7 %. Samo dopolnilno kemoterapijo je prejelo 17 % bolnic (4 % manj kot v prvem obdobju); 7 % je bilo samo operiranih, 10 % pa tudi obsevanih (v prvem obdobju pa je bilo od 21 %, ki so prejele kemoterapijo, 10 % samo operiranih, 11 % pa tudi obsevanih). V vseh treh obdobjih blizu 9 % bolnic ni bilo zdravljenih lokalno, pač pa le sistemsko, s kemoterapijo, hormoni ali s kombinacijo obeh vrst.

V vseh treh obdobjih je bila specifično zdravljena večina bolnic, 5050 (96 %) v letih 2001–2005. V tem obdobju se je začelo zdraviti na OI Ljubljana 58 % bolnic (podoben odstotek tudi v prejšnjih obdobjih), 18 % v UKC Maribor, 9 % v SB Nova Gorica, 8 % v SB Celje, po 3 % pa v SB Slovenj Gradec in SB Novo mesto. Po 10 ali manj bolnic se je začelo zdraviti še v drugih bolnišnicah, v UKC Ljubljana, v SB Murska Sobota, SB Izola, SB Trbovlje, SB Jesenice ter v bolnišnicah za porodništvo in ženske bolezni Postojna in Kranj.

Relativno preživetje se postopno veča, predvsem v zadnjem obdobju; v 15 letih se je petletno relativno preživetje povečalo za 14 % (Slika 2; Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: v zadnjem obdobju je petletno relativno preživetje bolnic z omejenim stadijem že več kot 95-odstotno in se je v primerjavi z leti 1991–1995 povečalo za 9 %, za 19 % se je povečalo tudi petletno relativno preživetje bolnic z razširjeno boleznijo, za 8 % pa bolnic z razsejano boleznijo. Napovedni dejavnik je tudi starost, saj so v zadnjem obdobju mlajše od 50 let imele za 10 % večje relativno preživetje kot stare 75 let in več (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 83 % (Slika 2); bolnice, ki preživijo prvo leto, pa lahko pričakujejo 87-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnic z rakom dojk še vedno statistično značilno manjše od evropskega povprečja (Slika 5).

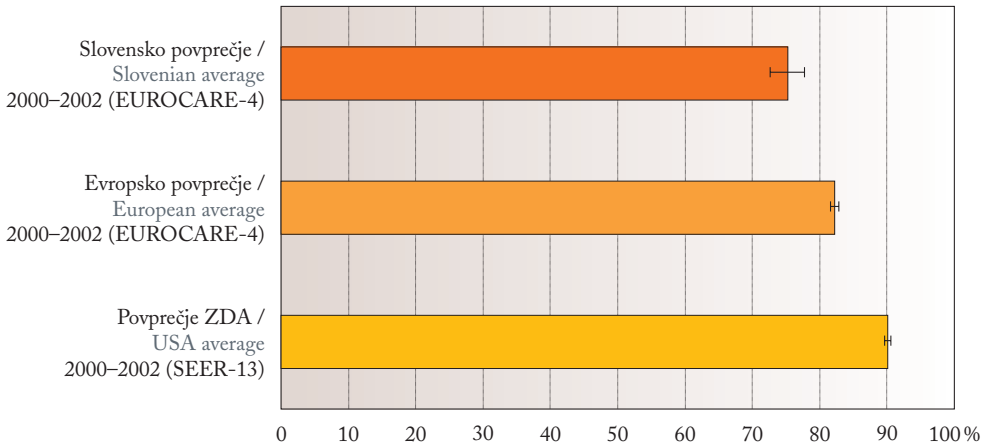
KLINIČNI KOMENTAR

Janez Žgajnar

Podatki, ki jih obravnavamo v tej publikaciji, so ohrabrujoči. Kažejo namreč, da se obravnava raka dojk v državi izboljšuje, kar se odslikava v vedno večjem preživetju bolnic vseh starosti ne glede na stadij ob postavitvi diagnoze in tudi v daljšem opazovanem obdobju. Omenjeni napredek je v večji meri posledica boljšega sistemskega zdravljenja, le v manjši meri pa premika k bolj omejenemu stadiju ob postavitvi diagnoze, oziroma h kakovosti področnega zdravljenja.

Ob pregledu podatkov še vedno vznemirja velika razpršenost zdravljenja po številnih zdravstvenih ustanovah, kar je v nasprotju z evropskimi priporočili in z načeli, sprejetimi v Sloveniji. Dokazano je, da je zdravljenje uspešnejše v centrih z dovolj znanja, opreme ter obenem z zadostnim številom novih bolnic (najmanj 150 letno), zato pričakujemo, da bodo odgovorni odločno ukrepali in bodo zdravljenje raka dojk omejili le na nekaj ustanov, ki izpolnjujejo evropske standarde.

Preživetje bolnic z omejenim stadijem je že sedaj odlično, kar posredno potrjuje izjemen pomen zgodnjega odkrivanja raka dojk. Z oportunističnim presejanjem, kot smo ga imeli (in ga še imamo) v Sloveniji, očitno večjega premika k večjemu deležu omejenih rakov ne moremo napraviti. Upamo lahko, da se bo program DORA kmalu razširil na celotno Slovenijo in bo v prihodnjem obdobju zmanjšal delež razširjene bolezni. V zadnjem obdobju se je delež omejenega raka dojk povečal le za 3 %, na 50 %. Pri tem moramo upoštevati, da se je prav v tem obdobju v kirurškem zdravljenju uveljavljala biopsija prve (sentinel) bezgavke in da pri 10–20 % bolnic najdemo



Slika 5: *Petletno relativno preživetje bolnic z rakom dojk (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of breast cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

the 5-year relative survival of patients with localized stage was already 95%, thus having increased by 9%, while the 5-year relative survival of patients with regional disease has increased by 19% and of patients with disseminated disease by 8%. Age is a prognostic factor as well, since in the last period all the patients under 50 years of age had 10% higher relative survival than those aged 75 years or older (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 83% (Figure 2); patients surviving the first year may expect to survive five years in 87%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of breast cancer patients in Slovenia is still statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Janez Žgajnar

The data presented in the current report of the CRS are encouraging. They indicate that breast cancer treatment in Slovenia is improving, which is reflected in increasingly better survival of patients in all age groups, regardless of the stage at diagnosis, and evident even through a longer observation period. This progress is mainly attributable to better systemic therapy and only to a lesser extent to the shift towards more localized stage at diagnosis or the quality of locoregional treatment.

The data review still raises concern due to wide dispersion of treatment throughout several healthcare institutions, which is in contradiction with the European recommendations as well as with the principles established in Slovenia. It has been proved that the treatment performed in centers with adequate knowledge and equipment, and at the same time a sufficient number of newly diagnosed patients (at least 150 per year), has better results, therefore we expect that the competent authorities will take the necessary measures to restrict breast cancer treatment to few institutions that meet the European standards.

The survival of patients with localized stage is already excellent, which indirectly proves the outstanding importance of early breast cancer detection. The opportunistic screening for breast cancer, which has been practiced in Slovenia, is apparently unable to contribute further to a greater

v bezgavkah zaradi natančnejše histopatološke preiskave zasevke, ki jih prej nismo našli. Povečan delež bolnic z omejenim stadijem bolezni je zato manjši, kot bi morda pričakovali.

V obravnavanem obdobju se je za 12 % (na skupaj 10 %) zmanjšal delež bolnic, ki so bile zdravljenje le lokalno – kirurško in/ali z obsevanjem. To je nedvomno posledica spremenjenih indikacij za sistemsko zdravljenje. Po drugi strani pa lahko pričakujemo, da se bo z razširitvijo mamografskega presejanja povečal delež neinvazivnega raka dojk in zelo majhnih invazivnih rakov, ki jih bomo zdravili le lokalno.

Vsekakor bi za celostno podobo kakovosti obravnave raka dojk in razlago rezultatov potrebovali tudi podatke, ki jih RRS tokrat ne prikazuje. Predvsem bi bilo zanimivo primerjati preživetja glede na ustanovo, kjer je zdravljenje potekalo. V Sloveniji je to še posebej zapleteno, ker bolniki (razen tistih z OI) prehajajo med številnimi ustanovami na poti od diagnostike do različnih vrst zdravljenj. Manjka tudi podatek, ki pa ga v našem registru ni, in sicer, koliko bolnic je bilo multidisciplinarno obravnavanih pred začetkom zdravljenja; prav pravilno prvo zdravljenje pa je ključno za izid zdravljenja.

Če se omejim na kirurško zdravljenje, naj naštejem le nekaj pomembnih kazalcev kakovosti zdravljenja, ki tudi niso dostopni: delež operacij z ohranitvijo dojke, število operacij za isto bolezen, delež predoperativnega sistemskega zdravljenja, rekonstrukcij po odstranitvi dojk in drugih. Doslej smo v Sloveniji občasno opravljali analize v posameznih ustanovah, kar pa ne odseva stanja v državi. Leta 2005 smo tako na OI opravili pri približno polovici bolnic konservirajočo operacijo dojke, kar je še vedno premajhen delež. Majhen ostaja tudi delež rekonstrukcij dojk po mastektomiji, čeprav je v zadnjih letih zrasel na 30 %. Šele sistematičen zajem vseh ključnih podatkov za ocenjevanje kakovosti zdravljenja bo omogočal tako potreben nadzor in primerjavo znotraj ustanov in med njimi. Zato je nujno, da zaživi Državni program obvladovanja raka, katerega del je tudi elektronski popis bolnika z rakom, ki bi bil povezan z RRS. Obravnava raka dojk mora biti zaupana le tistim, ki dosegajo zahtevana merila kakovosti.

Zaključimo lahko, da v Sloveniji počasi zmanjšujemo zaostanek za najboljšimi v svetu pri preživetju bolnic z rakom dojk, čeprav še zdaleč ni na želeni ravni. Predvsem bo treba čim prej omogočiti vsem bolnicam z rakom dojk v Sloveniji enako kakovostno celostno obravnavo. To se bo odrazilo tudi v rezultatih preživetja.

VIRI
Literature

Blamey L, Cataliotti R. The requirements of a specialist Breast Unit. Eur J Cancer 2000; 36: 2288–93. Revision 2004, www.eusoma.org.

Cserni G, Amendoeira I, Apostolikas N, Bellocq JP, Bianchi S, Bussolati G, et al. Pathological work-up of sentinel lymph nodes in breast cancer. Review of current data to be considered for the formulation of guidelines. European Working Group for Breast Screening Pathology. Eur J Cancer. 2003; 39: 1654–67.

Novak M, Žgajnar J: Kontrola kakovosti pri lokoregionalnem zdravljenju karcinoma dojk; Onkologija 2008, 1: 39–42.

Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E, eds. European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. Fourth Edition. European Commission. Luxembourg, Office for Official Publications of the European Communities, 2006.

KLINIČNI KOMENTAR
Elga Majdič

Čeprav podatki o načinu zdravljenja bolnic z rakom dojk, zbolelih v 15-letnem obdobju, ne kažejo, da se je delež bolnic, obsevanih v okviru prvega zdravljenja, v zadnjem obdobju (48 %) povečal v primerjavi z deležem obsevanih v prvem obdobju (51 %), pa se je povečalo absolutno število bolnic, ki smo jih z obsevanjem zdravili na OI Ljubljana z okrog 1700 na skoraj 2500 v letih 2001–2005. To število se še veča, saj smo v obdobju od junija 2006 do junija 2007 z obsevanjem zdravili več kot 1000 bolnic. V teh letih se je povečalo tako opazovano kot relativno

proportion of localized stages. Hopefully, the organized breast cancer screening program (DORA program) will soon spread throughout Slovenia and thus help to reduce the proportion of advanced disease in future. In the last period the proportion of localized breast cancer has increased by 3% only, thus amounting to 50%. Further to that, we have to take into account that in the very same period surgical treatment was upgraded by sentinel node biopsy and that more accurate histopathologic investigations help to detect metastases in 10–20% of patients, which would previously remain undetected. The proportion of patients with localized stage is therefore smaller than it might be expected.

In the observed period the proportion of patients treated only locally, either by radiotherapy and/or surgery has decreased by 12% (to a total of 10%). This is obviously a result of changed indications for systemic therapy. On the other hand, it may be expected that wider use of mammographic screening will result in a greater proportion of non-invasive breast cancers and very small invasive cancers that will be treated only locally.

Certainly, in order to present an overall image of quality in breast cancer treatment, and to explain the results, data beyond those presented by the CRS are needed. In particular, it will be interesting to compare survival with respect to the institution of treatment. In Slovenia, this issue is particularly complex since on their way from diagnosis to different treatment modalities, the patients (except those treated at the IO Ljubljana) are migrating between several institutions. We also miss information, neither available in our CRS, on how many patients had been subject to multidisciplinary approach prior to the beginning of therapy; it is generally accepted that appropriate primary treatment is the most important for a good outcome of treatment.

Speaking strictly about surgical therapy, let me point out just a few indicators of the quality of treatment that are not available: the proportion of breast preserving procedures, the number of surgeries for the same disease, the proportion of preoperative systemic therapy, breast reconstructions after mastectomy and others. So far, sporadic analyses have been carried out by individual institutions in Slovenia, which however do not reflect the actual situation in the country. Thus in 2005, approximately half of the patients underwent a breast preserving surgical procedure at the IO Ljubljana, the proportion still being too low. The proportion of breast reconstructions after mastectomy remains low as well, though it has increased to 30% in the recent years. Only a systematic pooling of all key data for the evaluation of the quality of treatment will facilitate the necessary supervision and comparison within different institutions and between them. Therefore it is necessary that the National Cancer Control Program is implemented as soon as possible, part of which is also an electronic cancer patients' record that would be linked with the CRS. Breast cancer treatment should be limited only to those institutions that meet the required quality standards.

We can conclude that in Slovenia we are gradually catching up with the state of the-art in the world as regards the survival of breast cancer patients, though the results obtained are still far from the desired. First of all, it will be necessary to ensure equal access to a quality comprehensive treatment for all breast cancer patients in Slovenia. This will certainly reflect in better survival results.

CLINICAL COMMENTARY

Elga Majdič

The data on the method of treatment in breast cancer patients diagnosed in the 15-year observation period do not show that the proportion of patients irradiated in the course of their primary treatment in the last period (48%) has increased as compared to the first period (51%), but nevertheless, the absolute number of patients treated by radiotherapy at the IO Ljubljana increased from previous 1700 to almost 2500 in the period 2001–2005. This number is still growing, since more than 1000 patients were treated by radiotherapy in the period from June 2006 to

preživetje (Tabela 3) in to predvsem v omejenem in lokalno razširjenem stadiju (Slika 3), torej v stadijih, v katerih ima radioterapija v zadnjih letih vedno pomembnejšo vlogo. Povečalo se je število delnih resekcij dojke s pooperativnim obsevanjem, pomembna sprememba pa je uvedba pooperativnega obsevanja po mastektomiji pri bolnicah z velikim tveganjem za lokalno ponovitev bolezni. Metaanaliza randomiziranih kliničnih študij je pokazala, da lokalni nadzor pomembno vpliva na preživetje. Ocenjujejo, da dodatek obsevanja po operaciji zmanjša verjetnost lokalne ponovitve pri vseh skupinah bolnic za dve tretjini, kar izboljša 15-letno absolutno preživetje bolnic po ohranitveni kirurgiji za 5,3 % in bolnic z zasevki v pazduhi po modificirani radikalni mastektomiji za 4,4 %, kar je primerljivo z učinkom sistemskega zdravljenja. Pri naših bolnicah tako dolge opazovalne dobe še nimamo, trend pa je očiten. Ob dosedanjih ugotovitvah o tem, kako učinkovito je pooperativno obsevanje, je pričakovati še razširitev te indikacije. Večje preživetje omogoča predvsem dober lokalni nadzor skupaj s sistemskim zdravljenjem, ki uničuje mikrometastaze.

V zadnjih letih smo s pomočjo novih naprav in novih tehnik obsevanja (3 D) izboljšali natančnost obsevanja, s čimer zmanjšamo možnost negativnih posledic na zdravem tkivu. Pričakovati je, da bo to dolgoročno pozitivno vplivalo tudi na preživetje naši bolnic.

VIRI
Literature

Clarke M, Colins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087–106.

Punglia R, Morrow M, Winer E, Harris J. Local therapy and survival in breast cancer. N Engl J Med 2007; 356: 2399–405.

Truong P, Woodward W, Buchholz T. Optimizing locoregional control and survival for women with breast cancer: a review of current developments in postmastectomy radiotherapy. Expert Rev. Anticancer Ther 2006; 6: 205–16.

KLINIČNI KOMENTAR
Tanja Čufer

Rak dojke je v Sloveniji še vedno najpogostejši rak in najpogostejši vzrok smrti za rakom pri ženskah. Zato je dobro obvladovanje te bolezni izrednega pomena za vso družbo. Znano je, da sta k dobremu obvladovanju, ki se je pokazalo z zmanjšanjem umrljivosti za rakom dojk, v ZDA in Evropi v zgodnjih devetdesetih letih prejšnjega stoletja pripomogla zgodnje odkrivanje bolezni s presejanjem in uvedba novih, učinkovitih načinov dopolnilnega sistemskega zdravljenja pri bolnicah z operabilnim rakom dojk. V Sloveniji se umrljivost zaradi raka dojk žal zmanjšuje prepočasi, se pa od leta 1999 nakazuje bolj izrazito padajoč trend; leta 1999 je bila starostno standardizirana umrljivost 45,9/100.000, v letih 2003–2005 pa okoli 39,0/100.000. Z uvedbo organiziranega presejanja za raka dojk pričakujemo še nadaljnje izboljšanje.

V obdobju 2001–2005 se je v Sloveniji pomembno povečalo petletno relativno preživetje bolnic z rakom dojk v primerjavi s petletnim preživetjem bolnic, ki so zbolele v letih 1996–2000 (83 % proti 77 %) in še bolj glede na obdobje 1991–1995, ko je bilo petletno preživetje samo 69 %. Medtem ko je petletno preživetje bolnic z rakom dojk, zbolelih v letih 1991–1995, kar za okoli 10 % zaostajalo za povprečnim evropskim preživetjem (EUROCARE-3), pa izsledki raziskave EUROCARE-4 kažejo, da smo pri bolnicah, zbolelih v letih 2000–2002, kljub temu, da še nismo imeli organiziranega presejanja za raka dojk, skoraj dosegli evropsko povprečje in za njim zaostajamo le še za nekaj odstotkov. Ti podatki so zelo ohrabrujoči. Dobra novica je tudi, da se je po letu 1995 začelo večati predvsem dolgotrajno, 3-, 5- in celo 10-letno preživetje. Izboljšala se je napoved izida pri nas še vedno zelo pogostega razširjenega raka dojk, ki je ob ustreznem zdravljenju tudi ozdravljiva bolezen. Napoved izida omejenega raka dojk, ki je bila že v prejšnjih obdobjih razmeroma dobra, pa se je še bolj popravila. Dobri rezultati so posledica tako zgodnejšega odkrivanja bolezni, saj se je povečal delež bolnic z omejeno

June 2007. In these years both observed as well as relative survival rates increased (Table 3), particularly as regards localized and regional disease (Figure 3), i. e. in the stages in which radiotherapy recently has been gaining in importance. The number of partial breast resections with postoperative irradiation has increased, and an important change has been introduced in form of postoperative irradiation following mastectomy in patients with high risk of local recurrence. Meta-analysis of randomized clinical studies has shown that local control significantly influences patient survival. It is estimated that adjuvant radiotherapy after surgery reduces the risk of local recurrence by two thirds in all groups of patients, which contributes to a 5.3% increase in the 15-year absolute survival of patients after conservative surgery and to a 4.4% increase in patients with axillary lymph node metastases after modified radical mastectomy, these results being comparable with the effects of systemic therapy. In our patients such a long observation period has not been available yet, however, the relevant trend is nevertheless obvious. Present findings on the effectiveness of postoperative irradiation are indicative of further expansion of these indications. Better survival results are attainable particularly by good local control of the disease combined with systemic treatment for the elimination of micrometastases.

In recent years, the accuracy of irradiation has been improved by means of new machines and novel 3D irradiation techniques, which reduces the risk of adverse effects on the healthy tissue. It is expected that such an approach will have a long-term positive impact on the survival of our patients.

CLINICAL COMMENTARY

Tanja Čufer

In Slovenia, breast cancer still represents the most frequent cancer and the most frequent cause of death in female population. Therefore, good control of the disease is of outstanding importance for the whole society. It is well known that in early 90's of the previous century good control and the associated decrease in breast cancer mortality rates in the United States and Europe were largely influenced by early detection of the disease with screening and the implementation of new effective methods of adjuvant systemic therapy in patients with operable breast cancer. In Slovenia, unfortunately, breast cancer mortality rates have been decreasing rather slowly, however, a more apparent decreasing trend has been noted since 1999: thus in 1999 the age-standardized mortality rate was 45.9/100,000 while in the years 2003–2005 it was approximately 39.0/100,000. Further progress may be expected with the introduction of an organized screening for breast cancer.

In the period 2001–2005, a significant increase in the 5-year relative survival of breast cancer patients was noted in Slovenia as compared to the 5-year survival of patients diagnosed in the period 1996–2000 (83% vs. 77%), the increase being even more apparent when compared with the period 1991–1995 when the 5-year survival reached only 69%. While the 5-year survival of breast cancer patients diagnosed in the years 1991–1995 lags behind the European average survival by some 10% (EUROCARE-3), the findings of EUROCARE-4 study show that in Slovenian patients diagnosed in the years 2000–2002 survival almost reached the European average, lagging behind only by few percents, despite the fact that no organized screening for breast cancer had been available in that period. These data are very encouraging. Another good news is that after the year 1995, particularly long-term survival, i. e. 3-. 5- and even 10-year survival of breast cancer patients increased. Improvement was noted in still rather common advanced forms of breast cancer, which is – subject to suitable treatment – a treatable disease and in the early disease, prognosis of which was already relatively favorable in the past periods. Favorable results are attributable to earlier detection, which is reflected in an increase in the proportion of patients with localized disease (from 43% in the period 1991–1995 to 50% in the period 2001–2005), as well as to more effective treatment, particularly adjuvant systemic therapy for operable breast cancer. After the year 1995, adjuvant therapy in all patients with

boleznijo (s 43 % v letih 1991–1995 na 50 % v letih 2001–2005), kot tudi boljšega zdravljenja, predvsem dopolnilnega sistemskega zdravljenja operabilnega raka dojk. V obdobju po letu 1995 se je v dopolnilno zdravljenje vseh bolnic s hormonsko odvisnim rakom dojk postopoma uvedlo za to vrsto raka najučinkovitejše hormonsko zdravljenje, uvedena je bila dopolnilna kemoterapija z antraciklini in po letu 2000 v vse večji meri tudi s taksani. Nadaljnje izboljšanje po letu 2000 je delno že posledica podaljšanega hormonskega zdravljenja hormonsko odvisne bolezni, ki bo skupaj z uvedbo aromataznih inhibitorjev v dopolnilno zdravljenje hormonsko odvisne bolezni in trastuzumaba v dopolnilno zdravljenje bolnic s HER2 pozitivnim rakom dojk leta 2005 nesporno še povečalo preživetje bolnic, ki trenutno zbolevajo in se zdravijo za rakom dojk.

Tudi preživetje bolnic z razsejanim rakom dojk ob postavitvi diagnoze se postopno veča, čeprav ne toliko, kot bi si želeli. Primerjava z nekaterimi drugimi skupinami bolnic kaže na to, da bi bilo mogoče preživetje bolnic z razsejano boleznijo še izboljšati. Glede na to, da je večina (okoli 70 %) rakov dojk hormonsko odvisnih, bi morali za povečanje preživetja bolnic z razsejanim rakom dojk pri nas predvsem posvetiti več pozornosti dobro vodenemu, dolgotrajnemu hormonskemu zdravljenju te bolezni. Ob pojavu vse več novih hormonskih zdravil za raka dojk, kot so aromatazni inhibitorji, fulvestrant in še nekatera druga, to ne bi smelo biti problem.

Ne nazadnje je dobra novica, da se je od leta 1995 le pričelo izboljševati tudi preživetje starejših bolnic z rakom dojk, ki pa tako kot tudi drugje v svetu tudi pri nas še vedno preveč zaostaja za preživetjem mlajših bolnic. Na tem področju bomo morali, ne samo v Sloveniji, ampak tudi v Evropi, še veliko narediti.

VIRI
Literature

Andre F, Slimane K, Bachelot T, Dunant A, Namer M, Barrelier A, et al. Breast cancer with synchronous metastases: Trends in survival during a 14-year period. J Clin Oncol 2005; 22: 3302–8.

Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005; 353: 1784–92.

Čufer T. Reducing the risk of late recurrence in hormone-responsive breast cancer. Ann Oncol 2007; 18 Suppl 8: viii18–25.

Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998; 351: 1451–67.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 356: 1687–717.

Matos E, Pajk B, Borštnar S, Čufer T. Dopolnilno zdravljenje bolnic z rakom dojke s trastuzumabom: trenutno priporočeni izbor zdravljenja na Onkološkem inštitutu v Ljubljani. Onkologija 2006; 10: 109–12.

Program DORA: http://dora.onko-i.si/.

hormone-dependent breast cancer was gradually upgraded with hormonal therapy, known to be the most effective therapy for this type of cancer. In addition, at that time, adjuvant chemotherapy with anthracyclins was introduced and after the year 2000 taxanes were added to anthracycline-based chemotherapy as well. Further improvement achieved after the year 2000 is partly a result of extended hormonal therapy, which will – together with the introduction of aromatase inhibitors into the adjuvant treatment of hormone-dependent disease, and of transtuzumab into the adjuvant therapy of patients with HER2 positive breast cancer in 2005 – undoubtedly contribute to an even better survival of patients who are currently diagnosed and treated for breast cancer.

The survival of patients with metastatic breast cancer at diagnosis has been gradually increasing, though not as much as desired. The comparison with some other groups of patients indicates that the survival of patients with disseminated disease could still be improved in our country. Considering that a majority (around 70%) of breast cancers are hormone-dependent, in order to improve the survival of patients with metastatic disease, we should pay more attention to well managed long-term hormonal therapy of this disease. With the development of ever new hormonal therapies for breast cancer, such as aromatase inhibitors, fulvestrant and some others, this should not be difficult.

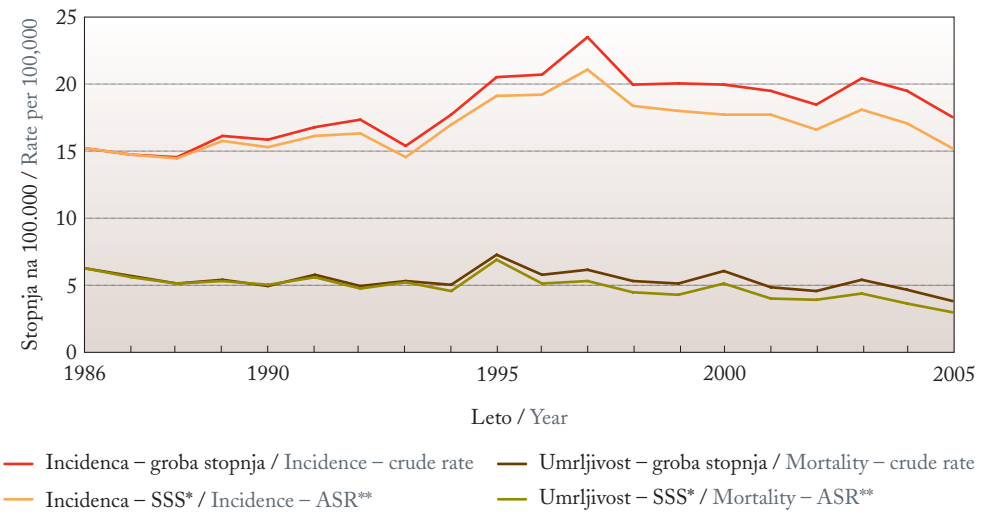
Last but not least, it is encouraging to note that since 1995, the survival of elderly breast cancer patients has finally started to increase as well, though as elsewhere in the world in Slovenia too it is still lagging too much behind the survival of younger patients. In this area a lot more needs to be done not only in Slovenia but also in whole Europe.

MATERNIČNI VRAT

MKB 10: C53

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom materničnega vratu zbolelo 2957 žensk. Kot je razvidno s Slike 1, se je incidenčna stopnja do leta 1997 večala, od takrat naprej pa se zmanjšuje za povprečno 2,1 % letno. Umrljivostna stopnja se pri bolnicah z rakom materničnega vratu ves čas opazovanja zmanjšuje, groba povprečno za 1,7 % letno, starostno standardizirana pa za povprečno 3,3 % letno.



Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka materničnega vratu, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of cervical cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 2937 primerov; 18 bolnic (0,6 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 2 bolnici, mlajši od 20 let, pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih.

Manj kot 1 % bolnic v vsakem obdobju ni imelo mikroskopsko potrjene bolezni. Največ je bilo ploščatoceličnih karcinomov (80 %), 11 % je bilo adenokarcinomov, 7 % je bilo drugih opredeljenih karcinomov, pri preostalih 3 % pa histološka vrsta ni bila natančneje opredeljena.

Več kot polovica bolnic zboli pred 50. letom starosti, okrog tretjina jih je ob diagnozi stara med 50 in 74 let, starejše bolnice so redke (Tabela 1). Deleži v posameznih starostnih skupinah se s časom niso bistveno spreminjali.

Tabela 1: *Število bolnic z rakom materničnega vratu po obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of cervical cancer patients by period of diagnosis with their proportions by age.*

	Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	901	55,8	36,5	7,7
1996–2000	1065	56,6	35,3	8,1
2001–2005	971	57,2	33,8	9,1

CERVIX UTERI

ICD 10: C53

EPIDEMIOLOGY

In the period 1991–2005, a total of 2957 women were diagnosed with cervical cancer. As evident from Figure 1, the crude incidence rate was increasing till 1997, since then it is decreasing by 2.1% annually on average. The mortality rate has been decreasing throughout the observation period, the crude rate by 1.7% annually on average, and the age-standardized by 3.3%.

The survival analysis included 2937 cases; 18 patients (0.6%) diagnosed only after death were not considered in the analysis, 2 patients less than 20 years of age are presented in the chapter on the survival of children and adolescents.

Less than 1% of patients in each time period did not have microscopically confirmed disease. The majority was planocellular carcinomas (80%), 11% were adenocarcinomas and 7% other types of carcinoma, while in the remaining 3% histological type was not precisely determined.

More than half of patients are diagnosed before 50 years of age, approximately one third are diagnosed at an age between 50–74 years, while those developing the disease aged 75 years or older are rare (Table 1). The proportions in individual age groups did not change significantly with time.

The proportion of patients diagnosed with localized stage of the disease has been increasing throughout the observation period; it was 62% in the last period (Table 2). While the proportion of patients with regional stage has decreased on the account of a greater proportion of patients with localized stage, the proportion of patients with disseminated and undefined stages has remained all the time practically the same.

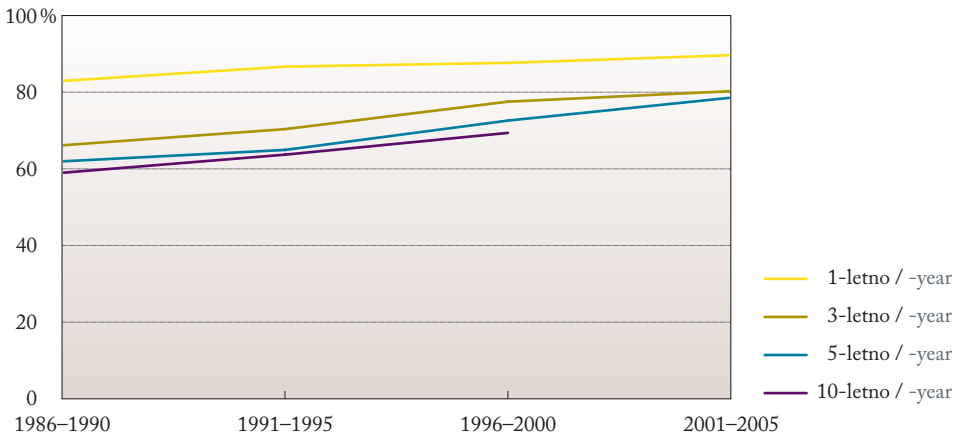
In the years 2001–2005, 5% of patients did not receive specific treatment. The proportion of untreated patients has remained approximately the same throughout the observation period. Among the patients receiving specific treatment in the period 2001–2005, 52% were treated by surgery alone, 10% received teleradiotherapy in addition to surgery, while in 5% this combination also included chemotherapy. Teleradiotherapy alone was used in 8% of patients, a combination of tele- and brachyradiotherapy with or without chemotherapy in 18%, while other combinations were used in less than 2% of patients. The proportion of patients treated only by surgery has been increasing throughout the observation period, mainly on the account of the decreasing proportion of postoperatively irradiated patients. The proportion of patients treated with a combination of tele- and brachyradiotherapy combined with chemotherapy has been increasing too.

In the period 2001–2005 the majority of patients started their treatment at the Department of Gynecology of the UMC Ljubljana (36%); 31% of patients started their treatment at the IO Ljubljana, 9% in the UMC Maribor, and the remaining 24% in a greater or lesser proportion in practically all general hospitals of Slovenia.

Tabela 2: *Število bolnic z rakom maternično vratu po obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of cervical cancer patients by period of diagnosis with their proportions by stage.*

	Ženske / Females				
Obdobje / Period	število / number (%)	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown
1991–1995	901	50,1	44,3	4,9	0,8
1996–2000	1065	54,6	41,1	3,5	0,8
2001–2005	971	61,7	34,0	3,4	0,9



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnic z rakom maternicnega vratu po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of cervical cancer patients by period of diagnosis.*

Ves čas opazovanja pa se je povečeval delež bolnic, ki jim je bila bolezen odkrita v omejenem stadiju bolezni; v zadnjem obdobju je bilo teh 62 % (Tabela 2). Na račun večjega deleža bolnic z omejenim stadijem se je zmanjšal delež bolnic z razširjenim stadijem, delež tistih z razsejanim in neznanim stadijem pa ostaja ves čas približno enak.

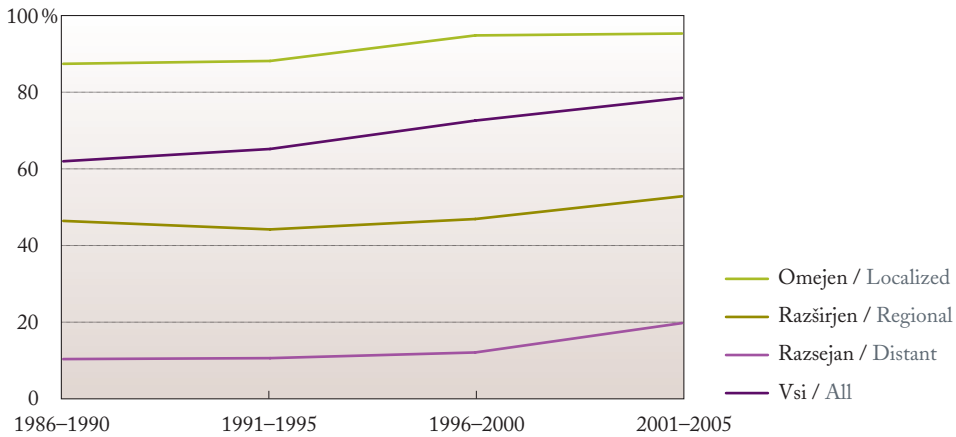
V letih 2001–2005 se ni specifično zdravilo 5 % bolnic. Delež nezdravljenih ostaja v celotnem obdobju analize približno enak. Med specifično zdravljenimi je bilo v letih 2001–2005 52 % bolnic samo operiranih, pri 10 % je bila operaciji dodana še teleradioterapija, pri 5 % pa so tej kombinaciji dodali še kemoterapijo. Samo s teleradioterapijo je bilo zdravljenih 8 % bolnic, s kombinacijo tele- in brahiradioterapije s kemoterapijo ali brez pa 18 %; druge kombinacije so uporabili pri manj kot 2 % bolnic. Delež samo operiranih se je ves čas opazovanja večal, predvsem na

Tabela 3: *Opazovano in relativno preživetje bolnic z rakom maternicnega vratu po obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of cervical cancer patients by period of diagnosis with 95% confidence interva (CI).*

	Opazovano preživetje / Observed survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	85,5 (83,2–87,8)	67,6 (64,6–70,7)	60,9 (57,8–64,2)
1996–2000	86,8 (84,7–88,8)	74,8 (72,3–77,5)	68,5 (65,8–71,4)
2001–2005	88,7 (86,7–90,7)	77,6 (75,0–80,3)	74,2 (71,3–77,1)

	Relativno preživetje / Relative survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	86,6 (84,2–88,9)	70,3 (67,0–73,5)	65,0 (61,5–68,5)
1996–2000	87,7 (85,6–89,8)	77,4 (74,7–80,2)	72,6 (69,6–75,6)
2001–2005	89,7 (87,6–91,7)	80,3 (77,5–83,1)	78,6 (75,5–81,7)



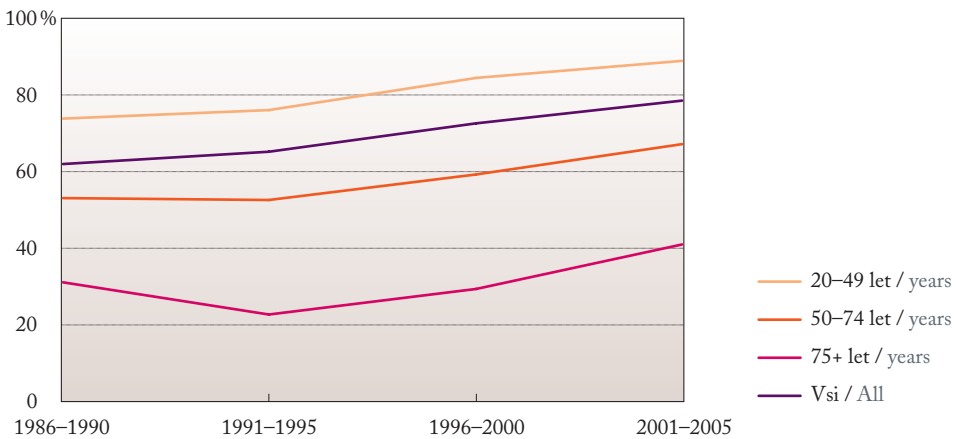
Slika 3: *Petletno relativno preživetje bolnic z rakom materničnega vratu po stadiju in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of cervical cancer patients by stage and period of diagnosis.*

The relative survival rate of patients with cervical cancer has been gradually increasing: thus in 15 years, the 5-year relative survival increased by 14% (Figure 2, Table 3). The relevance of stage at diagnosis is shown in Figure 3: in the last two periods, 5-year relative survival of patients with localized stage has reached 95%. The survival of patients with regional and disseminated disease has been increasing throughout the observation period as well; the 5-year relative survival of those diagnosed between the years 2001–2005 being 53% and 20% respectively. Age is a prognostic factor as well, since the 5-year relative survival in patients less than 50 years of age is 89%, while in those aged 75 years or older is 41% (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 79% (Figure 2); patients surviving the first year may expect to survive five years in 87%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of cervical cancer patients in Slovenia is equal to the European average (Figure 5).



Slika 4: *Petletno relativno preživetje bolnic z rakom materničnega vratu po starosti in obdobju postavitve diagnoze.*

Figure 4: *5-year relative survival of cervical cancer patients by age and period of diagnosis.*

račun manjšanja deleža bolnic, ki so bile poleg operacije še obsevane, in tistih, ki so prejele tele- in brahiradioterapijo. Povečuje se tudi delež bolnic, ki so bile zdravljene s kombinacijo tele- in brahiradioterapije in kemoterapije.

V obdobju 2001–2005 so največ bolnic začeli zdraviti na Ginekološki kliniki UKC Ljubljana (36 %). Na OI Ljubljana so začeli zdraviti 31 % bolnic, 9 % v UKC Maribor, preostalih 24 % pa so v večjem ali manjšem deležu začele zdravljenje v skoraj vseh slovenskih bolnišnicah.

Relativno preživetje bolnic z rakom materničnega vratu se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 14 % (Slika 2, Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnic z omejenim stadijem je v zadnjih dveh obdobjih 95 %. Ves čas se veča tudi preživetje bolnic z razširjenim in razsejanim stadijem; zbolele v letih 2001–2005 z razširjenim stadijem so imele petletno relativno preživetje 53 %, zbolele z razsejanim stadijem pa 20 %. Napovedni dejavnik je tudi starost, saj je petletno relativno preživetje mlajših od 50 let 89 %, starih 75 let in več pa 41 % (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 79 % (Slika 2, Tabela 3); bolnice, ki preživijo prvo leto, pa lahko pričakujejo 87-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnic z rakom materničnega vratu enako kot evropsko povprečje (Slika 5).

KLINIČNI KOMENTAR

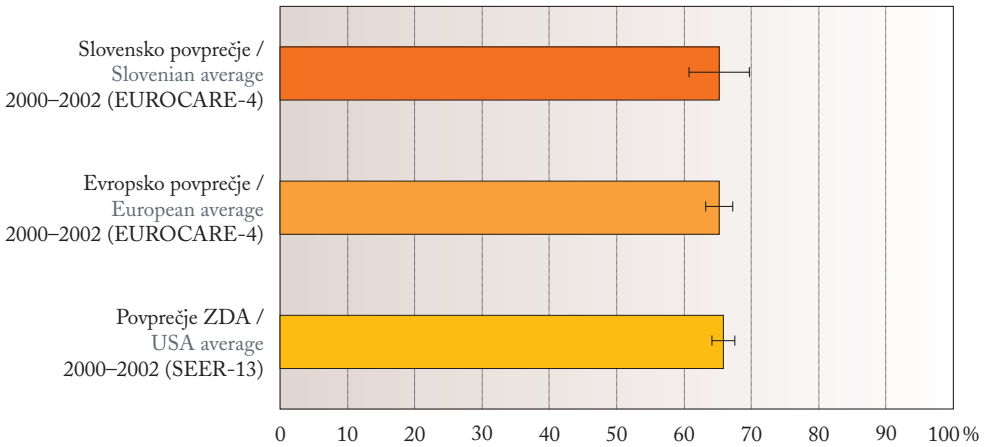
Albert Peter Fras

Praviloma so vse bolnice z rakom materničnega vratu predstavljene multidisciplinarnemu timskemu konziliju, ki izbere za vsako bolnico posebej individualizirani način zdravljenja. Seveda ta bistveno ne odstopa od dogovorjenih smernic zdravljenja ginekoloških rakov; smernice se posodabljajo, tako da upoštevajo vse znane novejše pristope pri zdravljenju.

Število bolnic, pri katerih specifično onkološko zdravljenje ni bilo odrejeno, je skoraj enako v vseh treh obdobjih. Pričakovati pa je treba, da se bo sčasoma število teh bolnic manjšalo, saj je z uvajanjem paliativnega zdravljenja bolnic z napredovalim rakom materničnega vratu v izrazito slabem splošnem stanju možno splošno stanje toliko izboljšati, da je moč izpeljati vsaj kurativno radioterapijo.

Primerjava treh petletnih obdobij 1991–1995, 1996–2000 in 2001–2005 kaže povečanje števila kirurških posegov; v zadnjem obdobju je že polovica bolnic zdravljena samo kirurško. To je mogoče zato, ker ima vedno več bolnic ob prvem zdravljenju nižji stadij bolezni in tako manj napovedno neugodnih kazalcev po kirurškem posegu (infiltrati v parametrijih, zasevki v pelvičnih bezgavkah in druge neugodne napovedne dejavnike). To potrjujejo tudi podatki o pooperativnem zdravljenju z obsevanjem samim ali v kombinaciji s kemoterapijo, saj po kurativnem kirurškem posegu manj bolnic nadaljuje s tem dopolnilnim zdravljenjem. Zagotovo lahko večji delež omejenega stadija pripišemo tudi organiziranemu presejalnemu programu za raka materničnega vratu ZORA, ki na državni ravni deluje od leta 2003. Pričakujemo, da se bo v naslednjih letih poleg manjšanja incidence raka materničnega vratu še naprej večal delež bolezni, odkrite v omejenem stadiju.

Napredovali stadiji raka materničnega vratu so izključna domena radioterapije ali kombinacije radioterapije in kemoterapije. Kombinacija radioterapije in kemoterapije je v zadnjih letih najpogostejši način zdravljenja bolnic z rakom materničnega vratu, ki imajo kljub napredovali bolezni ohranjeno splošno telesno kondicijo. Na to kaže tudi podatek, da se je v obdobju 2001–2005 v primerjavi z obdobjem 1991–1995 delež bolnic, zdravljenih kombinirano, povečal z 0,3 % na 8,1 %, medtem ko se je delež samo obsevanih (tele- in brahiterapija) zmanjšal s 16,3 % na 6,1 %. Pričakovati je treba, da bo uvajanje tridimenzionalnih načrtovanj v teleterapiji in brahiterapiji, ki omogoča povečanje kancericidnega odmerka ob manjši prizadetosti okolnih tkiv,



Slika 5: *Petletno relativno preživetje bolnic z rakom maternicnega vratu (povprecje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of cervical cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

CLINICAL COMMENTARY

Albert Peter Fras

As a rule, all patients with cervical cancer are presented at multidisciplinary team consultation meeting, where a treatment approach is selected for each patient individually. Of course, the selected approach does not deviate from the established guidelines for gynecological cancer treatment; however, the guidelines themselves are being updated by newly adopted treatment approaches.

The number of patients in whom specific oncological treatment was not indicated, remained almost the same in all three observation periods. However, it is expected that the number of these patients will gradually decrease, as the use of palliative therapy in patients with advanced cancer may improve their otherwise extremely poor general condition to such an extent, that at least curative radiotherapy is rendered feasible.

The comparison of three 5-year periods, i. e. 1991–1995, 1996–2000 and 2001–2005, shows an increase in the number of surgical procedures; in the last period half of the patients were treated surgically only. This is a consequence of an increasing number of patients with lower stages at first treatment, and thus with less unfavorable prognostic factors after the surgery (parametrial infiltrations, pelvic lymph node metastases and other unfavorable prognostic factors). This finding is confirmed by the data on less frequent postoperative treatment either with irradiation since less patients require such adjuvant therapy after a curative surgical intervention. An increasing proportion of localized disease can be ascribed to the organised cervical cancer screening programme ZORA, that has been implemented on the national level in 2003. It is expected that along with lower incidence of cervical cancer it will further increase the proportion of localized disease in the following years.

Advanced stages of cervical cancer are strictly the domain of radiotherapy or radiotherapy in combination with chemotherapy. In recent years, combination of radiotherapy and chemotherapy represents the most frequent method of treatment in patients with cervical cancer, when their general condition is adequate, despite an advanced stage of the disease. This is supported by the observation that in comparison with the period 1991–1995, in the period 2001–2005 the proportion of patients with combined treatment increased from 0.3% to 8.1%, while the proportion of those with irradiation alone (tele- and brachytherapy) decreased from 16.3% to 6.1%.

še dodatno izboljšalo možnosti zazdravitve napredovalih rakov materničnega vratu ob manjših poobsevalnih zapletih. Ti pozni zapleti namreč hudo prizadenejo kakovost življenja teh bolnic.

Z uvajanjem doktrine zdravljenja raka rodil je tudi vedno manj bolnišnic, v katerih pričnejo prvo specifično zdravljenje raka materničnega vratu. Vprašanje je, ali so pri začetnem zdravljenju v nespecializiranih ustanovah naključno odkrili raka materničnega vratu pri zdravljenju drugih ginekoloških bolezni. Da sodi zdravljenje raka materničnega vratu v ustanove, ki imajo s tem največje izkušnje, kažejo tudi podatki o večjem relativnem preživetju (65-odstotno relativno petletno preživetje v obdobju 1991–1995 in 79-odstotno v obdobju 2001–2005). Sprejetje in posodabljanje doktrine zdravljenja raka rodil je gotovo prispevalo k dvigu strokovnosti predvsem v osnovni ginekološki službi, saj je tako bolnicam omogočeno zdravljenje v visoko specializiranih ustanovah z največ izkušnjami (Ginekološka klinika UKC Ljubljana, OI Ljubljana, UKC Maribor).

VIRI
Literature

Fras AP, ed. Doktrina zdravljenja ginekoloških malignomov. Ljubljana: Onkološki inštitut; 1992.

Pompe-Kirn V, Zakotnik B, Zadnik V. Preživetje bolnikov z rakom v Sloveniji 1983–1997. Ljubljana: Register raka za Slovenijo. Onkološki inštitut Ljubljana; 2003.

Program ZORA: www.onko-i.si/zora.

Stržinar V, Baškovič M, Bebar S, Cerar O, Fras AP, Koritnik K, et al. Ginekološki malignomi: doktrina zdravljenja ginekoloških malignomov na Onkološkem inštitutu in Univerzitetni ginekološki kliniki. 2. rev. izd. Zveza slovenskih društev za boj proti raku, 2001.

It is expected that the implementation of three-dimensional radiation treatment planning in teleradiotherapy and brachytherapy, which facilitates increasing cancericidal dosages at lesser exposure of the surrounding tissue, will further improve the possibilities of achieving control of advanced cervical cancer and reducing the irradiation related complications. These late sequels severely affect the quality of patient's life.

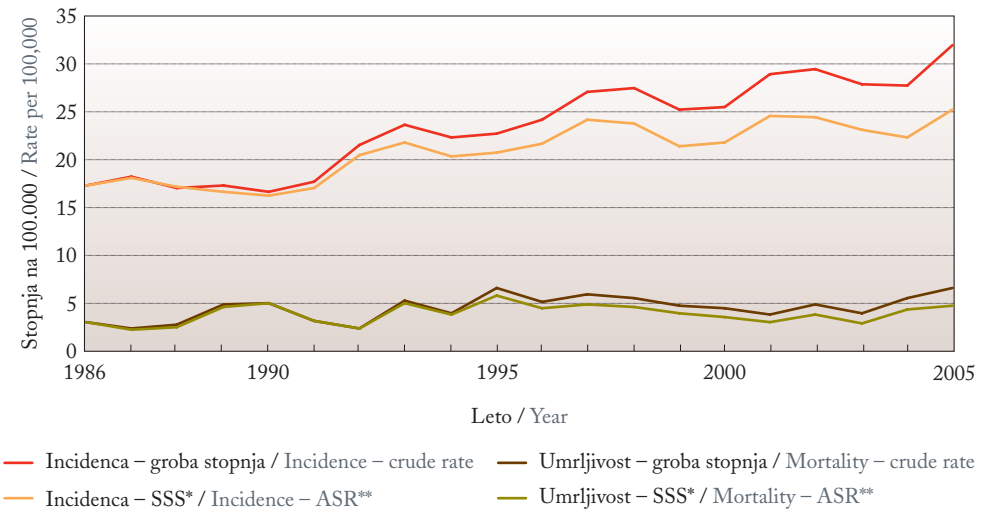
As a result of implementing the guidelines of gynecological cancer treatment, the number of hospitals starting a specific treatment for cervical cancer has been considerably reduced. The question is whether cervical cancer initially treated in non-specialized institutions has been detected incidentally, during treatment for other gynecological conditions. The fact that cervical cancer treatment should be performed in institutions with most experience in this area is further supported by the data on greater relative survival rates (65% relative 5-year survival in the period 1991–1995 vs. 79% in the period 2001–2005). The implementation of the guidelines for gynecological cancer treatment and their upgrading has certainly contributed towards improvement of expertise, particularly in primary oncological services, thus enabling the patients access to treatment in highly specialized institutions with most experience in the treatment of these cancers (UMC Ljubljana – Department of Gynecology, IO Ljubljana, UMC Maribor – Department of Perinatology and Gynecology).

MATERNIČNO TELO

MKB 10: C54

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom maternične telesa zbolelo 3942 žensk. Kot je razvidno s Slike 1, se obe incidenčni stopnji ves čas opazovanja večata, groba za povprečno 3,0 %, starostno standardizirana pa se veča počasneje (za 1,7 %), saj je rak maternične telesa bolezen predvsem starejših žensk (Tabela 1). Povečuje se tudi groba umrljivostna stopnja, povprečno za 2,6 % letno, medtem ko je starostno standardizirana umrljivostna stopnja praktično konstantna.



Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka maternične telesa, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of corpus uteri cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 3918 primerov; 24 bolnic (0,6 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

Manj kot 1 % bolnic v vsakem obdobju ni imel mikroskopsko potrjene bolezni. Praktično vsi mikroskopsko potrjeni primeri so bili adenokarcinomi ali drugi opredeljeni karcinomi; leiomiosarkomov je bilo le 0,4 %.

Več kot 70 % bolnic je zbolelo med 50. in 74. letom starosti, pred 50. letom je zbolelo manj kot 10 % bolnic. Delež starih 75 let in več se s časom veča; v zadnjem obdobju je znašal 21 % (Tabela 1).

Tabela 1: *Število bolnic z rakom maternične telesa po obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of corpus uteri cancer patients by period of diagnosis with their proportions by age.*

	Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	1108	8,0	76,5	15,4
1996–2000	1322	10,6	74,1	15,3
2001–2005	1488	8,1	70,6	21,3

CORPUS UTERI

ICD 10: C54

EPIDEMIOLOGY

In the period 1991–2005, a total of 3942 women were diagnosed with endometrial cancer. As evident from Figure 1, both incidence rates have been increasing throughout the observation period, the crude incidence rate by 3.0% annually on average. Age-standardized rate has been increasing more slowly (by 1.7%), since endometrial cancer is prevailingly a disease of elderly women (Table 1). Crude mortality rate has been increasing as well, by 2.6% annually on average, while the age-standardized mortality rate remains stable.

The survival analysis included 3918 cases; 24 patients (0.6%) diagnosed only after death were not considered in the analysis.

Less than 1% of patients in each time period did not have microscopically confirmed disease. Practically all microscopically confirmed cases were either adenocarcinomas or other specified carcinomas; there were only 0.4% of leiomyosarcomas.

More than 70% of patients were diagnosed at an age between 50 and 74 years, and less than 10% of patients were younger than 50 years. The proportion of those aged 75 years or older has been increasing with time, in the last period reaching 21% (Table 1).

In all three time-periods, approximately three fourths of patients were diagnosed with localized disease; the proportion of those with the disease diagnosed in regional stage has been increasing while patients with disseminated disease at diagnosis are rare (Table 2).

In the years 2001–2005, 6% of patients did not receive specific treatment. The proportion of untreated patients is practically the same throughout the study period. Among the patients receiving specific treatment in the period 2001–2005, 43% were treated by surgery alone while 45% received tele- and/or brachyradiotherapy in addition to surgery. Other combinations were used in less than 3% of the patients. The proportion of patients treated only by surgery has been increasing throughout the observation period, mainly on the account of the smaller proportion of postoperatively irradiated patients.

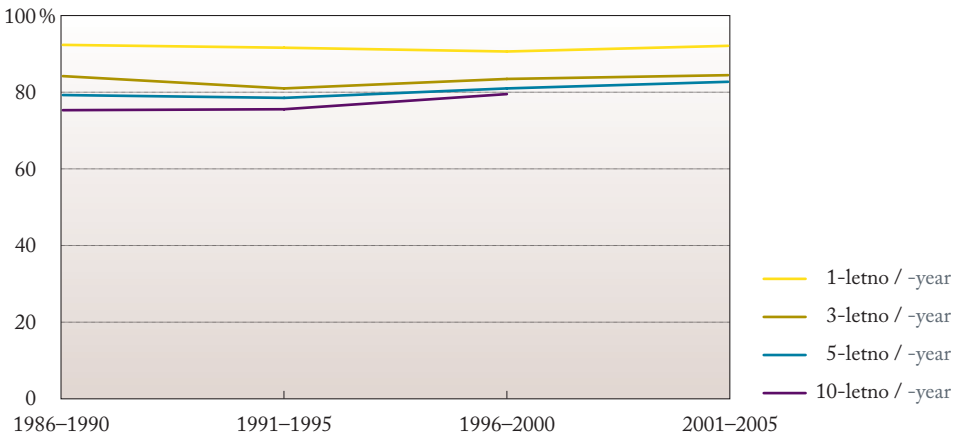
In the period 2001–2005, the majority of patients started their treatment at the Department of Gynecology of the UMC Ljubljana (43%), 15% of patients started their treatment at the IO Ljubljana, 12% in the UMC Maribor, and the remaining 23% in lesser proportions in practically all general hospitals of Slovenia.

The relative survival rate of patients with endometrial cancer has been gradually increasing: thus in 15 years, the 5-year relative survival increased by 4% (Figure 2, Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the recent period, the 5-year relative survival of patients with localized disease was 95%, while patients with advanced disease had 54% relative 5-year survival, and those with disseminated disease only 34%. The survival rates of patients with endometrial cancer by stage did not change significantly with time. Age is a prognostic

Tabela 2: *Število bolnic z rakom maternične telesa po obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of corpus uteri cancer patients by period of diagnosis with their proportions by stage.*

	Ženske / Females				
Obdobje / Period	število / number (%)	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown
1991–1995	1108	76,5	13,4	8,1	2,0
1996–2000	1322	76,3	15,6	6,1	2,0
2001–2005	1488	73,5	17,7	7,3	1,4



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnic z rakom maternicnega telesa po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of corpus uteri cancer patients by period of diagnosis.*

V vseh treh obdobjih je bila pri približno treh četrtinah bolnic ob diagnozi bolezen omejena; veča se delež tistih, ki jim bolezen odkrijejo v razširjenem stadiju, redke pa so bolnice z razsejano boleznijo ob diagnozi (Tabela 2).

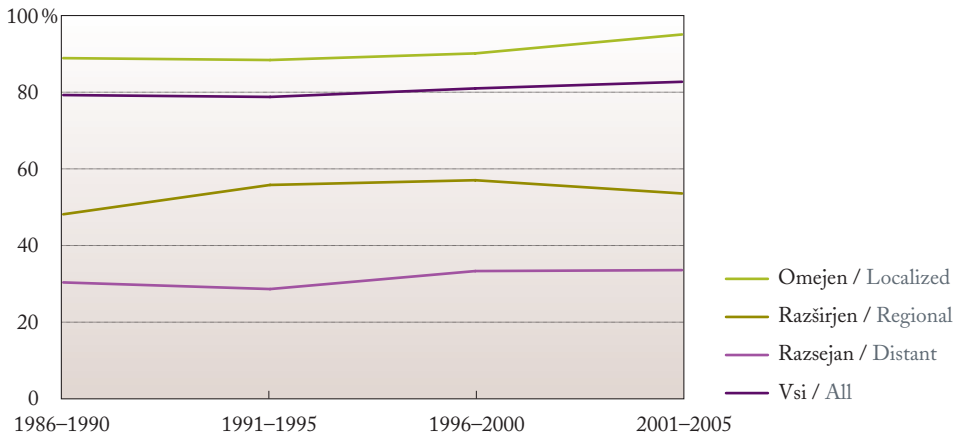
V letih 2001–2005 ni bilo specifično zdravljenih 6 % bolnic. Delež nezdravljenih je vse obdobje analize približno enak. Med specifično zdravljenimi je bilo v letih 2001–2005 43 % bolnic le operiranih, pri 45 % je bila operaciji dodana še tele- in/ali brahiradioterapija. Druge kombinacije so uporabili pri manj kot 3 % bolnic. Delež samo operiranih se je ves čas opazovanja večal, predvsem na račun manjšega deleža bolnic, ki so bile po operaciji dopolnilno zdravljene še z obsevanjem.

Tabela 3: *Opazovano in relativno preživetje bolnic z rakom maternicnega telesa po obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of corpus uteri cancer patients by period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	89,3 (87,5–91,1)	74,6 (72,1–77,2)	68,5 (65,8–71,3)
1996–2000	88,7 (87,0–90,5)	78,1 (75,9–80,4)	72,2 (69,8–74,6)
2001–2005	89,9 (88,4–91,5)	78,3 (76,2–80,5)	72,4 (70,0–74,9)

	Relativno preživetje / Relative survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	91,5 (89,7–93,4)	80,9 (78,1–83,7)	78,4 (75,2–81,6)
1996–2000	90,6 (88,9–92,4)	83,4 (81,0–85,8)	80,9 (78,1–83,6)
2001–2005	92,0 (90,4–93,6)	84,4 (82,1–86,7)	82,6 (79,8–85,5)



Slika 3: *Petletno relativno preživetje bolnic z rakom maternicnega telesa po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of corpus uteri cancer patients by stage and period of diagnosis.*

factor as well, since the 5-year relative survival in patients less than 50 years of age is 91%, while in those aged 75 years or older is 47% (Figure 4).

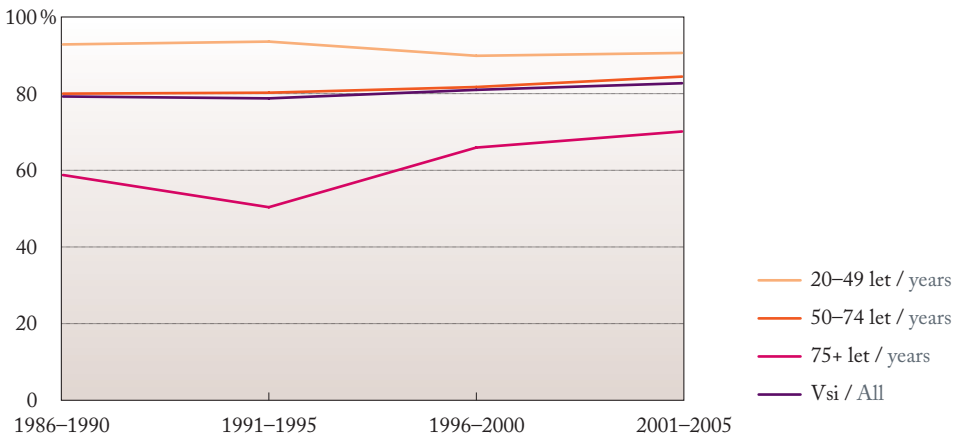
The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 83% (Figure 2); patients surviving the first year may expect to survive five years in 89%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of endometrial cancer patients in Slovenia is nearly equal to the European average (Figure 5).

CLINICAL COMMENTARY

Albert Peter Fras

Endometrial cancer is the most frequent type of gynecological cancer. The early symptoms also being the warning signs, most cancers are diagnosed at an operable stage, as surgery is the most suitable method of treatment. The adopted guidelines for gynecological cancer treatment include recommendations for diagnostic procedures that facilitate undelayed confirmation of the disease and thus also the beginning of treatment when the disease is confined to the endometrium.



Slika 4: *Petletno relativno preživetje bolnic z rakom maternicnega telesa po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of corpus uteri cancer patients by age and period of diagnosis.*

V obdobju 2001–2005 se je največ bolnic začelo zdraviti na Ginekološki kliniki UKC Ljubljana (43 %). Na OI Ljubljana je zdravljenje začelo 15 % bolnic, 12 % v UKC Maribor, preostalih 23 % pa v manjših deležih v praktično vseh slovenskih bolnišnicah.

Relativno preživetje bolnic z rakom maternicnega telesa se zmerno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 4 % (Slika 2, Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnic z omejenim stadijem je v zadnjem obdobju 95 %, medtem ko je pri bolnicah z razširjenim stadijem petletno relativno preživetje 54 %, z razsejanim pa 34 %. Preživetje bolnic z rakom maternicnega telesa po stadijih se s časom ni bistveno spreminjalo. Napovedni dejavnik je tudi starost, saj je petletno relativno preživetje mlajših od 50 let 91 %, starih 75 let in več pa 47 % (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 83 % (Slika 2); bolnice, ki preživijo prvo leto, pa lahko pričakujejo 89-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnic z rakom maternicnega telesa skoraj enako evropskemu povprečju (Slika 5).

KLINIČNI KOMENTAR

Albert Peter Fras

Rak maternicnega telesa je najpogostejši rak rodil. Ker so zgodnji znaki tudi opozorilni znaki, se večina bolezni diagnosticira v operabilnih stadijih. V sprejeti doktrini zdravljenja rakov rodil se tudi priporočajo diagnostični postopki, ki omogočajo čim hitrejšo potrditev bolezni, s tem pa tudi zdravljenje, ko je bolezen še omejena na maternično telo. Kirurško zdravljenje je najbolj ustrezno zdravljenje in tudi preživetje tako zdravljenih bolnic je največje. Dopolnilno zdravljenje z brahiterapijo ali teleterapijo je utečeni način zdravljenja, vendar se prav v zadnjem obdobju opaža, da se deloma opušča teleterapija kot dopolnilno zdravljenje, saj se s tem manjša verjetnost poobsevalnih zapletov, kot so fibroza male medenice, stenoze sečevodov, kronični radiocistitis in radioproktitis.

Klinični stadij II (FIGO) s potrjenim prodorom v maternični vrat je indikacija za radikalnejši kirurški poseg z odstranitvijo medeničnih bezgavk. Le pri medicinskih kontraindikacijah za operativni poseg se uporablja kombinacija teleterapije in brahiterapije, vendar je petletno preživetje bistveno manjše kot po operativnem posegu; po nekaterih navedbah je okoli 50 %. Pri ostanku bolezni v maternični votlini pa priporočajo histerektomijo kot odrešilni poseg.

Napredovali stadiji so izključno domena radioterapije, predvsem teleterapije ali kombinacije tele- in brahiterapije. Sama brahiterapija s svojimi tehničnimi možnostmi je možna le pri manjši skupini izbranih bolnic. Uvajanje intrakavitarne brahiterapije z obsevanji s hitrim pretokom odmerka (HDR) bo verjetno nekoliko razširilo indikacije za uporabo takega načina zdravljenja, vendar le pri bolnicah z boleznijo, omejeno na maternico.

Petletno relativno preživetje se je v 15-letnem obdobju povečalo. To lahko delno pripisujemo tudi temu, da je vedno več bolnic začelo specifično onkološko zdravljenje v bolnišnicah, ki imajo s tovrstnim zdravljenjem največ izkušenj (Ginekološka klinika UKC Ljubljana, OI Ljubljana ter UKC Maribor) in ne nazadnje tudi vedno višji strokovni ravni v osnovni ginekološki službi.

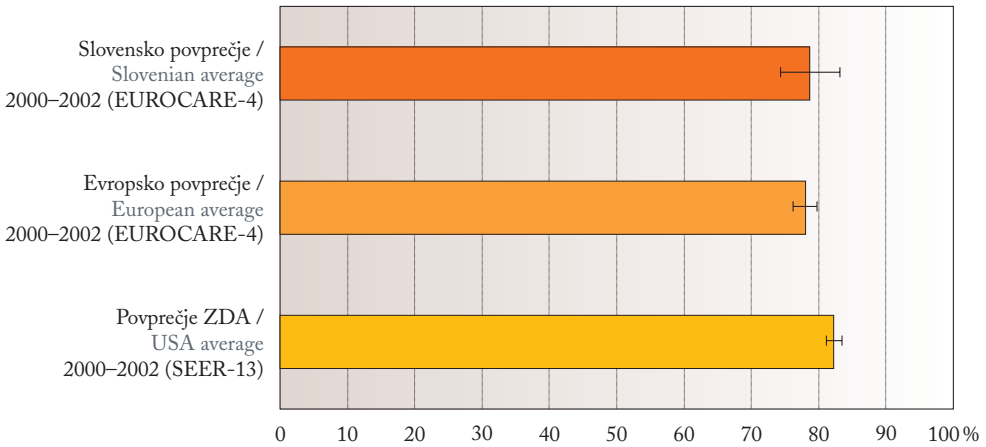
VIRI

Literature

Cohen CJ, Thomas GM. Endometrial Cancer. In: Holland JF, Frei E III, Bast R Jr, eds. Cancer Medicine, Fourth Edition. Baltimore: W&W; 1997.

Fras AP, Bebar S, Vrščaj Uršič M. Radikalna intrakavitarna brahiterapija endometrijskega karcinoma. In: Lukič F, Kocijan A, Demšar F, Bergant O, eds. Onkološki vikend, Šmarješke Toplice, november 1992. Zbornik. Ljubljana: Kancerološka sekcija slovenskega zdravniškega društva, Zveza slovenskih društev za boj proti raku; 1992.

Stržinar V, Baškovič M, Bebar S, Cerar O, Fras AP, Koritnik K, et al. Ginekološki malignomi: doktrina zdravljenja ginekoloških malignomov na Onkološkem inštitutu in Univerzitetni ginekološki kliniki. 2. rev. izd. Zveza slovenskih društev za boj proti raku, 2001.



Slika 5: *Petletno relativno preživetje bolnic z rakom maternične telesa (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of corpus uteri cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

Surgical treatment is the most appropriate and the survival of patients with such treatment is the highest. Adjuvant treatment with brachy- or teleradiotherapy is an established treatment approach, however, it has been noted particularly in the last period that teleradiotherapy as adjuvant treatment modality has been partly abandoned in order to reduce the possibility of post-irradiation sequels, such as pelvic fibrosis, stenoses of the urethers, chronic radiocystitis and radioproctitis.

Clinical stage II (FIGO) with confirmed invasion into the uterine cervix represents an indication for a radical surgical intervention with pelvic lymphadenectomy. A combination of teleradiotherapy and brachytherapy is indicated only in cases with medical contraindications for surgery; however, 5-year survival of these patients is significantly lower than with surgery, according to some reports being 50%. In cases with residual disease in the uterine cavity, hysterectomy is recommended as salvage therapy.

Advanced stages are strictly the domain of radiotherapy and in particular teletherapy or a combination of tele- and brachytherapy. Due to its technical potentials, brachytherapy alone is feasible only in a limited group of selected patients. The introduction of high-dose-rate intracavitary brachytherapy (HDR-ICR) will probably slightly broaden the indications for the use of such treatment modality, however only in patients with the disease confined to the uterus.

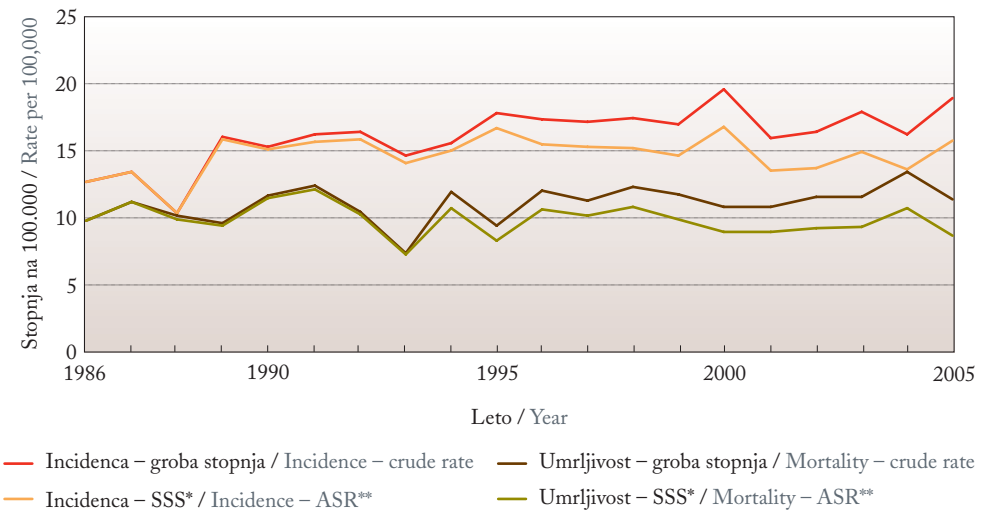
Comparing all three observation periods, the 5-year relative survival has slightly increased. This can be partly ascribed to the fact that a growing number of patients have started their specific oncological treatment at hospitals with the greatest experience in this type of treatment (UMC Ljubljana – Department of Gynecology, IO Ljubljana, and UMC Maribor – Department of Perinatology and Gynecology), and last but not least to the ever improving expertise of the primary gynecological services.

JAJČNIK

MKB 10: C56

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom jajčnika zbolelo 2661 žensk. Kot je razvidno s Slike 1, se v opazovanem obdobju grobi incidenčni in umrljivostni stopnji zmerno večata; incidenčna povprečno za 0,8 % in umrljivostna za povprečno 1,2 % letno. Obe starostno standardizirani stopnji kažeta padajoči trend; manjšata se za povprečno 0,5 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka jajčnika, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of ovarian cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 2331 primerov; 59 bolnic (0,2 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 32 mlajših od 20 let obravnavamo v poglavju o preživetju pri otrocih in mladostnikih, iz vseh analiz pa smo izvzeli tudi 239 primerov mejno malignih rakov jajčnika.

Približno 4 % bolnic v vsakem obdobju ni imelo mikroskopsko potrjene bolezni. Med mikroskopsko potrjenimi je bilo največ (86 %) adenokarcinomov, 5 % je bilo drugih opredeljenih ali neopredeljenih karcinomov, 2 % tumorjev je bilo kompleksnih mešanih in stromalnih tumorjev, ostalih histoloških vrst je bilo manj kot 1 %.

Skoraj dve tretjini bolnic zboli v starosti 50–74 let. Delež mlajših od 50 let je v vseh obdobjih opazovanja podoben, v zadnjem desetletju se je povečal delež starih 75 let in več (Tabela 1).

Tabela 1: *Število bolnic z rakom jajčnika po obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of ovarian cancer patients by period of diagnosis with their proportions by age.*

	Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	703	20,3	67,0	12,7
1996–2000	765	20,4	62,1	17,5
2001–2005	863	19,7	63,4	16,9

OVARY

ICD 10: C56

EPIDEMIOLOGY

In the period 1991–2005, a total of 2661 women were diagnosed with ovarian cancer. As evident from Figure 1, in the observed period crude incidence and mortality rates have been increasing slowly. The estimated annual percentage increase in crude incidence rate was 0.8% and in crude mortality rate 1.2%. However, both age-standardized rates indicate a decreasing trend by 0.5% per year on average.

The survival analysis included 2331 cases; 59 patients (0.2%) with ovarian cancer diagnosed only after death were not considered in the analysis, 32 patients under 20 years of age are presented in the chapter on the survival of children and adolescents. 239 cases of ovarian cancer of borderline malignancy were excluded from the analysis as well.

Approximately 4% of patients in each age group did not have microscopically confirmed disease. Among the microscopically confirmed cancers adenocarcinomas (86%) were prevailing, the rest were specified or non-specified carcinomas (5%), complex mixed and stromal tumors (2%) and other histological types (less than 1%).

Almost two-thirds of the patients present with the disease at an age between 50–74 years. The proportion of those less than 50 years of age is similar in all observation periods, while in the last decade, the proportion of patients aged 75 years or older has increased (Table 1).

Approximately three-quarters of patients were diagnosed with disseminated disease. The proportion of patients with disseminated disease is increasing with time, while the rate of those with localized or regional stage of the disease is decreasing. In approximately 3% of patients stage at diagnosis was not determined (Table 2).

In the period 2001–2005, 9% of patients did not receive specific treatment. The proportion of untreated patients slightly decreased, their percentage in the period 1991–1995 being 12%. Among the patients receiving specific treatment in the period 2001–2005, 65% were treated by surgery and chemotherapy, 15% underwent surgery alone, and 12% received chemotherapy alone while 5% of the patients had a combination of chemotherapy, surgery and radiotherapy. Other combinations were used in less than 5% of the patients. Compared to the period 1991–1995, in recent years significantly less patients had radiotherapy as primary treatment.

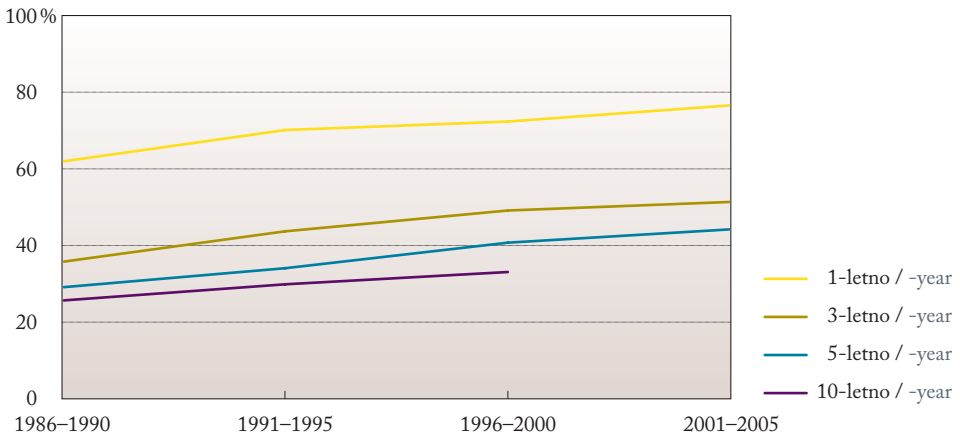
In the period 2001–2005, 30% of patients started their treatment at the Department of Gynecology of the UMC Ljubljana and the IO Ljubljana, 14% in the UMC Maribor, and the remaining 26% by smaller proportions in almost all general hospitals of Slovenia.

The relative survival rate of patients with ovarian cancer has been increasing: in 15 years, the relative 5-year survival increased by 10% (Figure 2, Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the recent period, the relative 5-year survival of patients with localized disease was 94%, patients with regional disease had 55% relative 5-year survival, and those with disseminated disease only 34%. A significant improvement in the relative 5-year survival rates

Tabela 2: *Število bolnic z rakom jajčnika po obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of ovarian cancer patients by period of diagnosis with their proportions by stage.*

	Ženske / Females				
Obdobje / Period	število / number (%)	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown
1991–1995	703	16,2	12,9	67,7	3,1
1996–2000	765	16,7	14,5	66,7	2,1
2001–2005	863	13,1	7,8	76,4	2,8



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnic z rakom jajčnika po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of ovarian cancer patients by period of diagnosis.*

Približno pri treh četrtinah bolnic je bila bolezen odkrita v razsejanem stadiju. Delež bolnic z razsejano boleznijo se s časom veča, manjša pa se delež odkritih v omejenem ali razširjenem stadiju bolezni. Približno pri 3 % bolnic stadij ob diagnozi ni bil določen (Tabela 2).

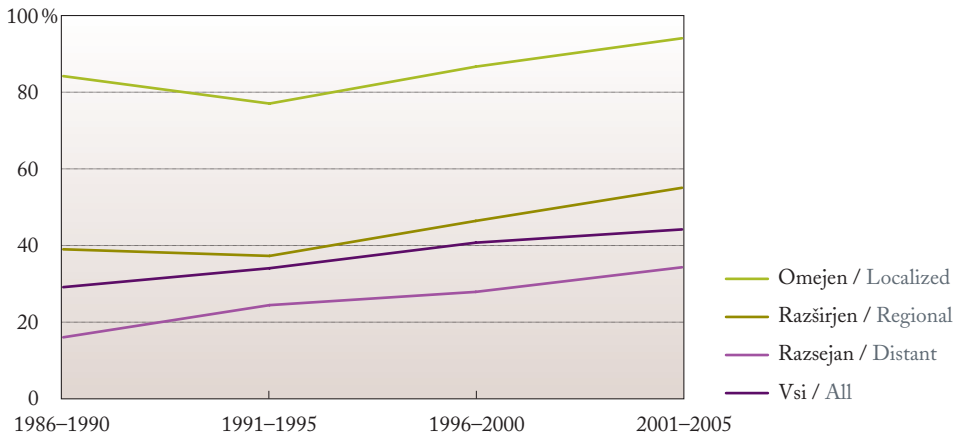
V obdobju 2001–2005 ni bilo specifično zdravljenih 9 % bolnic. Delež nezdravljenih bolnic se je nekoliko zmanjšal; v letih 1991–1995 ni bilo specifično zdravljenih 12 % bolnic. Med specifično zdravljenimi bolnicami jih je bilo v letih 2001–2005 65 % operiranih in zdravljenih s kemoterapijo, 15 % jih je bilo samo operiranih, 12 % pa je prejelo samo kemoterapijo; 5 % bolnic je bilo poleg kemoterapije in operacije še obsevanih. Druge kombinacije so uporabili pri manj kot 5 % bolnic. V primerjavi z obdobjem 1991–1995 je bilo v sklopu prvega zdravljenja v zadnjih letih obsevanih bistveno manj bolnic.

Tabela 3: *Opazovano in relativno preživetje bolnic z rakom jajčnika po obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of ovarian cancer patients by period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	68,8 (65,5–72,4)	41,0 (37,5–44,8)	30,7 (27,5–34,3)
1996–2000	70,9 (67,7–74,1)	45,9 (42,5–49,6)	36,2 (33,0–39,8)
2001–2005	75,2 (72,4–78,1)	48,4 (45,2–51,9)	39,7 (36,2–43,4)

	Relativno preživetje / Relative survival (%)		
	Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	70,2 (66,7–73,8)	43,6 (39,5–47,6)	34,2 (30,2–38,2)
1996–2000	72,4 (69,0–75,7)	49,0 (45,1–53,0)	40,7 (36,7–44,7)
2001–2005	76,6 (73,6–79,6)	51,4 (47,7–55,1)	44,2 (40,0–48,4)



Slika 3: *Petletno relativno preživetje bolnic z rakom jajčnika po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of ovarian cancer patients by stage and period of diagnosis.*

was evident in all stages. Age is a prognostic factor as well, since the relative 5-year survival in patients less than 50 years of age is 62%, while in those aged 75 years or older it is only 20%. An increasing time trend in survival was most apparent in the age group 50–74 years (Figure 4).

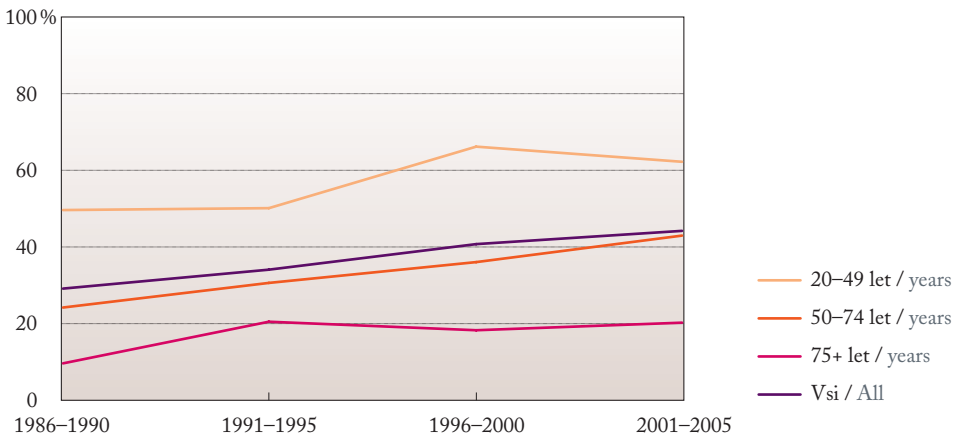
The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 44% (Figure 2); patients surviving the first year may expect to survive five years in 57%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of ovarian cancer patients in Slovenia is nearly equal to the European average (Figure 5).

CLINICAL COMMENTARY

Marjetka Uršič Vrščaj
Olga Cerar

The data on ovarian cancer in this presentation include only the data on invasive ovarian cancer without those of borderline malignancy. Ovarian tumors of borderline malignancy differ from the invasive type since their growth is not invasive, they rarely become recurrent, and even



Slika 4: *Petletno relativno preživetje bolnic z rakom jajčnika po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of ovarian cancer patients by age and period of diagnosis.*

V obdobju 2001–2005 je zdravljenje po 30 % bolnic pričelo na Ginekološki kliniki UKC Ljubljana in na OI Ljubljana, 14 % v UKC Maribor, preostalih 26 % pa v manjših deležih v skoraj vseh slovenskih splošnih bolnišnicah.

Relativno preživetje bolnic z rakom jajčnika se povečuje; v 15 letih se je petletno relativno preživetje povečalo za 10 % (Slika 2, Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnic z omejenim stadijem je v zadnjem obdobju 94 %, medtem ko je pri bolnicah z razširjenim stadijem petletno relativno preživetje 55 %, pri tistih z razsejanim pa le 34 %. Izboljšanje petletnih relativnih preživetij je značilno pri vseh stadijih. Napovedni dejavnik je tudi starost, saj je petletno relativno preživetje mlajših od 50 let 62 %, pri starih 75 let in več let pa je petletno relativno preživetje 20 %. Rastoči časovni trend preživetja je najbolj izrazit v starostni skupini 50–74 let (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 44 % (Slika 2); bolnice, ki preživijo prvo leto, pa lahko pričakujejo 57-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnic z rakom jajčnika skoraj enako evropskemu povprečju (Slika 5).

KLINIČNI KOMENTAR

Marjetka Uršič Vrščaj
Olga Cerar

Podatki o raku jajčnikov v tej knjigi vključujejo le podatke o invazivnem raku jajčnikov brez podatkov o mejno malignih tumorjih. Mejno maligni tumorji jajčnikov so klinično drugačni kot invazivni, ne rastejo invazivno, le redko in praviloma šele po mnogih letih recidivirajo, zato je ločevanje obeh skupin pomembno.

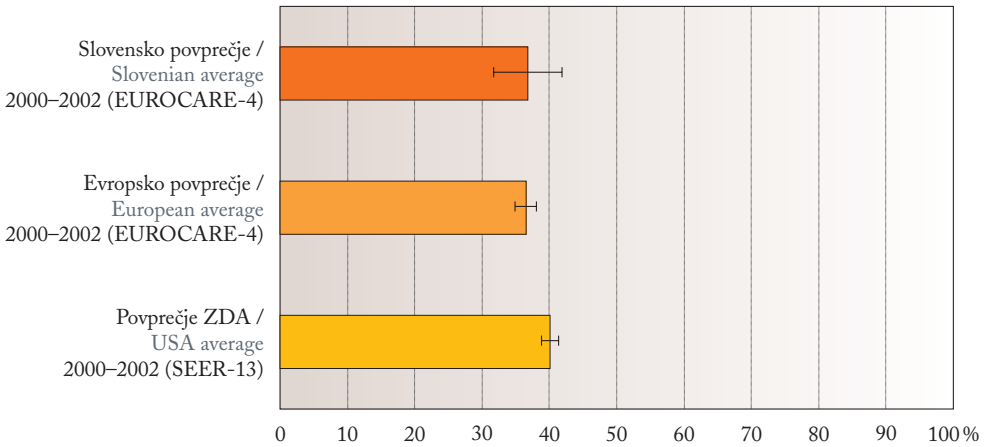
Podatek o visokem deležu razsejanega raka jajčnikov v obdobju 2001–2005 po vsej verjetnosti kaže na boljše upoštevanje smernic in izboljšanje diagnostičnih postopkov pri postavitvi pravilnega stadija bolezni, ki je ključni napovedni dejavnik in izhodišče za pravilno in učinkovito zdravljenje. Velik delež razsejanega raka še vedno odslikava pomanjkanje ustreznih metod za zgodnje odkrivanje tega raka, podobno kot drugod po Evropi.

Način zdravljenja invazivnega raka jajčnikov se je v tem 15-letnem obdobju spreminjal. V skladu s priporočili o učinkovitosti čim bolj radikalne odstranitve tumorskega tkiva, ki mu sledi sistemsko zdravljenje s citostatiki, se povečuje delež bolnic, zdravljenih kirurško in s sistemsko kemoterapijo. Skoraj 80 % bolnic, zdravljenih kirurško ali kirurško in s citostatiki (odvisno od razširjenosti bolezni) v obdobju 2001–2005 kaže na sodoben pristop pri zdravljenju raka jajčnikov.

Iz podatkov o prvem specifičnem zdravljenju bolnic z rakom jajčnikov je razvidno, da se prvo (kirurško) zdravljenje pri tretjini bolnic še vedno opravi po posameznih (številnih) bolnišnicah v Sloveniji. Ostanek tumorskega tkiva po kirurškem posegu je eden od najpomembnejših napovednih dejavnikov pri zdravljenju raka jajčnikov. Izkušenost ginekološko-kirurške ekipe, ki je predvsem odsev števila opravljenih tovrstnih posegov, je ključnega pomena. Kljub stalnemu izobraževanju in poudarjanju tega dejstva pa je delež bolnic, ki se zdravijo v manjših centrih v Sloveniji, v vseh treh obdobjih še vedno nespremenjen in ne kaže na izboljšanje.

Pomembno je, da se petletno relativno preživetje vseh bolnic z rakom jajčnikov postopno povečuje, tako pri omejeni, razširjeni in razsejani bolezni. Izboljšanje preživetja je najverjetneje posledica bolj agresivnega zdravljenja, vključno z uporabo novih, učinkovitejših citostatikov. Podatki so primerljivi s povprečjem ostalih evropskih držav. Izboljšanje relativnega preživetja se kaže tudi po desetih letih, kar je pri bolezni s slabo napovedjo izida, kot je rak jajčnikov, še toliko pomembneje.

Petletno relativno preživetje po starostnih obdobjih kaže za obdobje 2001–2005 v primerjavi z obdobjem 1996–2000 na nekatere spremembe. Čeprav se je v obdobju 2001–2005 petletno



Slika 5: *Petletno relativno preživetje bolnic z rakom jajčnika* (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of ovarian cancer patients* (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

* Nabor MKB10 kod v študiji EUROCARE-4 je nekoliko drugačen kot smo ga uporabili pri ostalih analizah predstavljenih v tem poglavju: v študiji EURCARE-4 so v analizo vključene tudi maligne neoplazme materničnih priveskov in Wolfovih vodov (MKB10: C570–C577).

* The ICD10 code selection in EUROCARE-4 study is slightly different in comparison to the selection applied in other analysis in this chapter: in EUROCARE-4 study the malignant neoplasm of uterine adnexa and Wolffian body (ICD10: C570–C577) are included.

then it generally takes years before their recurrence, therefore it is important to differentiate between the two groups.

The data on a high rate of disseminated ovarian cancer in the period 2001–2005 probably indicates more consistent following of the guidelines and improved diagnostic procedures at establishing the correct stage of the disease, which are a key prognostic factor and the basis for an appropriate and effective treatment. High rate of disseminated cancer still reflects the lack of suitable methods for early diagnosis of this cancer, likewise elsewhere in Europe.

In the last 15-year period, the mode of treatment for invasive ovarian cancer has been changing. In compliance with the recommendations on the effectiveness of maximum radical removal of tumor tissue, followed by a systemic treatment with cytotoxic drugs, the proportion of patients treated with a combination of surgery and chemotherapy is increasing. Almost 80% of patients treated surgically or by means of surgery and chemotherapy (depending on the extent of the disease) in the period 2001–2005 are indicative of a modern approach to the treatment of ovarian cancer.

The data on the primary specific treatment of patients with ovarian cancer show that in one-third of the patients the primary therapy (surgery) is still carried out in individual (several) hospitals in Slovenia. Tumor residue after surgery is one of the most important prognostic factors for ovarian cancer treatment. Experience and skills of surgical team, acquired mainly through numerous surgical interventions performed, are of key importance. Despite the permanent education and emphasizing that fact, the proportion of patients treated in minor centers throughout Slovenia has remained unchanged in all three observation periods, and there is no evidence of improvement in this respect.

It is important to note that 5-year survival of all patients with ovarian cancer is gradually increasing in localized as well as in regional and disseminated disease. Improvement in the survival is most probably attributable to a more aggressive treatment, including the use of new, more

relativno preživetje v številčno najmočnejši skupini bolnic med 50 in 74 leti povečalo, pa se pri bolnicah, starih 75 let in več, ni spremenilo, v starosti 20–49 let pa se je celo nekoliko zmanjšalo. Pri starejših bolnicah je zdravljenje raka zaradi pridruženih bolezni pogosto prilagojeno, krajše in zato manj kakovostno. Pomembno izboljšanje preživetja je zato težje pričakovati. Zmanjšanje petletnega relativnega preživetja pri mlajših bolnicah, starih 20–49 let, pa potrebuje spremljanje v daljšem obdobju in dodatne analize. Upoštevati je treba, da delež bolnic v tem starostnem obdobju predstavlja le petino vseh bolnic z rakom jajčnikov, zato slabše preživetje posameznic lahko hitreje vpliva na rezultat cele skupine. Že zbrani podatki kažejo, da je odstotek adenokarcinomov, najpogostejših malignih tumorjev jajčnikov, v tem starostnem obdobju približno enak, tako v obdobju 1996–2000 (89,1 %) kot tudi v obdobju 2001–2005 (88,2 %), kar ne kaže na spremenjeno patohistološko strukturo tumorjev in morebitno posledično drugačno napoved izida oz. preživetje. Delež omejenega, razširjenega in razsejanega raka jajčnikov se je pri mlajših spremenil podobno kot v drugih dveh starostnih skupinah. Kakšno je preživetje po enem in treh letih, kakšna je diferenciranost tumorjev, kako radikalni so kirurški posegi, in nenazadnje, v kolikšni meri lahko na preživetje vpliva t. i. konzervativno zdravljenje pri mlajših bolnicah itd. – vse to so vprašanja, ki jih bo z dodatnimi analizami potrebno razjasniti.

VIRI
Literature

Epithelial ovarian carcinoma: ESMO Clinical Recommendations for diagnosis, treatment and follow up. 2007. http://annonc.oxfordjournals.org/cgi/reprint/18/suppl_2/ii12.

NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V. I. 2007. www.nccn.org

NCCN Updates Ovarian Cancer Guidelines. 2008. www.nccn.org.

Register raka za Slovenijo. Poročilo za leto 2005, Onkološki inštitut Ljubljana, 2008.

Stržinar V, Baškovič M, Bebar S, Cerar O, Fras AP, Koritnik K, et al. Ginekološki malignomi. Doktrina zdravljenja ginekoloških malignomov na Onkološkem inštitutu in Univerzitetni ginekološki kliniki Ljubljana. 3. revidirana izd. Ljubljana: Zveza slovenskih društev za boj proti raku, 2002.

effective cytotoxic drugs. The data are comparable with the averages in other European countries. The improvement in relative survival is also evident after a 10-year period, which is ever more important in the case of diseases with poor prognosis, such as ovarian cancer.

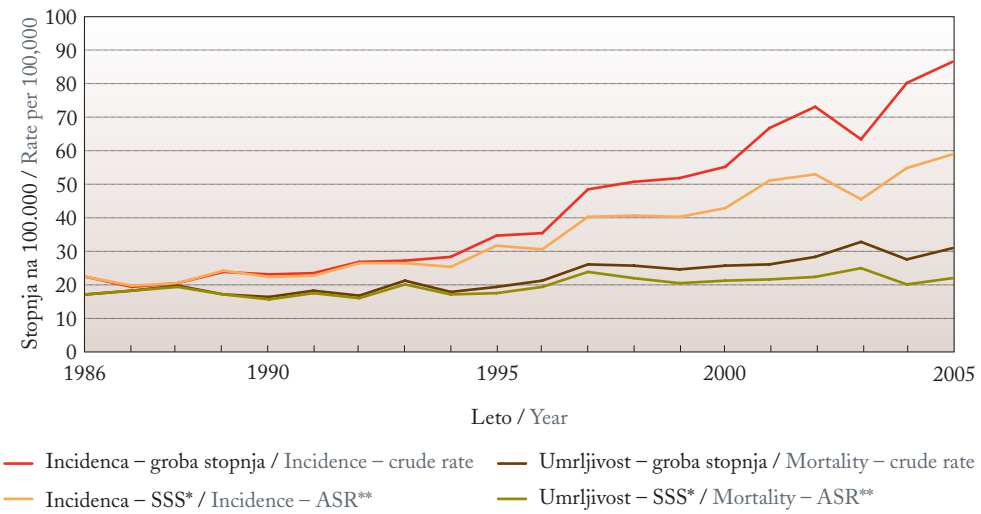
Five-year survival by age group for the period 2001–2005 points out some differences as compared to the period 1996–2000. Although in the period 2001–2005 the relative 5-year survival in the most numerous group of patients aged 50–74 years has increased, in the patients aged 75 years or older it remained unchanged, while in the age group 20–49 years it was even slightly lower. In older patients cancer-specific therapy often needs to be adjusted and reduced due to concomitant diseases, which renders it less effective. Therefore, a significant improvement in the survival can hardly be expected. The decreased 5-year relative survival of younger patients aged 20–49 years calls for a longer follow-up period and additional analyses. It should be taken into consideration that the proportion of patients in this age group represents only a fifth of all patients with ovarian cancer, and therefore poor survival in individual cases may easily influence the total score of the group. The data indicate that the percentage of adenocarcinomas, i. e. the most frequent malignant ovarian tumors, was in that age group practically the same in both periods: in 1996–2000 it was 89.1% and in 2001–2005 it was 88.2%. This is not indicative of a changed pathohistological tumor structure and thus of possibly different prognosis or survival. The proportion of localized, regional and disseminated ovarian cancers in younger patients was comparable with those in other age groups. What is the survival after one and three years, what is tumor differentiation, how radical are surgical interventions and, last but not least, to what extent may the so-called conservative treatment in younger patients influence their survival, etc.? – All these are the questions that need to be clarified in further analyses.

PROSTATA

MKB 10: C61

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom prostate zbolelo 7660 moških. Kot je razvidno s Slike 1, se groba in starostno standardizirana incidenčna stopnja ves čas opazovanja večata, groba povprečno za 10,0 % letno, starostno standardizirana pa povprečno za 6,9 % letno. Večata se tudi umrljivostni stopnji, groba povprečno za 4,4 % letno, starostno standardizirana pa povprečno za 2,1 % letno.



Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka prostate, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of prostatic cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 7299 primerov; 361 bolnikov (4,9 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

V obdobju 2001–2005 je bilo 91 % primerov raka prostate mikroskopsko potrjenih. Delež mikroskopsko potrjenih primerov se je v primerjavi z obdobjem 1991–1995 povečal za 2 %. V vseh treh obdobjih je imelo največ bolnikov adenokarcinom, v zadnjem obdobju je bil njegov delež 80 %, za 14 % večji kot v prvem. To povečanje ni posledica spremenjenih histoloških vrst tumorjev, pač pa večje natančnosti patologov pri pisanju histološkega izvida. Še vedno pa v zadnjem obdobju ostaja 19 % karcinomov neopredeljenih.

Tabela 1: *Število bolnikov z rakom prostate po obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of prostatic cancer patients by period of diagnosis with their proportions by age.*

	Moški / Males			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	1361	1,0	58,2	40,9
1996–2000	2323	0,9	68,1	30,9
2001–2005	3615	0,7	71,4	27,9

PROSTATE

ICD 10: C61

EPIDEMIOLOGY

In the period 1991–2005, a total of 7660 men were diagnosed with prostate cancer. As evident from Figure 1, the crude and age standardized incidence rates have been increasing throughout the observation period, the crude rate by 10.0% and the age-standardized rate by 6.9% annually on average. The mortality rates have been increasing as well, the crude rate by 4.4% and the age standardized by 2.1% annually on average.

The survival analysis included 7299 cases; 361 patients (4.9%) diagnosed only after death were not considered in the analysis.

In the period 2001–2005, 91% of prostate cancers were microscopically verified. In comparison with the period 1991–1995 the proportion of microscopically confirmed cases has increased by 2%. In all three time-periods, the majority of patients had adenocarcinoma, in the last period their proportion was 80%, which is by 14% more than in the first period. This increase is not a result of changed histological types, but should be attributed to greater accuracy of histological findings. However, in the last period 19% of carcinomas still remained undefined.

More than half of the patients are diagnosed at an age between 50 to 70 years, their proportion in the last period being almost three fourths (Table 1); in comparison with the first period, in the last one the proportion of patients aged 75 years or older has decreased by 13%, however, in absolute figures this still represents almost a half more new cases than in the period 1991–1995; the number of patients aged 50–74 years has increased threefold (from 792 to 2581 new cancer cases in the period 2001–2005). Prostate cancer before 50 years of age is extremely rare.

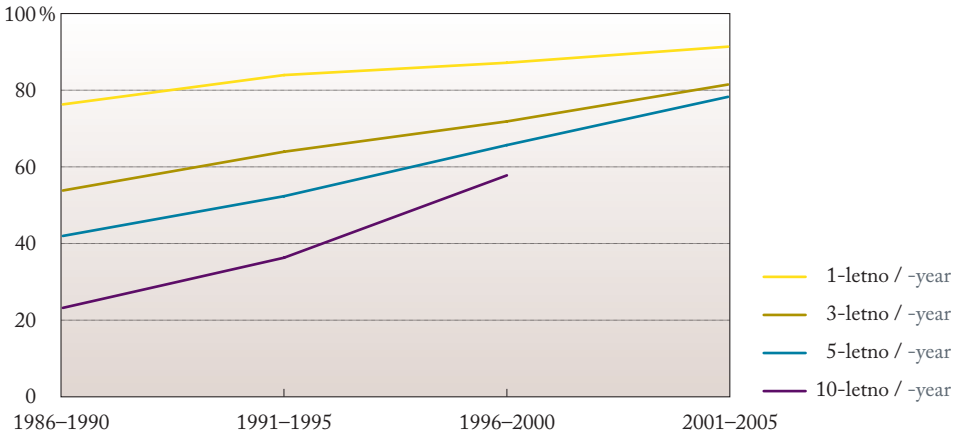
In all three time-periods, the majority of patients were diagnosed with localized disease; in the period 2001–2005 their proportion being 64% (Table 2). In the latter period, 17% of patients had regional and 10% disseminated disease; the proportion of patients with disseminated stage has been decreasing with time. In the first period there were 18% of patients with undefined stage, whereas in the last period their proportion was still 9%.

In the years 2001–2005, 11% of patients did not receive specific treatment. In comparison with the first period, the proportion of untreated patients has increased by almost 2%. Among those receiving specific treatment, 38% were treated with hormones and 30% with surgery only, 18% with a combination of surgery and hormones, 7% received radiotherapy besides hormonal treatment while 5% also had surgery, 1% of the patients received chemotherapy alone or in combination with other treatment modalities, while all other combinations represented less than 1%. In the course of the 15-year period, the most common therapeutic approaches have changed, the most frequent treatment modality in the period 1991–1995 being a combination of surgery and hormones (35%), followed by surgery alone (26%), while hormonal therapy alone was used in 14% of patients only.

Tabela 2: *Število bolnikov z rakom prostate po obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of prostatic cancer patients by period of diagnosis with their proportions by stage.*

	Moški / Males				
Obdobje / Period	število / number (%)	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown
1991–1995	1361	48,0	13,7	20,4	18,0
1996–2000	2323	52,6	14,6	15,9	16,8
2001–2005	3615	64,0	16,6	10,4	9,1



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom prostate po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of prostatic cancer patients by period of diagnosis.*

Več kot polovica bolnikov zboli v starosti 50–74 let, v zadnjem obdobju skoraj tri četrtine (Tabela 1); delež starih 75 let in več se je sicer v zadnjem obdobju v primerjavi s prvim zmanjšal za 13 %, vendar v absolutnih številkah to še vedno pomeni v tej starosti skoraj polovico več novih primerov kot v letih 1991–1995; število bolnikov v starosti 50–74 let se je povečalo za trikrat (s 792 na 2581 novih primerov raka v letih 2001–2005). Rak prostate je pred 50. letom starosti izjemno redka bolezen.

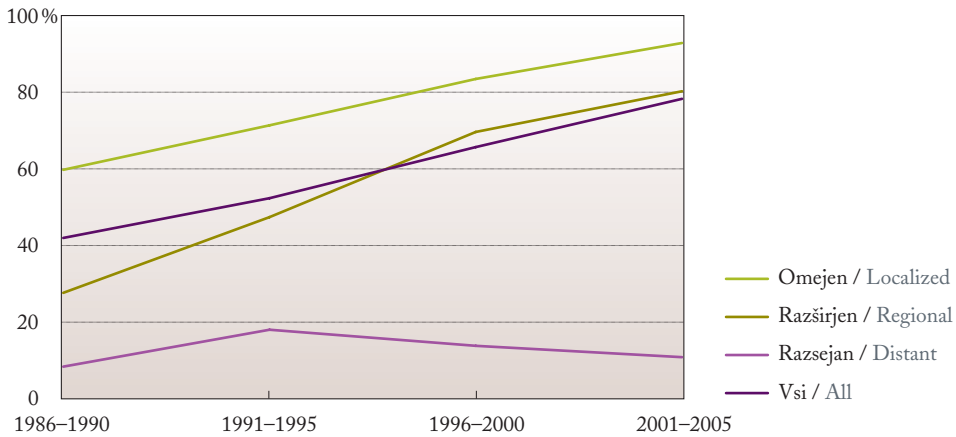
V vseh treh obdobjih je imelo največ bolnikov ob diagnozi omejeno bolezen; v letih 2001–2005 64 % (Tabela 2). V tem obdobju je imelo 17 % bolnikov razširjeni stadij, 10 % pa razsejanega; delež bolnikov z razsejanim stadijem se z leti manjša. V prvem obdobju stadija ni imelo določenega 18 % bolnikov, v zadnjem pa še vedno 9 %.

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom prostate po obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of prostatic cancer patients by period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)		
	Moški / Males		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	77,7 (75,6–80,0)	50,6 (48,0–53,4)	35,2 (32,7–37,8)
1996–2000	81,9 (80,3–83,5)	59,1 (57,1–61,1)	46,9 (44,9–49,0)
2001–2005	86,4 (85,3–87,5)	68,5 (67,0–70,1)	57,5 (55,7–59,4)

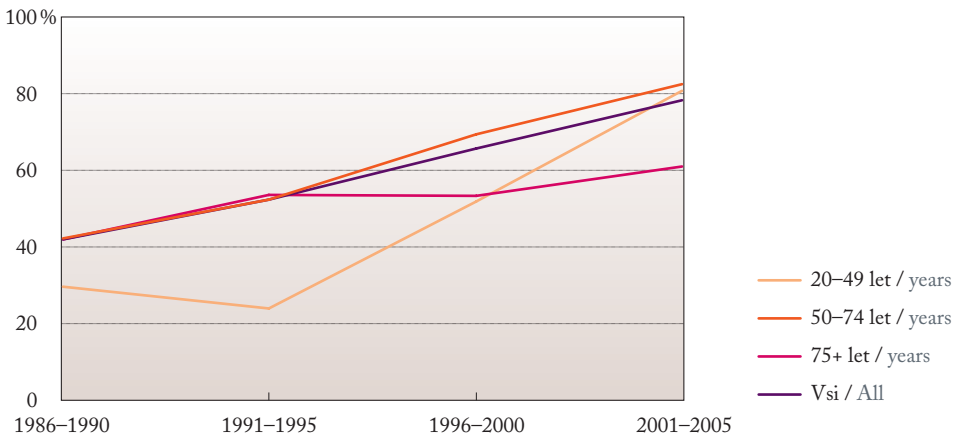
	Relativno preživetje / Relative survival (%)		
	Moški / Males		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	83,9 (81,4–86,3)	63,9 (60,4–67,3)	52,4 (48,4–56,3)
1996–2000	87,2 (85,6–88,9)	71,9 (69,4–74,4)	65,6 (62,7–68,5)
2001–2005	91,2 (90,0–92,4)	81,5 (79,7–83,4)	78,2 (75,6–80,8)



Slika 3: *Petletno relativno preživetje bolnikov z rakom prostate po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of prostatic cancer patients by stage and period of diagnosis.*

In the period 2001–2005, 30% of patients started their treatment in the UMC Ljubljana, 15% in GH Celje, 14% in the UMC Maribor, 12% in GH Slovenj Gradec, 6% in GH Murska Sobota, 4% each in GH Nova Gorica, GH Izola and GH Novo mesto, 3% at the IO Ljubljana and the remaining 8% in other hospitals and outpatient clinics for urology.

The relative survival rate of patients with prostate cancer has been increasing: in 15 years, the 5-year relative survival increased by 26% (Figure 2, Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last period, 5-year relative survival of patients with localized stage exceeded 90%, while in those with regional stage it increased by 33% in the 15-year period, in the patients diagnosed in the period 2001–2005 being 80%. Treatment outcome in patients with disseminated stage was less encouraging, as their already poor survival in the first period (18%) has underwent a further decrease, thus being in patients diagnosed in the years 2001–2005 only 11%. Survival has been increasing in all age groups, most obviously in those aged 50–74 years, in whom it has increased by 30% in the 15-year period; lesser increase in the survival (8% only) was observed in the oldest age group (Figure 4). The evaluation of time trend in the 5-year relative survival of patients aged 20–49 years is not reliable due to a small number of patients.



Slika 4: *Petletno relativno preživetje bolnikov z rakom prostate po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of prostatic cancer patients by age and period of diagnosis.*

V letih 2001–2005 ni bilo specifično zdravljenih 11 % bolnikov. Delež nezdravljenih se je v primerjavi s prvim obdobjem povečal za skoraj 2 %. Med specifično zdravljenimi je bilo 38 % bolnikov zdravljenih samo s hormoni, 30 % samo z operacijo, 18 % s kombinacijo operacije in hormonov, 7 % je poleg hormonske prejelo še radioterapijo, 5 % pa so še operirali, 1 % bolnikov je dobil kemoterapijo samo ali v kombinaciji z drugimi vrstami zdravljenja; vseh drugih kombinacij je bilo manj kot 1 %. Najpogostejši terapevtski pristopi so se v petnajstletnem obdobju spremenili, saj je bilo v obdobju 1991–1995 najpogostejše zdravljenje kombinacija operacije s hormoni (35 %), sledila mu je samo operacija (26 %), samo hormonsko pa je bilo zdravljenih le 14 % bolnikov.

V obdobju 2001–2005 je 30 % bolnikov zdravljenje začelo v UKC Ljubljana, 15 % v SB Celje, 14 % v UKC Maribor, 12 % v SB Slovenj Gradec, 6 % v SB Murska Sobota, po 4 % v SB Nova Gorica, SB Izola in SB Novo mesto, 3 % na OI Ljubljana, preostalih 8 % pa v drugih bolnišnicah in v uroloških ambulantah.

Relativno preživetje bolnikov z rakom prostate se veča; v 15 letih se je petletno relativno preživetje povečalo za 26 % (Slika 2, Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjem obdobju preseglo 90 %, pri bolnikih z razširjenim stadijem pa se je v 15 letih povečalo za 33 % in je bilo pri tistih, diagnosticiranih v letih 2001–2005, 80-odstotno. Manj spodbuden je izid zdravljenja bolnikov z razsejanim stadijem, saj se pri njih že tako majhno preživetje od prvega obdobja (18 %) manjša in je bilo pri bolnikih, diagnosticiranih v letih 2001–2005, le 11-odstotno.

Preživetje se veča v vseh starostnih skupinah, najbolj pri starih 50–74 let, kjer se je v 15 letih povečalo za 30 %, manj pa pri najstarejših, pri katerih se je povečalo le za 8 % (Slika 4). Vrednotenje časovnega trenda petletnega relativnega preživetja bolnikov, starih 20–49 let, pa ni zanesljivo, saj je bolnikov malo.

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 78 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 85-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom prostate statistično značilno manjše od evropskega povprečja (Slika 5).

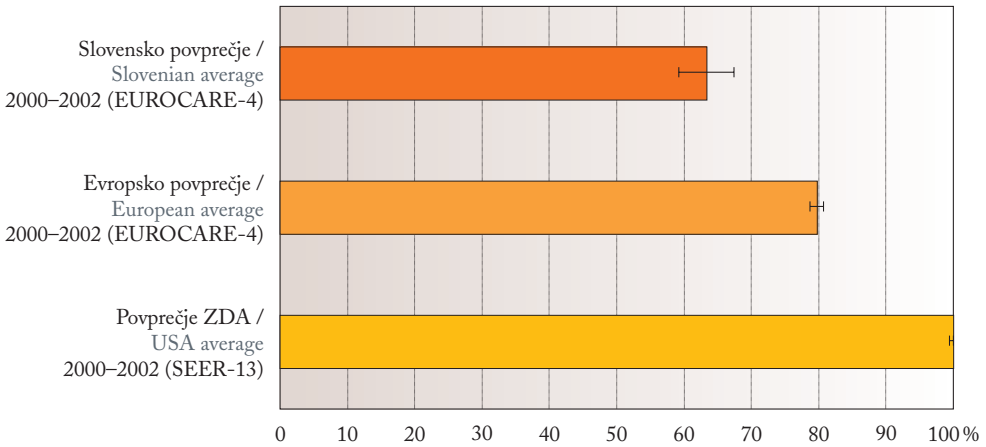
KLINIČNI KOMENTAR

Andrej Kmetec

Iz prikazanih podatkov je razvidno, da se incidenca raka prostate vztrajno veča; veča se predvsem groba stopnja, kar je razumljivo, saj se povprečna starost moških veča, manj izrazit je porast starostno standardizirane stopnje. Naraščanja incidence raka prostate si ne moremo razlagati le z boljšim prijavljanjem bolezni in z boljšim odkrivanjem bolezni, ker pri vse več moških opravimo test PSA. Ob večanju incidence se veča tudi umrljivostna stopnja, čeprav počasneje, kar kaže na to, da kljub zgodnjemu odkrivanju in večanju preživetja še vedno preveč bolnikov umre zaradi te bolezni. Pregled umrljivosti v nekaterih evropskih državah, ZDA in na Japonskem kaže, da se ponekod umrljivost zmanjšuje, samo na Japonskem naj ne bi bila posledica presejanja s PSA.

Histološko je rak potrjen v več kot 90 %. Histološka preiskava ni bila opravljena pri manj kot 10 % bolnikih, ki so pretežno moški v visoki starosti s spremljajočimi težjimi boleznimi, kjer sumimo, da gre za raka prostate le na osnovi tipanja trde, grčasto spremenjene prostate in visokih vrednosti PSA.

Več kot 85 % bolnikov je dobilo eno od ustreznih zdravljenj: hormonsko, kirurško, obsevalno ali kombinacijo teh vrst zdravljenja. Število bolnikov, ki so bili radikalno kirurško zdravljeni, se je v zadnjem desetletju skoraj podvojilo. V zadnjih letih opažamo, da se povečuje število radikalnih prostatektomij pri lokaliziranem raku prostate za 10–12 % letno. Verjetno je to tudi eden od vzrokov, da se je v zadnjih letih povečalo predvsem relativno preživetje po petih letih in se



Slika 5: *Petletno relativno preživetje bolnikov z rakom prostate (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of prostatic cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 78% (Figure 2); patients surviving the first year may expect to survive five years in 85%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of prostate cancer patients in Slovenia is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Andrej Kmetec

As evident from the presented data, the incidence of prostate cancer is steadily increasing, particularly the crude rate, which is understandable since the life expectancy of men is increasing; the increase in age-standardized rates is less prominent. The increasing incidence of prostate cancer cannot be explained only by more systematic reporting of the disease and better cancer detection due to more frequent use of the PSA test in males. Along with the increasing incidence the mortality rate is increasing too, though at a slower trend, which shows that despite early diagnosis and better survival still too many patients die from this disease. A survey of mortality rates in certain European countries, the United States and in Japan shows that in some areas the mortality is decreasing, however, except in Japan, this trend should not be associated with PSA screening.

Cancer is histologically confirmed in over 90% of cases. Histological examination has not been performed in less than 10% of patients, mostly men at an advanced age with severe concomitant diseases, where the presence of prostate cancer was suspected only on the basis of palpation of a nodular prostate and high PSA levels.

More than 85% of patients received one of the suitable treatments: hormones, surgery, irradiation or a combination of these. The number of patients undergoing radical surgery has almost doubled in the past decade. In recent years we note that the number of radical prostatectomies in localized prostate cancer has been increasing by 10–12% per year. Probably this is one of the reasons for an increase in the 5-year relative survival in last years, which is already approaching 80%. Another reason may lie in a greater proportion of the localized prostate cancer, particularly in the middle age group, which means that the disease is detected at an early stage

že bliža 80 %. Drugi vzrok je morda večji delež omejenega raka prostate, predvsem v srednji življenjski dobi, kar pomeni, da gre za zgodaj odkrito obliko bolezni, pri kateri je še možna ozdravitev. S tem v zvezi se je za polovico znižal odstotek razsejane oblike raka, kar pomeni, da smo uspeli s pravočasno diagnostično preiskavo odkriti zgodnje oblike raka in povečali možnost ozdravitve ter preživetje bolnikov, vendar predvsem pri omejeni in razširjeni obliki bolezni.

Žal se relativno preživetje manjša pri razsejani obliki raka, morda zaradi bolj maligne, slabo diferencirane vrste raka, pozne prepoznave razširjenosti bolezni ali pa začnemo prepozno intenzivno zdraviti, zlasti s kombiniranimi načini zdravljenja.

V zadnjem desetletju se vztrajno veča odstotek moških, ki zbolijo v srednji življenjski dobi, v starosti 50–74 let, zmanjšuje pa se odstotek tistih, ki jim odkrijemo bolezen po 75. letu. To kaže, da s testiranjem PSA uspemo odkriti bolezen v začetni fazi razvoja, ko je še omejena na žlezo in je zdravljenje lahko bolj radikalno, zato je tudi preživetje bolnikov boljše, saj je rak prostate bolezen, ki se razvija počasi in se klinično izrazi šele po 10 do 14 letih.

Pri bolnikih, ki jim odkrijemo bolezen v starosti 75 let ali več, gre pogosto za napredovalo bolezen ali za bolj maligne vrste raka, ki jih je samo s testom PSA težje odkriti, če ni hkrati tudi težav z uriniranjem. Tako si lahko delno razlagamo slabše relativno preživetje v tej starostni skupini. Poleg tega se pri tej starosti težje odločimo za bolj radikalne vrste zdravljenja (zlasti kirurško), prevladuje predvsem paliativni način zdravljenja, kar pa nikakor ne pomeni slabše kakovosti zdravljenja ali celo opustitve zdravljenja. K slabšemu preživetju pa prispevajo tudi dodatne bolezni starostnikov, ki včasih ovirajo izbiro ustreznega načina zdravljenja.

Rak prostate je bolezen, ki sama po sebi ne povzroča nobenih težav, če ni pridruženo še benigno povečanje prostate in s tem motnja uriniranja. Odkrivanje bolezni sloni predvsem na testiranju s PSA in zavedanju moških o potrebnih preventivnih pregledih.

VIRI
Literature

Cookson MM. Prostate cancer: screening and early detection. Cancer Control 2001; 8: 133–40.

Colombel M, Xavier M, Florence ML, Jean Marie M. Longterm survival after prostatectomy. Eur Urol Suppl 2006; 5: 127.

European Associacion of Urology. Guidelines on prostate cancer, 2005.

Marugame T, Mizuno S. Comparison of prostate cancer mortality in five countries: France, Italy, Japan, UK and USA from the WHO mortality database (1960–2000). Jpn J Clin Oncol 2005; 35: 690–1.

Myers PR. Localised prostate cancer: important of conduct for radical prostatectomy. Eur Urol Suppl; 2001: 10–4.

Schröder FH, Gosselaar C, Roemeling S, Postma R, Roobol JM, Bangma CH. PSA and the detection of prostate cancer after 2005. Part I. Eur Urol Suppl 4, 2006: 2–12.

Schröder FH, Alexander FE, Bangma CH, Hugsson J, Smith DS. Screening and early detection of prostate cancer. Prostate 2000; 44: 255–63.

Wallsh PC. Radical prostatectomy for localised prostate cancer provides durable cancer control with excellent quality of life: a structured debate. J Urol 2000; 163: 1802–7.

KLINIČNI KOMENTAR
Borut Kragelj

Ena od pomembnih značilnosti raka prostate je pogosto počasen naraven potek bolezni. Računalniški modeli kažejo, da je potrebno približno 15 let, da se iz PIN razvije invaziven karcinom, ki ostane v povprečju še nadaljnjih 6 let omejen na prostato. Tudi pri bolnikih z že klinično jasnim sistemskim razsojem povprečno preživetje presega 5 let. Rak prostate zmanjšuje preživetje le pri bolnikih z oddaljenimi zasevki in morda pri manjšem delu bolnikov z zasevki v področnih bezgavkah oziroma z lokalno napredovalimi tumorji. In le pri teh je morda lahko petletno preživetje odvisno od ustrezno vodenega in pravočasno pričetega sistemskega zdravljenja. Bolnike, pri katerih je rak omejen na prostato, sama bolezen življenjsko ne ogroža. Čeprav se zasevki pri manjšem delu teh bolnikov sicer lahko pojavijo v petletnem obdobju

when cure is still possible. Further to that, the proportion of disseminated cancer has been reduced by half, indicating that timely diagnosis has enabled us to detect the disease at an early stage and thus improve the patients' chances of cure and survival, however prevailingly in the case of localized and regional forms of the disease.

Unfortunately, the relative survival in disseminated disease has been decreasing, perhaps due to a more malignant poorly differentiated cancer type, late staging of the disease or delayed intensive therapy, and in particular combined treatment modality.

In the last decade, the proportion of males diagnosed at an age between 50 to 74 years has been steadily increasing, while the proportion of those with the disease diagnosed aged 75 years or older is decreasing. This indicates that by means of the PSA test, the disease can be detected at an early stage when it is still confined to the gland and thus the treatment can be more radical, and accordingly also the patients' survival is better; namely, prostate cancer is a slowly progressing disease which becomes clinically manifest only 10–14 years from the onset.

In patients with the disease detected when aged 75 years or older, it often turns out that the patient either has regionally advanced disease or a more malignant caner type, which cannot be easily detected by PSA test alone, if the patient does not also present with urine voiding problems. This may partly explain worse survival of patients in this age group. Besides, at this age it is difficult to decide for more radical treatment (particularly surgical); palliative treatment is therefore prevailing, which by no means implies a lower quality of treatment or even abandonment of therapy. Worse survival is further aggravated by concomitant diseases of the elderly, which sometimes pose severe obstacles to the choice of suitable therapy.

Prostate cancer is a disease, which in itself does not cause any difficulties if not associated with benign hyperplasia of the prostate and urine voiding problems. Its detection is primarily based on the PSA test and the awareness of male population about the need of preventive medical checks.

CLINICAL COMMENTARY

Borut Kragelj

One of the important features of prostate cancer is frequently a slow natural course of the disease. Computer models demonstrate that it takes approximately 15 years before a PIN progresses into an invasive carcinoma, the latter remaining confined to the prostate for another 6 years on average. Even in patients with clinically evident systemic dissemination the average survival exceeds 5 years. Prostate cancer is associated with a lower survival only in patients with distant metastases and perhaps in a small proportion of patients with regional lymph node metastases or locally advanced tumors. In the latter only, the 5-year survival may depend on an adequately managed and timely introduced systemic therapy. In patients with cancer confined to the prostate this is not a life-threatening disease. Although in a smaller proportion of these patients metastases may appear within five years from diagnosis, patients with poorly differentiated tumors will die in 5 to 10 years from diagnosis, while those with well differentiated carcinomas may survive even more than 15 years.

Therefore, the 5-year survival in prostate cancer is primarily a measure of effective early diagnosis, indicating the ratio between patients with localized or regional disease or even distant metastases at the time of diagnosis. Early detection of prostate cancer is still based on the evaluation of PSA serum concentration. The rationale of organized early detection by means of this method is still under study. In Europe, the accessibility of PSA test and diagnosis by means of prostate biopsy and histological examination of the bioptic tissue sample varies a lot, although it is of key importance for the differences in 5-year survival.

po diagnozi, pa je rak vzrok smrti bolnikov s slabo diferenciranimi tumorji ponavadi v obdobju 5–10 let po diagnozi, z dobro diferenciranimi karcinomi pa šele po več kot 15 letih.

Petletno preživetje je zato pri raku prostate v prvi vrsti merilo uspešnosti zgodnjega odkrivanja bolezni in kaže na razmerja med bolniki, ki imajo ob diagnozi omejeno ali razširjeno bolezen, ali pa že oddaljene zasevke. Zgodnje odkrivanje raka prostate še vedno temelji na določanju serumske koncentracije PSA. Smiselnost organiziranega zgodnjega odkrivanja s to metodo je še vedno predmet raziskav. Dostopnost do individualne zgodnje diagnostike, določanja PSA oziroma do diagnoze z biopsijo prostate in s histološkim pregledom bioptičnega tkiva je v Evropi zelo različna, vendar ključna za razlike v petletnem preživetju.

Podatki RRS kažejo, da so se tudi pri nas v obdobju od 1991 do 2005 zgodile velike spremembe. Zmanjševanje deleža bolnikov z razsejano boleznijo ob diagnozi na eni strani in na drugi strani večanje deleža bolnikov z omejeno boleznijo ima za posledico vedno večje petletno preživetje. To kaže tudi na vedno bolj dostopno in tudi uspešno individualno zgodnje odkrivanje bolezni. Zgodnejše odkrivanje karcinomov se kaže tudi z relativnim in absolutnim povečanjem števila novo odkritih rakov prostate pri moških, starih 50–74 let. Prav odkrivanje raka pri vedno mlajših moških v končni fazi obeta, da se bo v prihodnosti zmanjšala tudi specifična umrljivost.

Ne glede na prikazano izboljšanje pa prikazani rezultati ne dopuščajo, da bi bili z doseženimi rezultati povsem zadovoljni. Še zlasti, če jih primerjamo s preliminarnimi poročili organiziranega zgodnjega odkrivanja. V poročilu ERSPC (European Randomized Study of Screening for Prostate Cancer) tako navajajo, da je bilo več kot 90 % primerov raka ob diagnozi omejenih na prostato (stadij T1 in T2), po drugi strani pa navajajo zgolj sporadične primere že ob diagnozi prisotnega razsoja (v poročilih Rotterdama in Goeteborga je bil razsoj ugotovljen pri 6 od 1670 bolnikov). Podobna slika kot pri nas je na področjih, kjer je razširjeno individualno presejanje. V regijah ZDA, ki jih pokrivajo registri raka, združeni v projekt SEER (Surveillance, Epidemiology and End Results Project) ima le 4 % bolnikov ob diagnozi prisotne zasevke; 91 % bolnikov ima ob diagnozi omejeno ali področno razširjeno bolezen, za 4 % bolnikov podatki niso znani. Temu ustreza tudi 98,9 % petletno preživetje bolnikov, zbolelih v letih 1996–2004.

Zanimiv je tudi dokaj stalen delež bolnikov z razširjeno boleznijo. Glede na metodologijo RRS so to bolniki z zasevki v področnih bezgavkah. Ugotavljanje stadija bolezni je pri raku prostate težavno. Med standardne preiskave za zamejitev bolezni je v Sloveniji vključena zgolj scintigrafija skeleta. Slikovne preiskave, s katerimi bi lahko ugotovili področne zasevke, se izvajajo le izjemoma. Nenazadnje verjetno tudi zaradi njihove nenatančnosti. Klinično določen stadij je zato nezanesljiv in praviloma podcenjen. Področni zasevki so zato večinoma ugotovljeni na osnovi pelvične limfadenektomije. V tem primeru je glede na približno 300 letno opravljenih prostatektomij po podatkih RRS pri približno 120 bolnikih ugotovljen razsoj v področne bezgavke. Delež je presenetljivo visok glede na to, da imajo bolniki večinoma opravljeno standardno in ne razširjeno pelvično limfadenektomijo.

Po podatkih RRS je delež bolnikov, ki so v sklopu začetnega zdravljenja prejeli obsevanje, nizek. Vsaj delno je bila temu vzrok zastarelost in pomanjkanje aparatov za perkutano obsevanje in za sodobno brahiradioterapijo neprimerna oprema na radiološkem oddelku. Razmere so se začele izboljševati šele po letu 2001, ko smo lahko z razpoložljivo opremo zadostili vsaj minimalnim standardom kakovosti perkutanega obsevanja z uvedbo 3D konformalnega obsevanja. Težave zaradi premajhnega števila obsevalnih naprav so se zmanjšale šele po letu 2006. Še počasneje so se razmere izboljševale na oddelku za brahiradioterapijo. S prekinitvijo brahiradioterapije raka prostate v letu 2003 se je sodoben način obsevanja tudi pri brahiradioterapiji začel odvijati šele konec leta 2006.

Z izboljševanjem možnosti obsevanja se je povečevalo tudi število obsevanih bolnikov. V letih 2004 in 2005, za kateri so podatki o obsevanju dostopni tudi v elektronski obliki, je bilo obsevanih 233 bolnikov. Upoštevani so zgolj tisti, pri katerih je bil cilj zdravljenja ozdravitev.

The data of the CRS show that in the period 1991–2005 major changes occurred in Slovenia as well. A decrease in the proportion of patients with disseminated disease at diagnosis on the one hand, and an increase in the proportion of patients with localized disease on the other, has resulted in a progressively better 5-year survival. This is indicative of a more accessible and also more successful early detection of the disease. Earlier detection of carcinomas is also reflected in a relative and absolute increase in the number of newly detected prostate cancers in males aged 50–74 years. Finally, the detection of cancer in ever younger male population gives hope that in the future the specific mortality rates may decrease accordingly.

Irrespective of the presented improvement, we should not be fully satisfied with the results obtained, particularly, if they are compared against the preliminary reports of organized early detection. Thus ERSPC (European Randomized Study of Screening for Prostate Cancer) reports that at the time of diagnosis more than 90% of cancers are confined to the prostate (stages T1 and T2), while cases of disseminated disease at diagnosis are reported only sporadically (in the report from Rotterdam and Goeteborg dissemination was found in 6 out of 1670 patients). A similar situation as in Slovenia is found in the regions with widely used individual screening. In the USA regions covered by cancer registries joined in the SEER project (Surveillance, Epidemiology and End Results Project) only 4% of patients present with metastases at diagnosis; 91% of patients have localized or regional disease at diagnosis while the relevant data for 4% of patients are not available. This is consistent with 98.9% 5-year survival of patients diagnosed in the period 1996–2004.

The relatively stable proportion of patients with regional disease is interesting too. According to the methodology of the CRS, these are the patients with regional lymph node metastases. Staging of prostate cancer is difficult. In Slovenia, the standard procedures for staging of the disease include only bone scintigraphy. Imaging methods for the detection of regional metastases are applied only exceptionally, a possible reason for that being their inaccuracy. Clinically determined stage is therefore unreliable and generally underestimated. Thus, regional metastases are mostly determined on the basis of pelvic lymphadenectomy. In this case, according to the data of the CRS, in approximately 300 prostatectomies performed yearly, dissemination into regional lymph nodes is found in some 120 patients. The proportion is surprisingly high in view of the fact that most patients underwent a standard rather than an extended pelvic lymphadenectomy.

According to the CRS data, the proportion of patients receiving radiotherapy as part of their primary treatment is low. This is at least to a certain extent attributable to the obsolete and lacking devices for percutaneous irradiation and the existing equipment at brachytherapy department that is not in compliance with modern standards. The situation started to improve only after the year 2001, when the available equipment fulfilled at least minimum quality requirements for percutaneous irradiation by means of 3D conformal irradiation. Problems due to an insufficient number of irradiation machines became less evident only after 2006. At the brachyradiotherapy department the improvement was even slower. By the interruption of brachyradiotherapy of prostate cancer in 2003, up-to-date irradiation techniques in brachyradiotherapy started to be used only in the end of 2006.

With the improvement of radiation facilities, the number of irradiated patients increased as well. In the years 2004 and 2005, for which the data on irradiation treatment are available in electronic form too, 233 patients received radiotherapy. Only those treated with curative intent were considered. Owing to the above mentioned reasons, all those patients were treated exclusively with percutaneous irradiation. In 210 of total 233 patients irradiation was the only form of local treatment while the rest of them were irradiated after previous prostatectomy. It is interesting to note, just in two years, an increase in the number of patients treated with the combination of prostatectomy and irradiation, where radiotherapy was applied either immediately after prostatectomy

Vsi so bili zaradi že omenjenih razlogov zdravljeni izključno s perkutanim obsevanjem. Pri 210 (od 233) bolnikih je bilo obsevanje edina oblika lokalnega zdravljenja, ostali pa so bili obsevani po predhodni prostatektomiji. Zanimivo je, da že v teh dveh letih lahko ugotovimo porast števila bolnikov, ki so zdravljeni s kombinacijo prostatektomije in obsevanja, bodisi z obsevanjem neposredno po prostatektomiji bodisi ob biokemični ponovitvi in/ali lokalnem recidivu. Če upoštevamo zgolj leti 2004 in 2005, lahko ugotovimo, da se bolniki v Sloveniji le nekoliko manj pogosto odločajo za zdravljenje z obsevanjem kot drugod po Evropi oziroma v ZDA. V tem dveletnem obdobju bolnikom sicer nismo nudili možnosti obsevanja z brahiradioterapijo, vendar sedanje izkušnje po ponovni uvedbi brahiradioterapije konec leta 2006 kažejo, da se število obsevanih bolnikov tudi z uvedbo brahiradioterpije ni bistveno povečalo. Razlog za to je najverjetneje, da možnosti zdravljenja predstavi bolniku urolog in le izjemoma multidisciplinarni konzilij.

VIRI
Literature

Albertsen PC, Hanley J, Fine J. Twenty year outcome following conservative management of clinically localized prostate cancer. JAMA 2005, 293: 2095–101.

Bill-Axelson A, Holmberg L, Ruutu M. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005; 352: 1977–84

Collin SM, Martin RM, Metcalfe C. prostate-cancer mortality in the USA and UK in 1975–2004: an ecological study. Lancet Oncol 2008; 9: 445–52.

Loblaw DA, Virgo KS, Nam R. Initial hormonal management of androgen – sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American society of Clinical Oncology practice guideline. J Clin Oncol 2007; 25: 1569–605.

Messing EM, Manola J, Sarosdy M. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node positive prostate cancer. N Engl J Med 1999; 341: 1781–8.

Murai M, Barry M. Epidemiology and natural history of bladder cancer. In: McConnell J, Denis L, Akaza H, Khoury S, Schalken J, eds. Prostate cancer. Editions 21, Paris 2006: 37–54.

Roobol MJ, Grenabo A, Schroeder FH. Interval cancers in prostate cancer screening: comparing 2 and 4 year screening intervals in European Randomized Study of Screening for Prostate Cancer, Gothenburg and Rotterdam. 2007.

Studer UE, Colette L, Whelan P. Using PSA to guide timing of androgen deprivation in patients with T0-4, N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30981). Eur Urol 2008; 53: 941–9.

KLINIČNI KOMENTAR
Tanja Čufer

Rak prostate postaja vedno pogosteje odkriti rak pri moških. Incidenca bolezni se po svetu in pri nas strmo veča. Medtem ko je bila leta 1990 starostno standardizirana incidenčna stopnja v Sloveniji 32,5/100.000, je bila leta 2005 že 84,8/100.000. Mnoge evropske države, še zlasti pa ZDA, imajo še veliko večjo incidenčno stopnjo tega raka. Tako velik porast incidence raka prostate je pripisati oportunističnemu presejanju z določanjem PSA v krvi pri moških, starih 50 let in več. Velik delež tako odkritega raka prostate je biološko malo agresiven, ne povzroča težav in ne ogroža življenja. Posledica tega je strm porast incidence, medtem ko se umrljivost za rakom prostate ob vedno boljšem preživetju tako v Evropi kot v ZDA zmanjšuje.

In kako je pri nas? Ob pričakovanem močnem porastu incidence se umrljivost za rakom prostate pri nas žal še vedno veča. Umrljivost za rakom prostate je v Sloveniji precej večja kot v Evropi. Tudi petletno preživetje bolnikov z rakom prostate je pri nas za okoli 15 % manjše kot v Evropi. To velja tako za obdobje raziskave EUROCARE-3, ki zajema obdobje 1990–1994, kot tudi za kasnejše obdobje, zajeto v raziskavo EUROCARE-4. Bolniki, zboleli pri nas v letih 2000–2002, so imeli 63-odstotno petletno relativno preživetje, medtem ko je bilo evropsko povprečje 80 %. Tako 3-, 5- kot še bolj 10-letno preživetje bolnikov se pri nas sicer povečuje, žal pa ostaja razkorak med našimi in evropskim povprečjem enako velik. V zadnjem obdobju tudi pri nas odkrivamo

or at biochemical and/or local recurrence. Taking into account only the years 2004 and 2005, it turns out that the patients in Slovenia decide for radiotherapy slightly less often than elsewhere in Europe or in the USA. In this two-year period the patients were not offered the possibility of treatment with brachyradiotherapy, however the experience after reintroducing brachyradiotherapy in 2006 has shown that even then the number of irradiated patients has not increased significantly. In all probability the reason lies in the fact that the patient learns about treatment possibilities from an urologist and only exceptionally from a multidisciplinary team of experts.

CLINICAL COMMENTARY

Tanja Čufer

Prostate cancer is nowadays ever more frequently detected cancer in males. The incidence of this disease in the world as well as in Slovenia is rapidly increasing. While in 1990 the age-standardized incidence rate in Slovenia was 32.5/100,000, in the year 2005 it was already 84.8/100,000. Many European countries, and in particular the USA, face an even higher incidence rates of this cancer. Such a high increase in the incidence of prostate cancer can be ascribed to the opportunistic screening by PSA determination in the blood in males aged 50 years or older. A large proportion of prostate cancers detected in this way are of low-grade malignancy, do not cause any difficulties and are not a life-threatening disease. As a result, the incidence increases rapidly but the mortality due to prostate cancer is on decline in some parts of Europe as well as in the USA, due to better survival rates.

And what is the situation in Slovenia? Along with the expected high increase in the incidence, unfortunately the prostate cancer related mortality in Slovenia is still increasing. Thus prostate cancer mortality rates in Slovenia are much higher than elsewhere in Europe. The 5-year survival of prostate cancer patients in our country is by approximately 15% lower than in other European countries. This applies to the time of EUROCARE-3 study, which covers the period 1990–1994, as well as to the later period of EUROCARE-4 study. Patients diagnosed in Slovenia in the years 2000–2002 had 63% 5-year relative survival while the European average was 80%. Although in Slovenia the 3-, 5- and particularly the 10-year survival of patients is increasing, unfortunately its lagging behind the European average is not getting any lesser. In the last period also in our country more and more cancers are detected in a localized stage, however the absolute numbers of patients with regional or disseminated disease are increasing rather than decreasing. No improvement in the survival can be expected without advances in the treatment of regional and disseminated disease.

In the last period, the 5-year survival of patients with localized and regional stages has increased; thus the 5-year survival of patients with regional disease has increased from 69% in the period 1996–2000 to 80% in the period 2001–2005. However, the 5-year survival of patients with disseminated disease has even decreased. This is indicative of a relatively adequate treatment of lower stages of prostate cancer but not also of disseminated disease. In the former, a local surgical and/or irradiation therapy plays an important role, which is obviously adequate in our case. However, in locally advanced and particularly in disseminated disease hormone therapy is of crucial importance. In a majority of patients with regional or even disseminated disease a well managed hormone therapy may result in long lasting remissions and a relatively high 5-year survival rates. If we are to increase the survival of prostate cancer patients, more attention should be attributed to well managed hormone therapy of this disease. Minor improvement in the survival may be expected by introducing cytostatic therapy for hormone-independent prostate cancer. It is fact however, that a great majority of prostate cancers are hormone-dependent in the beginning of treatment and that such treatment may result in several years of remission. Therefore all our efforts should be directed into improving this treatment approach.

vse več raka v omejenem stadiju, žal pa se število bolnikov z razširjeno ali razsejano boleznijo v absolutnem številu ne zmanjšuje, ampak se celo veča. Brez napredka v zdravljenju razširjene in razsejane bolezni ni pričakovati večjega preživetja.

V zadnjem obdobju se je sicer petletno preživetje bolnikov z omejenim in razširjenim stadijem bolezni povečalo; petletno preživetje bolnikov z razširjenim stadijem se je povečalo s 69 % v obdobju 1996–2000 na 80 % v obdobju 2001–2005. Žal pa se je pri nas zmanjšalo petletno preživetje bolnikov z razsejano boleznijo. To kaže na dokaj ustrezno zdravljenje nižjih stadijev raka prostate, ne pa razsejane bolezni. V prvem primeru je pomembno lokalno kirurško in/ali obsevalno zdravljenje, ki je očitno pri nas ustrezno. Pri lokalno razširjeni in še v večji meri pri razsejani bolezni pa je izrednega pomena hormonsko zdravljenje raka prostate. Z dobro vodenim hormonskim zdravljenjem je pri veliki večini bolnikov z razširjeno ali celo razsejano boleznijo mogoče doseči večletne zazdravitve in razmeroma veliko petletno preživetje. Če želimo pri nas povečati preživetje bolnikov z rakom prostate, moramo več pozornosti nameniti dobro vodenemu hormonskemu zdravljenju te bolezni. Z uvajanjem citostatskega zdravljenja hormonsko neodzivnega raka prostate sicer lahko pričakujemo manjše izboljšanje preživetja. Dejstvo pa je, da je velika večina raka prostate v začetku zdravljenja hormonsko odvisnih in da je s tem zdravljenjem mogoče doseči večletno zazdravitev, zato je treba vse napore usmeriti v izboljšanje tega zdravljenja.

Tako v svetu kot pri nas je predvsem slabo preživetje starejših bolnikov, starih 75 let in več. Medtem ko so se relativna petletna preživetja mlajših bolnikov povečala, se preživetje bolnikov, starih 75 let in več, praktično ne povečuje. Zdravljenju starejših bolnikov bo zato v prihodnosti potrebno posvetiti več pozornosti.

VIRI
Literature

Borštnar S, Čufer T. Zdravljenje hormonsko neodvisnega raka prostate. Onkologija 2006; 10: 50–53.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18: 581–92.

Seidenfeld J, Samson JD, Hasselblad V, Aronson N, Albertsen PC, Bennett CL, et al. Single-therapy androgen supression in men with advanced prostate cancer: A systematic review and meta-analysis. Ann Intern Med 2000; 132: 566–77.

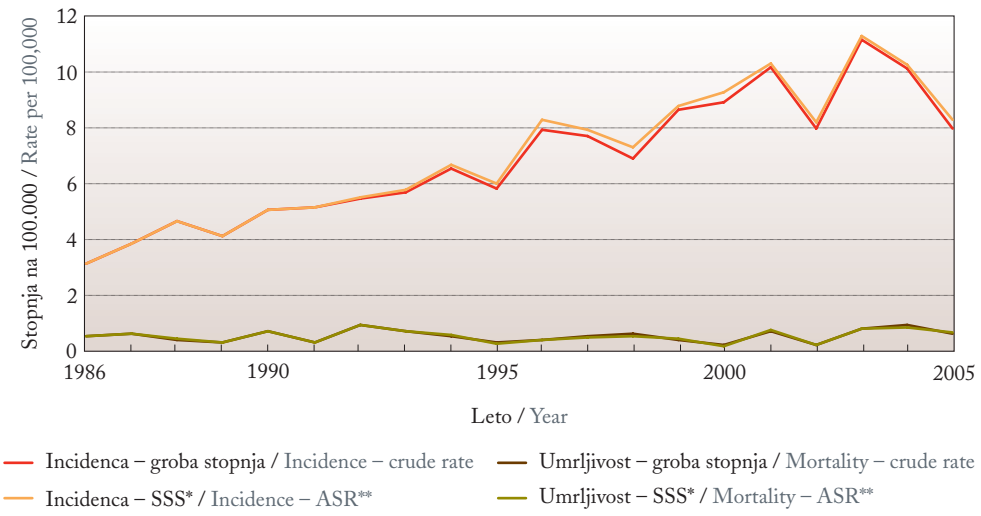
In the world as well as in Slovenia particularly poor survival is observed in patients aged 75 years or older. While the 5-year relative survivals of younger patients increased during the last years, there is practically no improvement in the survival of patients aged 75 years or older. Therefore, in the future more attention should be paid to the treatment of older patients.

MODO

MKB 10: C62

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom mod zbolelo 1129 moških. Kot je razvidno s Slike 1, se groba in starostno standardizirana incidenčna stopnja ves čas opazovanja povečujeta, groba stopnja povprečno za 4,7 % letno. Ker večina moških zboli pred 50. letom starosti, je starostno standardizirana stopnja večja od grobe. Vsako leto umre le nekaj bolnikov z rakom mod; časovna trenda obeh umrljivostnih stopenj sta zato stabilna, njune vrednosti pa le okrog 1/100.000.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka mod, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of testicular cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1075 primerov; 4 primeri (0,4 %) niso upoštevani, ker jim je bila diagnoza postavljena po smrti, 50 mlajših od 20 let pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih.

V obdobju 1996–2005 so bili mikroskopsko potrjeni vsi primeri; le dva primera iz obdobja 1991–1995 nista imela mikroskopske potrditve. V celotnem obdobju je imelo 48 % bolnikov seminom, 21 % mešani tumor kličnih celic, 11 % embrionalni karcinom ter po 7 % teratokarcinom in horiokarcinom. Ostale histološke vrste so bile redke. V zadnjih letih se veča delež mešanih tumorjev kličnih celic in horiokarcinomov, manjša pa se delež embrionalnih karcinomov in teratokarcinomov; delež seminomov ostaja ves čas opazovanja približno enak.

Tabela 1: *Število bolnikov z rakom mod po obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of testicular cancer patients by period of diagnosis with their proportions by age.*

	Moški / Males			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	262	93,1	6,1	0,8
1996–2000	365	92,9	7,1	0,0
2001–2005	448	94,9	5,1	0,0

TESTIS

ICD 10: C62

EPIDEMIOLOGY

In the period 1991–2005, a total of 1129 males were diagnosed with testicular cancer. As evident from Figure 1, the crude and age-standardized incidence rates have been increasing. The estimated annual percentage increase in crude incidence rate was 4.7%. As the majority of patients are diagnosed before 50 years of age, the age-standardized rate is higher than the crude rate. Every year there are only few deaths due to testicular cancer. Therefore, the time trends of both mortality rates are stable, their values ranging around 1/100,000.

The survival analysis included 1075 cases; 4 cases (0.4%) diagnosed only after death were not considered in the analysis, 50 patients less than 20 years of age are presented in the chapter on the survival of children and adolescents.

In the period 1996–2005, all the cases were microscopically verified, while in the period 1991–1995 only two cases lacked microscopic confirmation. In the total observation period, 48% of patients had seminoma, 21% mixed germ-cell tumors, 11% embryonal carcinoma, while teratocarcinoma and choriocarcinoma was found in 7% of patients each. Other histological types were rare. In recent years, the proportion of mixed germ-cell tumors and choriocarcinomas has been increasing while the proportion of embryonal carcinomas and teratocarcinomas exhibited a downward trend; the proportion of seminomas has remained practically the same throughout the observation period.

The majority of patients were diagnosed before 50 years of age, approximately 6% were diagnosed at an age between 50–74 years; in the whole observation period there were only two patients who developed the disease aged 75 years or older (Table 1).

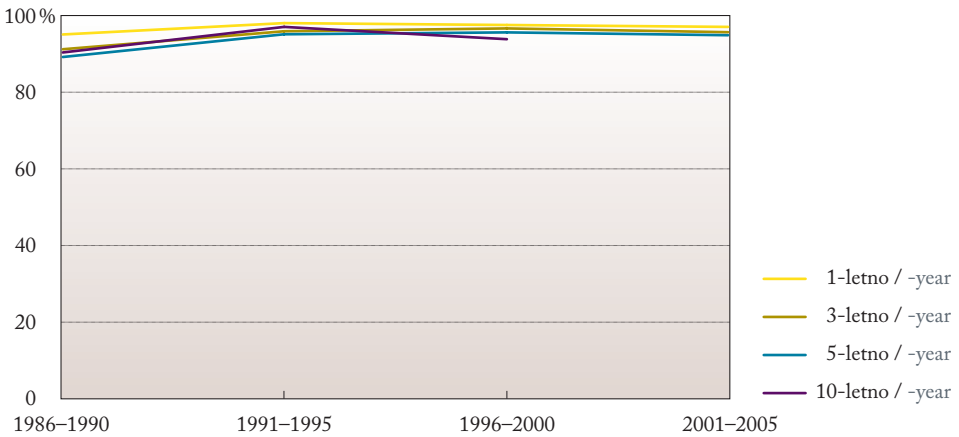
The majority of patients are diagnosed with localized disease, in the last period their proportion being 58% (Table 2). In the latter period 2001–2005, one third of patients had regional and 9% disseminated disease at diagnosis; the proportion of patients with disseminated stage has been decreasing with time.

In the whole observation period only 6 patients did not receive specific treatment. Among the patients receiving specific treatment in the period 2001–2005, 78% were treated by surgery and chemotherapy, 19% underwent surgery only, while the rest were irradiated in addition to surgery and chemotherapy.

In the period 2001–2005, 48% started their treatment in the UMC Ljubljana, 16% in the UMC Maribor and 12% in the GH Celje. Individual patients started their treatment in other Slovenian general hospitals and at the IO Ljubljana. Practically all patients (99%), irrespective of the hospital of their initial treatment, were in the course of their primary treatment referred to the IO Ljubljana.

Tabela 2: *Število bolnikov z rakom mod po obdobju postavitve diagnoze ter njihovi deleži po stadiju.*
Table 2: *Number of testicular cancer patients by period of diagnosis with their proportions by stage.*

	Moški / Males				
Obdobje / Period	število / number (%)	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown
1991–1995	262	46,6	40,1	12,6	0,8
1996–2000	365	57,3	27,4	15,3	0,0
2001–2005	448	57,6	33,3	8,5	0,7



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom mod po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of testicular cancer patients by period of diagnosis.*

Večina bolnikov je zbolela pred 50. letom starosti, 6 % jih je bilo ob diagnozi starih med 50 in 74 let; v vsem opazovanem obdobju sta le dva bolnika zbolela v starosti 75 let in več (Tabela 1).

Največ bolnikov ima ob diagnozi omejen stadij bolezni; v zadnjem obdobju je bilo teh bolnikov 58 % (Tabela 2). V obdobju 2001–2005 je bila pri tretjini bolnikov ob diagnozi bolezen v razširjenem stadiju, pri 9 % pa v razsejanem; delež bolnikov z razsejanim stadijem se s časom manjša.

V vsem opazovanem obdobju le 6 bolnikov ni bilo specifično zdravljenih. Med specifično zdravljenimi je bilo v letih 2001–2005 78 % bolnikov zdravljenih z operacijo in kemoterapijo, 19 % jih je bilo samo operiranih, ostali so bili poleg operacije in kemoterapije še obsevani.

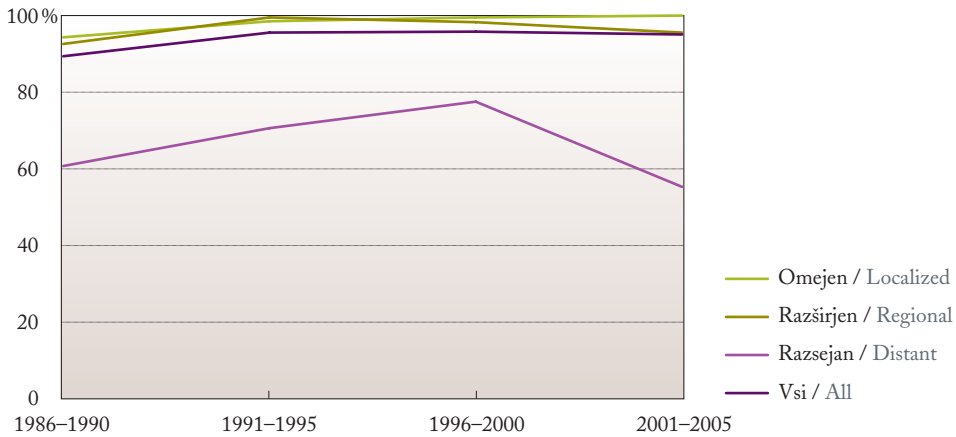
V obdobju 2001–2005 se je 48 % bolnikov začelo zdraviti v UKC Ljubljana, 16 % v UKC Maribor in 12 % v SB Celje. Posamezne bolnike so pričeli zdraviti še v ostalih slovenskih splošnih

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom mod po obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of testicular cancer patients by period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)		
	Moški / Males		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	97,7 (95,9–99,5)	94,3 (91,5–97,1)	93,5 (90,6–96,5)
1996–2000	97,3 (95,6–98,9)	95,3 (93,2–97,5)	94,2 (91,9–96,7)
2001–2005	96,9 (95,3–98,5)	94,2 (92,0–96,4)	93,4 (91,1–95,9)

	Relativno preživetje / Relative survival (%)		
	Moški / Males		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	98,1 (96,3–100,0)	95,4 (92,5–98,3)	95,2 (92,1–98,2)
1996–2000	97,5 (95,8–99,2)	96,0 (93,8–98,2)	95,7 (93,2–98,1)
2001–2005	97,1 (95,5–98,8)	95,0 (92,8–97,2)	95,0 (92,5–97,5)

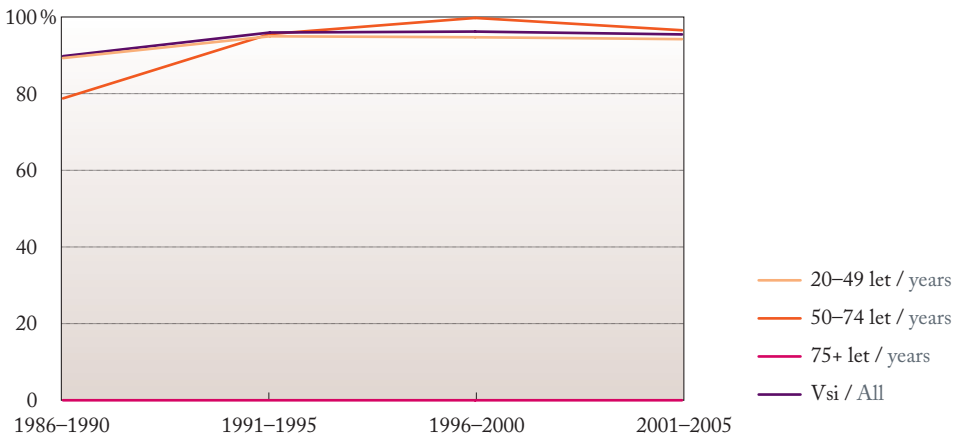


Slika 3: *Petletno relativno preživetje bolnikov z rakom mod po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of testicular cancer patients by stage and period of diagnosis.*

In the last 15 years, the relative survival rate of patients with testicular cancer is not increasing any more: in all three observation periods the 5-year relative survival ranged around 95% (Figure 2, Table 3). In the period 2001–2005, all patients with localized stage at diagnosis survived 5 years; among the patients with regional disease and those with disseminated disease there were 96% and 55% of 5-year survivors respectively (Figure 3). The estimation of negative time trend in the 5-year relative survival of patients with disseminated stage is not reliable due to a small number of patients. Age is not a relevant prognostic factor of survival in patients with testicular cancer (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 95% (Figure 2); patients surviving the first year may expect to survive five years in 98%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the crude 5-year relative survival of Slovenian patients with testicular cancer was nearly equal to the European average (Figure 5).



Slika 4: *Petletno relativno preživetje bolnikov z rakom mod po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of testicular cancer patients by age and period of diagnosis.*

bolnišnicah in na OI Ljubljana. Skoraj vsi bolniki (99 %), ne glede na bolnišnico začetka zdravljenja, pa so bili v okviru prvega zdravljenja obravnavani na OI Ljubljana.

Relativno preživetje bolnikov z rakom mod se v zadnjih 15 letih ne povečuje več; petletno relativno preživetje je v vseh obdobjih okrog 95 % (Slika 2, Tabela 3). Med leti 2001–2005 so pet let preživeli vsi bolniki z omejenim stadijem bolezni ob diagnozi, 96 % tistih z razširjeno boleznijo in 55 % bolnikov z razsejanim stadijem (Slika 3). Vrednotenje negativnega časovnega trenda petletnega relativnega preživetja bolnikov z razsejanim stadijem pa ni zanesljivo, saj je bolnikov malo. Starost ni pomemben napovedni dejavnik preživetja bolnikov z rakom mod (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 95 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 98-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je grobo petletno relativno preživetje slovenskih bolnikov z rakom mod skoraj enako evropskemu povprečju (Slika 5).

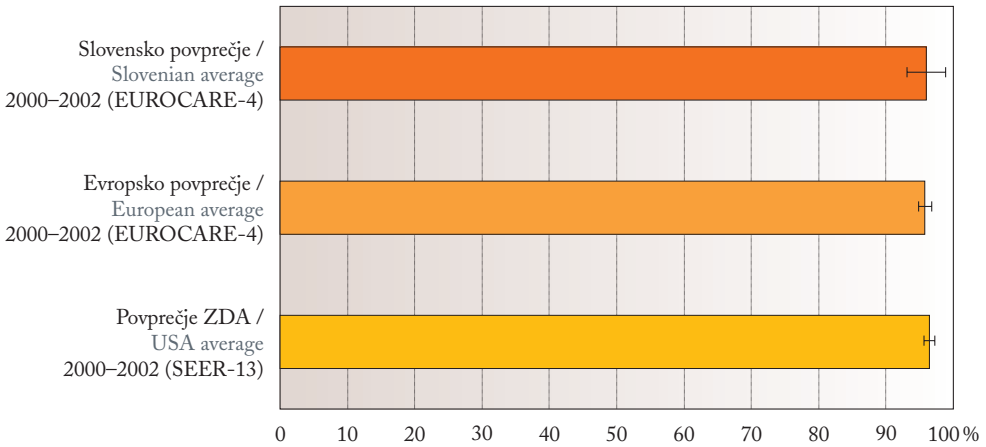
KLINIČNI KOMENTAR

Breda Škrbinc

Tumorji mod sodijo v skupino redkih vrst raka (1–2 % vseh vrst raka pri moških), vendar se incidenca te bolezni v »razvitem« svetu strmo veča; to velja tudi za Slovenijo. Vzrok za to ni povsem pojasnjen, kot vzročni dejavnik veljajo še neodkriti dejavniki v okolju, ki v času intrauterinega razvoja in verjetno tudi kasneje vplivajo na krhko hormonsko ravnovesje, potrebno za normalen razvoj gonad.

Tumorji mod so v številnih pogledih edinstvena vrsta raka. Pojavljajo se pretežno pri mladih moških (najpogosteje med 18. in 30. letom starosti), njihova osnovna značilnost je, da so praktično ozdravljivi. V fazi omejene bolezni je ozdravljivost skoraj 100 %, v razširjeni in zgodnji razsejani fazi preko 80 %, tudi še v kasni razsejani fazi je bolezen potencialno ozdravljiva, vendar se možnost ozdravitve z napredovanjem bolezni pomembno manjša. Bistvenega pomena za dober uspeh zdravljenja te vrste raka v vseh fazah bolezni je dobro sodelovanje bolnikov z brezhibno usklajenim multidisciplinarnim timom izkušenih strokovnjakov, usmerjenih v zdravljenje raka mod. Skupno preživetje bolnikov, zbolelih za rakom mod v obdobju 2001–2005, kakor tudi preživetje podskupin bolnikov z omejeno in razširjeno obliko bolezni, je bilo v Sloveniji optimalno, v razsejani fazi bolezni pa analiza kaže trend upadanja preživetja glede na preteklo desetletje. V tem petletnem obdobju smo zdravili bistveno manj bolnikov z razsejanim rakom mod (relativno in absolutno) kot v prejšnjih dveh petletnih obdobjih (Tabela 3), kar govori v prid vedno boljše ozaveščenosti Slovencev o tej vrsti raka. Ravno zaradi majhnega števila bolnikov z razsejano boleznijo pa je trend upadanja težko ovrednotiti.

Dejstvo je, da je skupina bolnikov z razsejano obliko bolezni zelo nehomogena. Bolniki z razsejanim rakom mod so v klasifikacijah, ki jih v klinični praksi uporabljamo za načrtovanje intenzitete zdravljenja, razvrščeni v dobro, srednje dobro in slabo napovedno skupino z bistveno različnimi možnostmi ozdravitve. Možnosti ozdravitve so bistveno večje, če imajo bolniki zasevke le v pljučih in bezgavkah (okrog 80 % verjetnost ozdravitve), ne pa tudi v drugih visceralnih organih, kosteh in centralnem živčevju; na možnosti ozdravitve pa deloma vpliva tudi histološka vrsta tumorja mod. Podatka, kakšna je bila sestava bolnikov glede na napovedne skupine in histološko vrsto, nimamo. Možno je, da smo v zadnjem petletnem obdobju zdravili sorazmerno večji delež bolnikov z napovedno slabšo obliko razsejanega raka mod. Druga, zopet špekulativna možnost, ki bi po vseh merilih lahko tudi vplivala na preživetje bolnikov z razsejanim rakom mod, je kadrovska in organizacijska turbulenca, ki je po upokojitvi več dolgoletnih izkušenih članov tima za zdravljenje bolnikov z rakom mod zaznamovala preteklo petletno obdobje. Še dodatna, zopet špekulativna možnost razlage negativnega trenda preživetja bolnikov z razsejanim rakom mod pa bi lahko bila, da se analogno s skokovitim porastom incidence



Slika 5: *Petletno relativno preživetje bolnikov z rakom mod (povpreče in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of testicular cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

CLINICAL COMMENTARY

Breda Škrbinc

Testicular tumors belong to the group of rare cancers (1–2% of all cancers in males). However the incidence in the developed world as well as in Slovenia is on a steep increase. The reason for that has not been fully explained yet, but it is presumed that so far unidentified environmental factors in the course of intrauterine development, and possibly also later on, may influence the sensitive hormone balance which is a prerequisite for a normal development of the gonads.

In many respects, testicular tumors are a unique type of cancer. It occurs prevailingly in young males (most frequently at an age between 18 and 30 years), their main feature being that they are virtually curable. In the stage of localized disease the cure rate is almost 100%, while in the stage of regional spread and early dissemination is over 80%; even in the stage of late dissemination the disease remains potentially curable, however, with further progression of the disease the chances of cure are getting significantly smaller. A good cooperation of the patient with a well-coordinated multidisciplinary team of experts experienced in testicular cancer treatment is of essential importance for a favorable treatment outcome in all stages of this disease. Overall survival of patients diagnosed with testicular cancer in the period 2001–2005, as well as the survival of subgroups of patients with localized and regional stages of the disease in Slovenia was optimal, while in the disseminated stage, the analysis indicated a downward trend in the survival in comparison with the past decade. In the last 5-year period the number of patients treated for disseminated testicular cancer (relative and absolute) was significantly lower than in the previous two 5-year periods (Table 3), which is indicative of a greater awareness of this cancer among the Slovenian population. The very small number of patients with disseminated disease renders the downward trends difficult to evaluate.

As a matter of fact, the group of patients with disseminated disease is very heterogeneous. In the classification systems used in clinical practice for planning treatment intensity, patients with testicular cancer are distributed into groups with good, moderately good and poor prognosis, with significantly different chances of cure. The chances of cure are significantly higher if the patient presents with metastases in the lung and lymph nodes only (the chance of cure is around 80%) and not also in other visceral organs, bones and the central nervous system; besides, the possibility of cure is partly also influenced by tumor histological type. Information on the composition

raka mod spreminjajo tudi lastnosti te vrste raka, ki lahko postaja manj občutljiv na standardne oblike zdravljenja, v prvi vrsti na kemoterapijo.

Gledano v celoti je v zadnjem petletnem obdobju uspeh zdravljenja bolnikov z rakom mod dober, še posebej v skupini z dobro in srednje dobro napovedjo izida bolezni; ocena manjšanja preživetja bolnikov s slabo napovedjo izida pa je zaradi majhnega števila bolnikov v tej skupini nezanesljiva. Vseeno pa je treba v naslednjem obdobju posvetiti posebno pozornost tej skupini bolnikov, da jim nudimo vse dostopne možnosti za ozdravitev.

VIRI
Literature

Huddart RA, O'Doherty MJ, Padhani A, Rustin GJS, Mead GM, Johnathan K. Joffe JK, et al. Fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC trial TE22 – the NCRI testis tumour clinical study group. JCO 2007; 25: 3090–5.

Martin OV, Shialis T, Lester JN, Scrimshaw MD, Boobis AR, Voulvoulis N. Testicular dysgenesis syndrome and the estrogen hypothesis: a quantitative meta-analysis. Environmental Health Perspectives 2008; 116: 149–57.

Pont J, Höltl W. Keimzelltumoren des Mannes. Bremen: UNI MED Verlag, 2004.

Schmoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberger C, et al. European consensus on diagnostis and treatment of germ cell cancer: a report of the European German Cell Cancer Consensus Group (EGCCCG). European urology 2008; 53: 497–513.

of patients with respect to the prognostic groups and histological type is not available in current analysis. It is possible that in the last 5-year period we treated a greater proportion of patients with prognostically less favorable type of disseminated testicular cancer. The other, hypothetic possibility that might by all criteria also influence the survival of patients with disseminated testicular cancer is associated with staff and organizational turbulence which marked the past 5-year period, after a number of experienced and long-standing members of the team for testicular tumor treatment had retired. Yet another, also a hypothetic explanation of the downward trend in the survival of patients with disseminated testicular cancer could be that along with the rapid increase in the incidence of testicular cancer the properties of this cancer have been changing too; thus it may become less sensitive to standard modalities of treatment, in particular to chemotherapy.

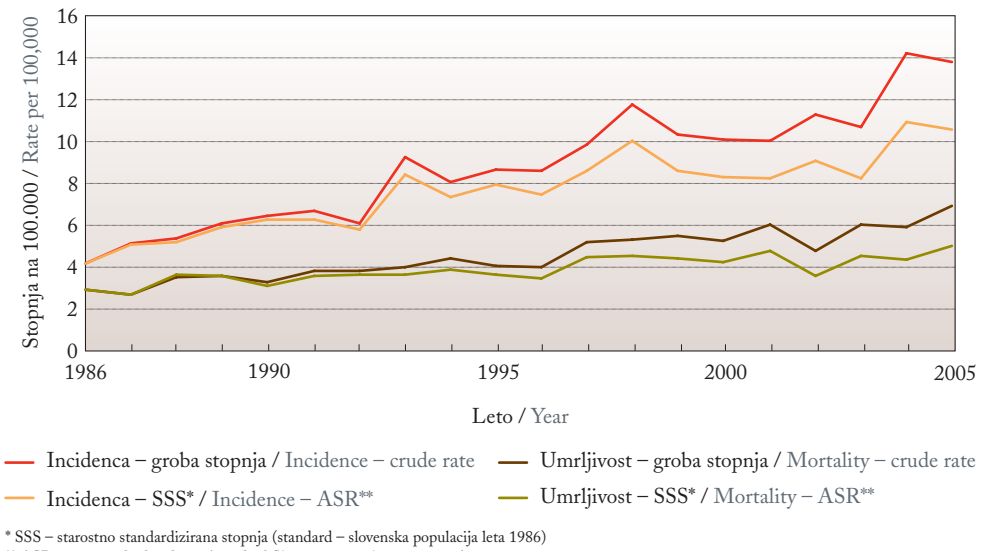
On the whole, in the last 5-year period the success of treatment in patients with testicular cancer is good, particularly in the group with favorable or moderately favorable prognosis; the evaluation of a decrease in the survival of patients with poor prognosis is unreliable due to a small number of patients in this group. Nevertheless, in the future, particular attention should be devoted to this group of patients in order to offer them all the available options for cure.

LEDVICA

MKB 10: C64, C65

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za ledvičnim rakom zbolelo 3093 ljudi, od tega 1869 moških in 1224 žensk. Kot je razvidno s Slike 1, se groba in starostno standardizirana incidenčna stopnja od leta 1991 večata, groba stopnja povprečno za 4,8 % letno, starostno standardizirana pa za 3,1 %. Prav tako se večata obe umrljivostni stopnji, groba povprečno za 4,0 % letno, starostno standardizirana pa povprečno za 2,0 % letno.



Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja ledvičnega raka, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of kidney cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 2927 primerov; 166 bolnikov (5,7 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

Odstotek mikroskopsko potrjenih primerov se je zmanjšal z 90 % v letih 1991–1995 na 86 % v letih 2001–2005. V zadnjem obdobju je bilo 75 % adenokarcinomov, 9 % drugih opredeljenih histoloških vrst, 15 % malignomov pa ni imelo opredeljene histološke vrste. V primerjavi s prvim obdobjem se je v zadnjem delež histološko neopredeljenih tumorjev povečal za 4 %.

Starost največjega deleža zbolelih je bila ob diagnozi med 50–74 leti. Pred 50. letom zboli manj kot 15 % bolnikov (Tabela 1). Predvsem pri ženskah se s časom veča delež starih 75 let in več, manjša pa delež starih 50–74 let.

Tabela 1: *Število bolnikov z ledvičnim rakom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of kidney cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	419	17,2	70,2	12,6	337	11,6	72,1	16,3
1996–2000	614	14,5	72,6	12,9	372	11,3	70,2	18,5
2001–2005	752	14,5	69,4	16,1	433	12,0	59,4	28,6

KIDNEY

ICD 10: C64, C65

EPIDEMIOLOGY

In the period 1991–2005, a total of 3093 persons were diagnosed with kidney cancer, of these 1869 males and 1224 females. As evident from Figure 1, the crude and age standardized incidence rates have been increasing since 1991, the crude rate by 4.8% and the age-standardized rate by 3.1% annually on average. The mortality rates have been increasing as well, the crude rate by 4.0% and the age standardized by 2.0% annually on average.

The survival analysis included 2927 cases; 166 patients (5.7%) diagnosed only after death, were not considered in the analysis.

The percentage of microscopically confirmed cases decreased from 90% in the period 1991–1995 to 86% in the period 2001–2005. In the last period, 75% were adenocarcinomas and 9% other defined histological types while in 15% of malignomas histological type was not determined. In comparison with the first period, in the last one the proportion of histologically undefined tumors increased by 4%.

Age of the majority of patients at diagnosis ranged between 50 and 74 years. Less than 15% of patients will develop the disease before the age of 50 (Table 1). Particularly in females, the proportion of patients aged 75 years or older is increasing with time, while the proportion of those at an age between 50–74 years is decreasing (Table 1).

In all three time-periods, slightly over a half of patients were diagnosed with localized disease; in the period 2001–2005 there were approximately 55% such patients. In 18% of males and 21% of females the disease was diagnosed in regional stage and in 23% of males and 18% of females in disseminated stage. The proportions of males with disseminated disease and females with regional disease were increasing with time (Table 2).

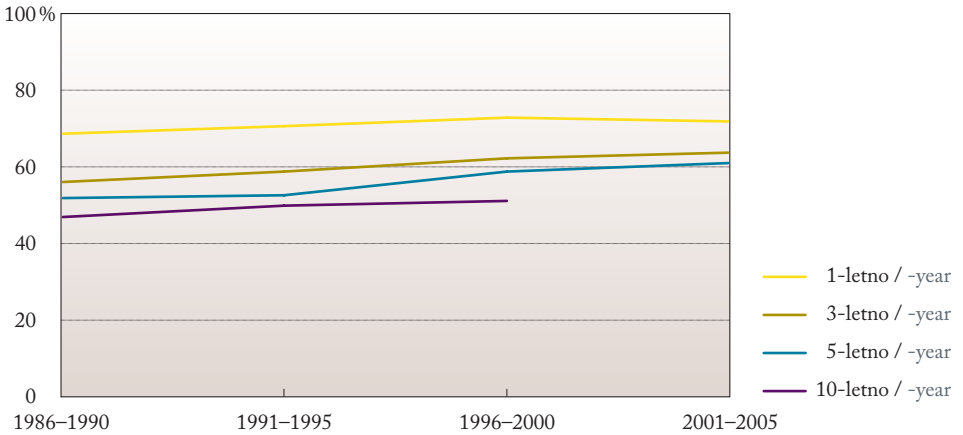
In the period 2001–2005, 16% of patients did not receive specific treatment, i. e. 3% more than in the first period. In the period 2001–2005, 89% of patients with specific treatment underwent surgery. In 82% of patients primary treatment consisted of surgery alone, while 7% had surgery plus chemotherapy and/or irradiation; the remaining 11% of patients were treated with other combinations.

In the period 2001–2005, 47% of patients started their treatment in the UMC Ljubljana, 15% in the UMC Maribor, 9% in GH Celje and Slovenj Gradec, 7% in GH Novo mesto, and 4% each at the IO Ljubljana and GH Izola, while 5% of patients started their treatment in other Slovenian hospitals.

The relative survival rate of patients with kidney cancer has been gradually increasing: in 15 years, the 5-year relative survival increased by 8% (Figure 2), in males slightly more than in females (Table 3). The relevance of stage at diagnosis is shown in Figure 3; in the last period, relative 5-year survival of patients with localized stage has reached near to 90%. The 5-year relative

Tabela 2: *Število bolnikov z ledvičnim rakom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*
Table 2: *Number of kidney cancer patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	419	55,6	18,1	18,6	7,6	337	58,2	16,3	16,6	8,9
1996–2000	614	59,9	15,6	19,4	5,0	372	57,0	16,7	18,5	7,8
2001–2005	752	54,1	18,2	22,6	5,1	433	55,0	20,6	18,2	6,2



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z ledvičnim rakom po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of kidney cancer patients by period of diagnosis.*

V vseh treh obdobjih je imela dobra polovica bolnikov ob diagnozi omejeno bolezen; v obdobju 2001–2005 je bilo takih okrog 55 % bolnikov. Pri 18 % moških in 21 % žensk je bila bolezen odkrita v razširjenem stadiju, pri 23 % moških in 18 % žensk pa v razsejanem. Pri moških se je s časom večal delež bolnikov z razsejanim stadijem, pri ženskah pa z razširjenim (Tabela 2).

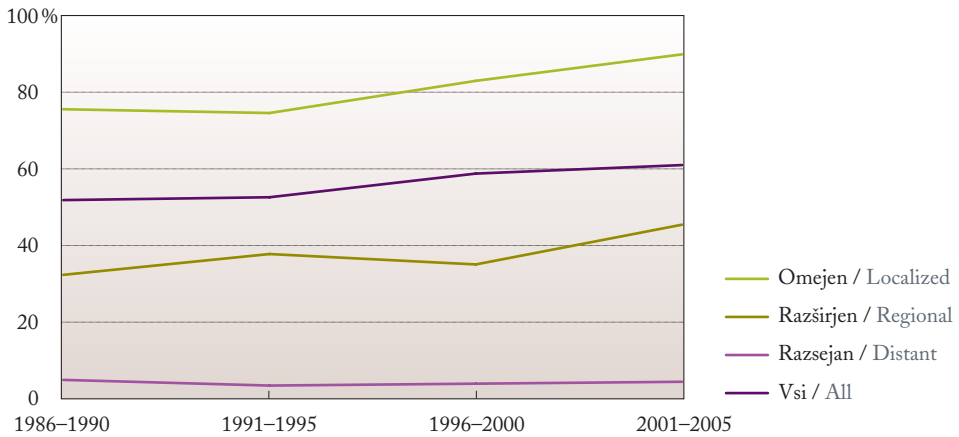
V obdobju 2001–2005 ni bilo specifično zdravljenih 16 % bolnikov, za 3 % več kot v prvem obdobju. Med specifično zdravljenimi je bilo v letih 2001–2005 89 % bolnikov operiranih. Pri 82 % bolnikov je bilo prvo zdravljenje zaključeno z operacijo, 7 % je poleg operacije prejelo še kemoterapijo in/ali obsevanje; ostalih 11 % bolnikov je bilo zdravljenih z različnimi drugimi kombinacijami.

Tabela 3: *Opazovano in relativno preživetje bolnikov z ledvičnim rakom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of kidney cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	66,6 (62,2–71,3)	50,8 (46,3–55,9)	41,3 (36,8–46,3)	70,6 (65,9–75,7)	56,1 (51,0–61,6)	48,1 (43,0–53,7)
1996–2000	69,1 (65,5–72,8)	54,4 (50,6–58,5)	47,1 (43,3–51,2)	73,1 (68,7–77,8)	60,5 (55,7–65,7)	54,3 (49,5–59,6)
2001–2005	69,0 (65,8–72,4)	56,7 (53,3–60,4)	48,6 (44,7–52,7)	70,2 (66,0–74,7)	58,4 (53,9–63,3)	53,4 (48,6–58,5)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	69,2 (64,3–74,1)	57,3 (51,6–63,0)	50,4 (44,3–56,5)	72,3 (67,2–77,5)	60,5 (54,5–66,5)	54,7 (48,3–61,1)
1996–2000	71,5 (67,6–75,3)	60,5 (55,9–65,0)	56,5 (51,6–61,5)	74,9 (70,1–79,6)	65,1 (59,5–70,7)	61,8 (55,8–67,8)
2001–2005	71,6 (68,1–75,1)	63,7 (59,6–67,8)	59,8 (54,7–65,0)	72,2 (67,6–76,8)	64,0 (58,6–69,3)	62,6 (56,6–68,7)

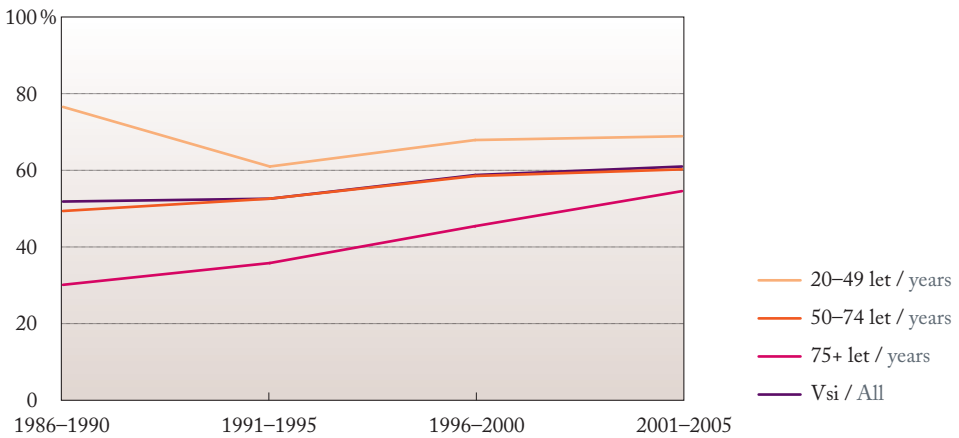


Slika 3: *Petletno relativno preživetje bolnikov z ledvičnim rakom po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of kidney cancer patients by stage and period of diagnosis.*

survival of patients with regional stage of the disease is near to 50%, whereas patients with disseminated disease had only 5% 5-year relative survival. Age is a prognostic factor as well, since the relative survival is the lowest in patients aged 75 years or older, while survival at diagnosis in the age group 50–74 years was lagging behind the relative survival of those diagnosed before the age of 50 throughout the observation period (Figure 4).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 61% (Figure 2); patients surviving the first year may expect to survive five years in 83%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002 the survival of patients with kidney cancer in Slovenia is below (statistically not significant) the European average (Figure 5).



Slika 4: *Petletno relativno preživetje bolnikov z ledvičnim rakom po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of kidney cancer patients by age and period of diagnosis.*

V obdobju 2001–2005 se je 47 % bolnikov pričelo zdraviti v UKC Ljubljana, 15 % v UKC Maribor, po 9 % SB Celje in SB Slovenj Gradec, 7 % v SB Novo mesto, po 4 % na OI Ljubljana in v SB Izola, 5 % bolnikov pa je začelo zdravljenje v drugih slovenskih bolnišnicah.

Relativno preživetje bolnikov z ledvičnim rakom se postopno veča; v 15 letih se je petletno relativno preživetje povečalo za 8 % (Slika 2), pri moških nekaj več kot pri ženskah (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem se je v zadnjem obdobju približalo 90 %. Petletno relativno preživetje bolnikov z razširjenim stadijem se približuje 50 %, bolniki z razsejano boleznijo ob diagnozi pa imajo le 5-odstotno petletno relativno preživetje. Napovedni dejavnik je tudi starost, saj je relativno preživetje najmanjše pri starih 75 let in več, preživetje ob diagnozi pri starih 50–74 let pa ves čas opazovanja zaostaja za relativnim preživetjem pri zbolelih pred 50. letom starosti (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 61 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 83-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z ledvičnim rakom statistično neznačilno manjše od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

Mirjana Žumer Pregelj

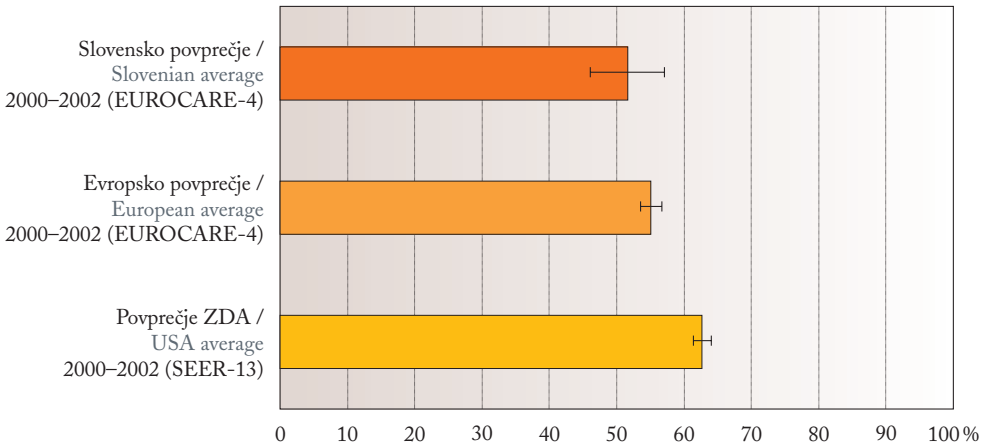
Za uspešno zdravljenje ledvičnega raka je najpomembnejše, da je čim prej odkrit. Dokler je rak omejen na ledvico, večinoma ne povzroča težav. V taki obliki je praviloma odkrit naključno, pri preiskavi z UZ, in je v velikem odstotku ozdravljiv. Žal je odstotek omejenega ledvičnega raka v zadnjih petnajstih letih skoraj nespremenjen in niha pri okrog 50 % vseh ledvičnih rakov.

Zdravljenje omejenega ledvičnega raka je operativno. Pri tumorjih, ki so v premeru manjši od 4 cm, napravimo, če je le mogoče, delno nefrektomijo (nephron-sparing surgery), pri večjih pa praviloma odstranimo celo ledvico skupaj s pripadajočo maščobno kapsulo; če je le mogoče, odstranimo še področne bezgavke; od lege tumorja je odvisna še morebitna odstranitev nadledvične žleze. Pri majhnih tumorjih, najdenih pri starih in zelo šibkih bolnikih, je možna radiofrekvenčna ablacija tumorja. To je uspešno le pri tumorjih, ki imajo premer, manjši od 3 cm. Pri bolnikih, pri katerih poseg v anesteziji ni mogoč, pa preostane le opazovanje.

Statistični podatki kažejo, da se je v 15-letnem obdobju povečalo preživetje bolnikov z omejeno boleznijo s 76 % na 90 %. To je mogoče pojasniti s tem, da se odkrije vedno več manjših tumorjev, v premeru velikih 3–4 cm, pogosto pa najdejo, citološko potrdijo in zdravijo tudi zelo majhne tumorje, manjše od 2 cm. Sama operativna tehnika se namreč v teh letih ni bistveno spremenila in ne prispeva k izboljšanju preživetja. Pri razširjenem raku je potreben obsežnejši operativni poseg z odstranitvijo bezgavk in morebitnega tumorskega tromba iz ledvične odvodnice.

Petletno preživetje bolnikov, starih 50–75 let, se zmerno veča; to bi lahko pojasnili s pogostejšimi pregledi UZ zaradi drugih bolezni, pri moških predvsem zaradi težav s prostato. Večje preživetje v starosti 75 let in več je morda posledica boljše kondicije starostnikov in uspešnejšega zdravljenja vzporednih bolezni, kar omogoča operativni poseg tudi pri starejših bolnikih.

Odstotek razsejanega ledvičnega raka se vse opazovano obdobje giblje med 18 in 22 % vseh ledvičnih rakov in je predvsem pri ženskah v rahlem porastu, verjetno zaradi daljše življenjske dobe. Petletno preživetje se pri tem stadiju tudi v obdobju med 1991 in 2005 ni izboljšalo in je le okrog 4,5 %. V tem stadiju bolezni je običajno možna le embolizacija tumorja, včasih resekcija solitarne metastaze, redko paliativna nefrektomija. Če je bolnik še v zadovoljivi kondiciji, je dodano še sistemsko zdravljenje z imunoterapijo (pri nas interferon). V zadnjih letih pa se vedno bolj uveljavljajo pri zdravljenju ledvičnega raka v tem stadiju tarčna zdravila, ki jih dajejo onkologi, in bodo prav gotovo vplivala na preživetje bolnikov z razsejanim ledvičnim rakom v naslednjih letih.



Slika 5: *Petletno relativno preživetje bolnikov z ledvičnim rakom* (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of kidney cancer patients* (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

* Nabor MKB10 kod v študiji EUROCARE-4 je nekoliko drugačen kot smo ga uporabili pri ostalih analizah predstavljenih v tem poglavju: v študiji EURCARE-4 so v analizo vključene tudi maligne neoplazme sečovoda (MKB10: C66) in maligne neoplazbe drugih urinarnih organov (MKB10: C68).

* The ICD10 code selection in EUROCARE-4 study in slightly different in comparison to the selection applied in other analysis in this chapter: in EUROCARE-4 study the malignant neoplasm of ureter (ICD10: C66) malignant neoplasm of other and unspecified urinary organs (ICD10: C68) are also included.

CLINICAL COMMENTARY

Mirjana Žumer Pregelj

For successful treatment of kidney cancer it is of essential importance that it is detected as soon as possible. As long as cancer is limited to the kidney, it generally does not cause any problems. At this stage, it is as a rule detected incidentally, on US examination, and is curable in a high percentage of cases. Unfortunately, in the last 15 years the proportion of localized kidney cancer has remained almost unchanged, representing around 50% of all kidney cancers.

The treatment of choice for localized kidney cancer is surgery. In tumors smaller than 4 cm in diameter, partial nephrectomy (nephron-sparing surgery) is performed whenever possible; in bigger tumors a whole kidney is removed together with the adjoining renal capsule; if feasible, regional lymph nodes are removed as well and, depending on tumor site, possibly also the adrenal gland. In small tumors found in old and very weak patients, radiofrequency tumor ablation may be used. This however is successful only in tumors measuring less than 3 cm in diameter. Patients, in whom surgery under anesthesia is not feasible, are subjected to follow-up observation only.

Statistical data show that in the 15-year period the survival of patients with localized disease has increased from 76% to 90%. This can be explained by the fact that more and more small tumors are detected, measuring 3–4 cm in diameter; frequently even very small tumors under 2 cm of size are found, cytologically confirmed and treated as well. The surgical technique itself has not changed significantly in these years and therefore does not contribute towards a better survival. Regionally advanced cancer requires a more extensive surgical procedure with lymphadenectomy and removal of a possible tumor thrombus from the renal vein.

Five-year survival of patients aged 50–74 years is moderately increasing, which could be explained with more frequent US examinations for other diseases, in males particularly for prostate-related

Za zaključek naj poudarim, da bi preiskava z UZ, ki je popolnoma neinvazivna preiskava in je v vedno širši rabi, v rokah veščega pregledovalca ohranila marsikatero življenje vsako leto. To je edini pregled, ki omogoča odkritje ledvičnega raka v zgodnji fazi. Preiskavo z UZ običajno napravijo pri sumu na žolčne kamne, pri neznačilnih težavah v trebuhu, pri nepojasnjenem hujšanju, ob kontroli zaradi drugih bolezni (npr. ledvičnih kamnov, težav s prostato itd.), neredko pa prav na željo bolnika kot preventivni pregled.

VIRI
Literature

Albers P. Tretment Aprouches in renal cell carcinoma: past, present and future perspectives. Eur Urol Suppl 2008; 7: 36–45.

Ljunberg B, Hanbury DC, Kuczyk MA, at al. Renal Cell Carcinoma guideline. Eur Urol 2007; 51: 1502–10.

Kean T, Gilatt D, Evans CP, Tubaro A. Current and future trends in the Treatment of renal cancer. Eur Urol Suppl 2007; 6: 374–84.

Žumer Pregelj M, Šurlan M, Černelč B. Paliativno zdravljenje obsežnega ledvičnega karcinoma z vraščanjem tumorja v veno kavo in desni atrij. In: Drugi slovenski urološki kongres z mednarodno udeležbo in Simpozij medicinskih sester in zdravstvenih tehnikov. Ljubljana: Lek; 2002.

KLINIČNI KOMENTAR
Tanja Čufer

Ledvični rak je razmeroma redek rak, vendar se incidenca te bolezni v svetu in pri nas veča. Žal z rastočim trendom incidence raste tudi trend umrljivosti. Razlog za večanje incidence ponekod po svetu iščejo v večjem številu preiskav z UZ, kar ima za posledico odkrivanje zgodnejših stadijev biološko manj agresivne bolezni. Pri nas glede na to, da se porazdelitev stadijev v zadnjih 15 letih ni bistveno spremenila, vzroka večje incidence verjetno ni iskati v pogostejših radioloških preiskavah. Glede na nespremenjene stadije bolezni in glede na to, da pri zdravljenju raka ledvic žal do začetka tega stoletja nismo imeli novih orodij, se skladno s porastom incidence pričakovano povečuje tudi umrljivost za to boleznijo. Dobra novica pa je, da umrljivost za tem rakom pri nas v zadnjem desetletju ni sledila rasti incidence.

Preživetje bolnikov z ledvičnim rakom pri nas še vedno zaostaja za evropskim povprečjem, tudi pri bolnikih, zdravljenih v letih 2000–2002; v kolikšni meri je ta zaostanek pripisati večjim tumorjem ob diagnozi ali preveč razpršenemu kirurškemu zdravljenju, pa mora biti predmet natančnejših raziskav.

V zadnjem obdobju so se v Sloveniji povečala predvsem dolgotrajno, petletno preživetje in preživetje bolnikov z omejeno in tudi razširjeno boleznijo, medtem ko se preživetje bolnikov z razsejano boleznijo ni spremenilo. To je pričakovano in v skladu z opažanji drugje po Evropi. Za omejeno in razširjeno bolezen imamo na voljo razmeroma učinkovito kirurško zdravljenje, medtem ko za zdravljenje razsejane bolezni do leta 2005 ni bilo na voljo zdravil. Večje preživetje bolnikov z omejeno in po letu 2000 tudi z razširjeno boleznijo je posledica izpopolnjenih kirurških metod zdravljenja, boljše pooperativne oskrbe in tudi večjega deleža bolnikov, ki so bili pri nas deležni tega zdravljenja. Povečanje preživetja bolnikov z razsejano boleznijo pa je pričakovati po letu 2005, ko smo tako pri nas kot v svetu v zdravljenje te bolezni uvedli nova, učinkovita tarčna zdravila.

V skladu z dolgoletnimi opažanji pri nas in po svetu je preživetje žensk z ledvičnim rakom večje od preživetja moških, ne glede na stadij bolezni. To se kaže tudi pri naših bolnikih. Nedvoumne razlage za to ni, zanimivo pa bo opazovati vpliv tarčnih zdravil na ta pojav v naslednjih letih. Spodbudno je tudi opažanje, da se je ob porastu preživetij vseh starostnih skupin bolnikov pri nas v obdobju po letu 1995 strmo povečevalo 5-letno preživetje tudi bolnikov, starejših od 75 let, in se v obdobju 2001–2005 že zelo približalo preživetju bolnikov v starosti 50–74 let (55 % in 61 %).

Ledvični rak je bolezen, pri kateri sicer zaostajamo v preživetju za evropskim povprečjem, vendar rezultate izboljšujemo. Dober uspeh pri omejenem stadiju je bil do sedaj posledica ustreznega,

problems. A higher survival in the age group 75 years or older is perhaps attributable to a better general condition of the elderly as well as to more successful treatment of their concomitant diseases, which renders surgery feasible in older patients as well.

The percentage of disseminated disease has been ranging between 18% and 22% of all kidney cancers throughout the observation period, and has undergone a slight upward trend particularly in females, probably due to their longer lifespan. Also in the period 1991–2005 5-year survival in this stage did not get any better, being only 4.5%. At this stage tumor embolization is generally the only option available, occasionally resection of a solitary metastasis and rarely palliative nephrectomy can be performed. If the patient is still in a relatively good general condition, systemic treatment with immunotherapy (in our case interferon) is used in addition. In recent years, targeted systemic therapy applied by oncologists is becoming increasingly important in the treatment of disseminated kidney cancer, and it will certainly influence the survival of these patients in the following years.

In conclusion, let me point out that an US examination, which is a totally non-invasive and widely used method, when used by an experienced diagnostician may save lots of life every year. This is the only examination that has the potential of detecting kidney cancer in an early stage. US examination is generally performed in suspected bile stones, unspecific abdominal disorders, unexplained body weight loss, on a follow-up for other diseases (e. g. kidney stones, prostate-related problems, etc), and not infrequently at a request of the patient as a preventive check-up.

CLINICAL COMMENTARY

Tanja Čufer

Kidney cancer is a relatively rare disease, however its incidence worldwide as well as in Slovenia is on the increase. Unfortunately, the upward trend in incidence is associated with the same trend in mortality rates. In some countries the increasing incidence is attributed to a greater number of US examinations, which results in the detection of earlier stages of biologically less aggressive disease. In Slovenia, considering that stage distribution has not changed significantly in the last 15 years, the reason for higher incidence probably should not be sought in more frequent radiological examinations. Taking into account unchanged stage distribution and the fact that until the beginning of this century no new tools had been available in the treatment for kidney cancer, it is encouraging, that in the last decade the mortality for this cancer in Slovenia was lagging behind the increasing incidence rates.

The survival of patients with kidney cancer in Slovenia is still below the European average, also in patients treated in the years 2000–2002; more in-depth studies are warranted in order to establish to what extent this backlog is due to larger tumors at diagnosis or to overdispersed surgical treatment.

In the last period, mainly a long-term, 5-year survival and the survival of patients with localized as well as with regional disease have increased, whereas the survival of patients with disseminated disease has remained unchanged. This is expected and consistent with the findings in other parts of Europe. While there is a relatively effective surgical treatment available for localized and regional disease, there was no effective systemic therapy available for disseminated disease until 2005. A higher survival of patients with localized, and after the year 2000 also with regional disease, is a result of upgraded surgical methods and better postoperative care. An increase in the survival of patients with disseminated disease may be expected after the year 2005, when in Slovenia, likewise elsewhere in the world, new and effective targeted systemic therapies have been introduced in the treatment for this disease.

In accordance with long-term observations in Slovenia and worldwide, the survival of females with kidney cancer is higher than the survival of males, irrespective of the stage of disease. This

edinega do sedaj dokazano učinkovitega, kirurškega zdravljenja. Pričakovati je, da bo uvedba tarčnih zdravil v naslednjih letih še izboljšala preživetje bolnikov s tem rakom.

VIRI
Literature

Čufer T. Rak ledvic. Onkologija 2005; 9: 76–79.
Snoj N, Čufer T. Biološko in tarčno zdravljenje karcinomov. Onkologija 2007; 11: 72–76.

is also evident in our patients. There is no clear explanation for that, but it will be interesting to follow the impact of targeted systemic therapies on this phenomenon in the following years.

It is also encouraging to note that along with an increase in the survival of patients in all age groups after the year 1995, there was a steep increase in 5-year survival of patients aged 75 years or older in the period 2001–2005, closely approaching the survival of patients in the age group 50–74 years (55% and 61% respectively).

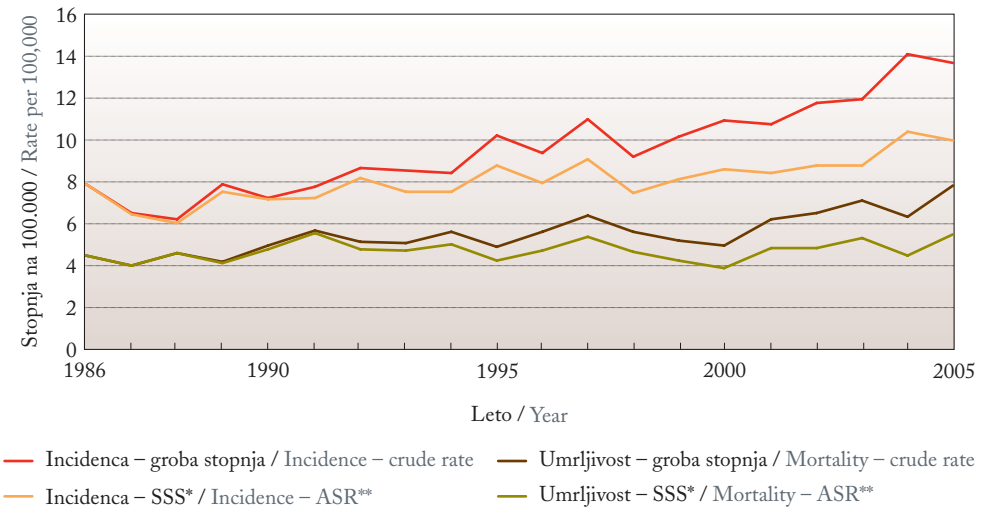
Although the survival of kidney cancer patients in Slovenia lags behind the European average, the results are improving. So far, notable success achieved in the localized stage has been the result of the only proven effective treatment – surgery. It is expected that in the following years the implementation of targeted systemic therapies will further improve the survival of patients with this cancer.

SEČNI MEHUR

MKB 10: C67

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom sečnega mehurja zbolelo 3213 ljudi, od tega 2390 moških in 823 žensk. Kot je razvidno s Slike 1, se groba in starostno standardizirana incidenčna in umrljivostna stopnja od leta 1991 povečujeta. Groba incidenčna stopnja se veča hitreje, povprečno za 3,7 % letno, kot starostno standardizirana (1,8 %). Groba umrljivostna stopnja se veča povprečno za 2,2 %, starostno standardizirana umrljivostna stopnja pa je bila vse obdobje konstantna.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka sečnega mehurja, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of bladder cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 3114 primerov; 99 bolnikov (3,2 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

V obdobju 2001–2005 je bilo 96 % primerov raka mikroskopsko potrjenih. Delež mikroskopsko potrjenih se je v primerjavi z obdobjem 1991–1995 povečal za 2 %. V vseh treh obdobjih je imelo največ bolnikov karcinom prehodnega epitela, v zadnjem obdobju 88 %, po 2 % je bilo adeno- in ploščatoceličnih karcinomov, pri 8 % histološka vrsta ni bila natančneje opredeljena.

Tabela 1: *Število bolnikov z rakom sečnega mehurja po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of bladdder cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	657	4,4	66,2	29,4	211	2,4	59,2	38,4
1996–2000	760	4,9	69,1	26,1	244	5,3	59,4	35,2
2001–2005	917	4,6	65,3	30,1	325	4,6	49,5	45,8

URINARY BLADDER

MKB 10: C67

EPIDEMIOLOGY

In the period 1991–2005, a total of 3213 persons were diagnosed with cancer of the urinary bladder, of these 2390 males and 823 females. As evident from Figure 1, since 1991, crude as well as age-standardized incidence and mortality rates have been increasing. Thus crude incidence rate has been increasing more rapidly than age-standardized rate, by 3.7% vs. 1.8% per year respectively. The crude mortality rate has been increasing by 2.2% on average while the age-standardized mortality rate remained stable throughout the observation period.

The survival analysis included 3114 cases; 99 patients (3.2%) diagnosed only after death were not considered in the analysis.

In the period 2001–2005, 96% of cancers were microscopically verified. In comparison with the period 1991–1995 the proportion of microscopically confirmed cases has increased by 2%. In all three time-periods, the majority of patients presented with carcinoma of the transitional epithelium, in the last period there were 88% such patients, adeno- and planocellular carcinomas were diagnosed in 2% each, while histological type was not precisely determined in 8% of cases.

The majority of patients were diagnosed at an age between 50 and 74 years; in these age-groups, there was approximately 65% of males and 50% of females (Table 1). In the period 2001–2005, the proportion of females aged between 50–74 years decreased while the proportion of those diagnosed at the age of 75 years or older increased. Less than 5% of patients will develop the disease before the age of 50.

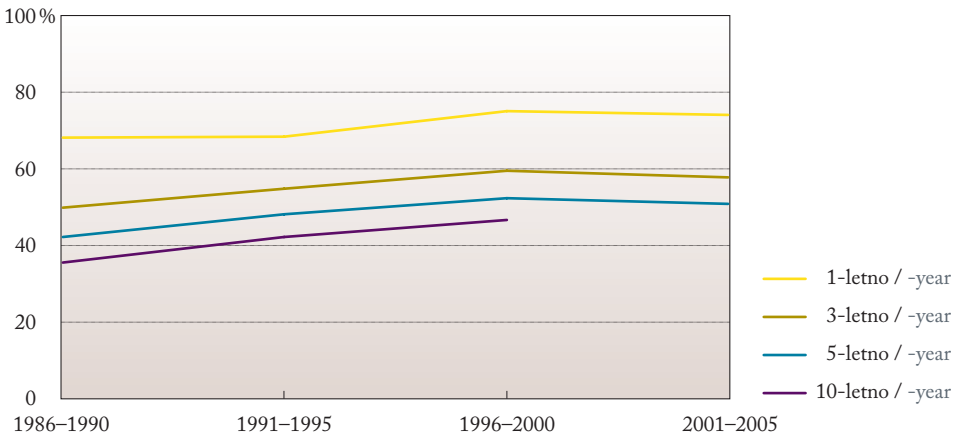
In all three time-periods, the majority of patients were diagnosed with localized disease; in the period 2001–2005 there were 70% such patients (Table 2). As compared to the period 1991–1995, in the last period the proportion of localized stage in males increased by 6% and in females by 12%; in the latter the proportion of regional stage decreased by 9%. Approximately 20% of patients were diagnosed with regional disease. The proportions of patients with disseminated stage have increased with time, mainly on the account of smaller proportion of patients with an undefined stage.

In the period 2001–2005, 7% of patients did not receive specific treatment. The proportion of untreated patients did not change significantly throughout the observation periods; among those diagnosed in the period 1991–1995, there were 8% of patients without specific treatment. Among the patients receiving specific treatment in the period 2001–2005, in 61% the primary treatment was completed by surgery (there are no data in CRS on how many there were radical cystectiomies and how many transurethral resections) 12% received radiotherapy and chemotherapy in addition to surgery, 10% received irradiation treatment after surgery, another 10% was treated with the combination of surgery, chemotherapy and irradiation; 7% of patients were treated with other combinations.

Tabela 2: *Število bolnikov z rakom sečnega mehurja po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of bladdder cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	657	65,8	20,7	4,4	9,1	211	58,3	26,5	3,3	11,8
1996–2000	760	71,3	19,6	3,4	5,7	244	70,5	19,3	8,6	1,6
2001–2005	917	71,5	19,4	6,1	2,9	325	70,5	17,5	5,5	6,5



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom sečnega mehurja po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of bladder cancer patients by period of diagnosis.*

Največji delež zbolelih je bil ob diagnozi star med 50 in 74 let, med moškimi jih je bilo v tej starostni skupini 65 %, med ženskami pa 50 % (Tabela 1). V obdobju 2001–2005 se je zmanjšal delež žensk, starih 50–74 let, in povečal delež starih ob diagnozi 75 let in več. Pred 50. letom zboli manj kot 5 % bolnikov.

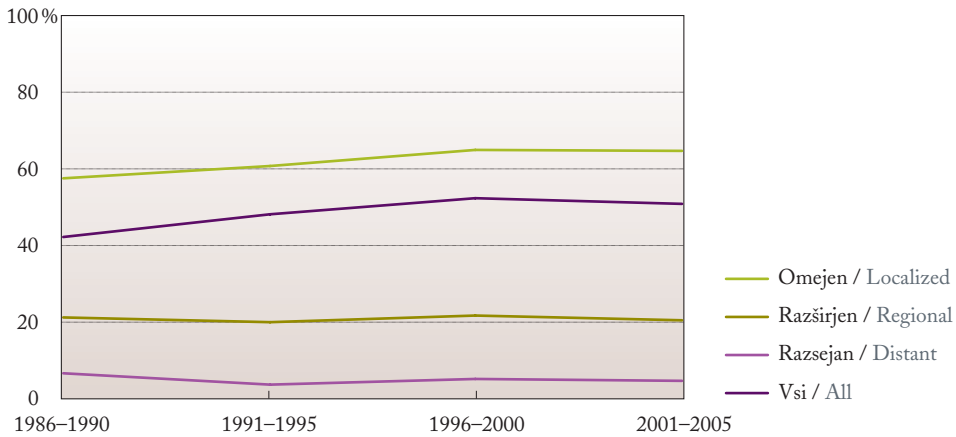
V vseh treh obdobjih je imelo ob diagnozi največ bolnikov omejeno bolezen; v obdobju 2001–2005 jih je bilo okrog 70 % (Tabela 2). Pri moških se je v zadnjem obdobju v primerjavi z obdobjem 1991–1995 povečal delež omejenega stadija za 6 %, pri ženskah pa za 12 %; pri zadnjih se je zmanjšal delež razširjenega stadija za 9 %. Z razširjenim stadijem je bilo diagnosticiranih blizu 20 % bolnikov. Delež bolnikov z razsejanim stadijem se je sčasoma večal, predvsem na račun manjšega deleža bolnikov, pri katerih stadij ni bil opredeljen.

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom sečnega mehurja po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of bladder cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	65,6 (62,1–69,3)	46,0 (42,3–49,9)	34,4 (31,0–38,2)	60,2 (53,9–67,2)	43,6 (37,4–50,8)	37,4 (31,4–44,6)
1996–2000	70,9 (67,8–74,2)	50,5 (47,1–54,2)	38,7 (35,4–42,3)	71,7 (66,3–77,6)	50,0 (44,1–56,7)	42,6 (36,8–49,3)
2001–2005	71,2 (68,3–74,2)	50,1 (47,0–53,5)	37,9 (34,4–41,6)	67,4 (62,5–72,7)	45,0 (39,9–50,8)	37,2 (31,8–43,4)

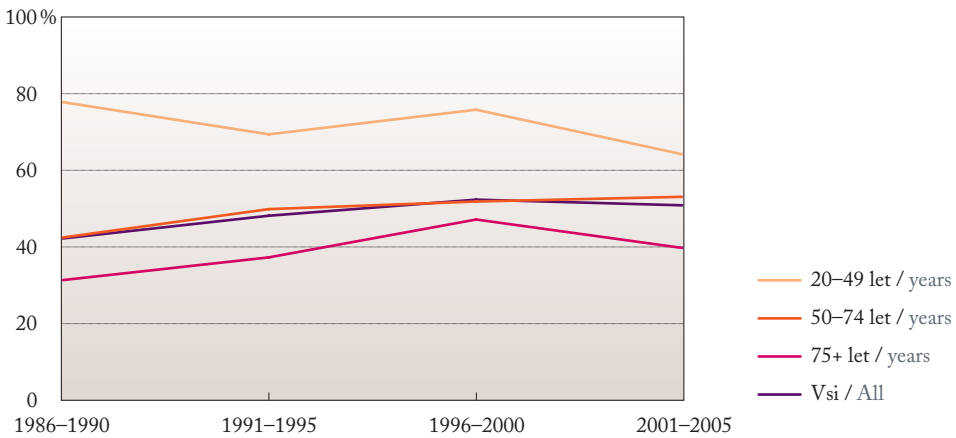
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	69,9 (65,9–73,9)	55,6 (50,8–60,4)	47,6 (42,3–52,9)	63,8 (56,4–71,2)	51,9 (43,3–60,5)	50,2 (40,6–59,8)
1996–2000	75,0 (71,5–78,5)	59,9 (55,6–64,3)	51,9 (47,0–56,7)	75,2 (69,1–81,4)	57,7 (50,0–65,4)	54,2 (45,7–62,7)
2001–2005	75,2 (72,0–78,4)	59,7 (55,6–63,7)	51,4 (46,3–56,5)	70,8 (65,3–76,4)	52,8 (46,0–59,6)	48,9 (40,7–57,1)



Slika 3: *Petletno relativno preživetje bolnikov z rakom sečnega mehurja po stadiju in obdobju postavitve diagnoze.*
Figure 3: *5-year relative survival of bladder cancer patients by stage and period of diagnosis.*

In the period 2001–2005, 40% of patients started their treatment in the UMC Ljubljana, 15% each in the UMC Maribor and GH Celje, 6% each in GH Novo mesto, GH Slovenj Gradec, GH Izola and GH Nova Gorica, 3% in GH Murska Sobota and 2% at the IO Ljubljana.

In the 15-year observation period, the relative survival of patient with bladder cancer has not changed significantly; in the last period it even decreased (to 51% vs. 53% in 1996–2000) (Figure 2), to a greater extent in females than in males (Table 3). Stage at diagnosis is a relevant prognostic factor of disease outcome as the best survival is observed in patients with localized stage, but nevertheless, even in these patients no significant improvement has been achieved in the last observation period (Figure 3). In the period 2001–2005, 5-year relative survival rate of patients with localized stage was 65%. Age is a prognostic factor as well, since the relative survival is the lowest in patients aged 75 years or older, where it underwent the strongest decrease in the last observation period; a minor improvement was observed only in patients diagnosed at an age between 50–74 years; the evaluation of survival in younger patients is not reliable because their number is too small (Figure 4).



Slika 4: *Petletno relativno preživetje bolnikov z rakom sečnega mehurja po starosti in obdobju postavitve diagnoze.*
Figure 4: *5-year relative survival of bladder cancer patients by age and period of diagnosis.*

V obdobju 2001–2005 se ni specifično zdravilo 7 % bolnikov. Delež nezdravljenih bolnikov se v vseh obdobjih ni bistveno spreminjal; med bolniki, zbolelimi v letih 1991–1995, se jih ni specifično zdravilo 8 %. Med specifično zdravljenimi v letih 2001–2005 se je pri 61 % primerov prvo zdravljenje zaključilo z operacijo (natančnejših podatkov o tem, koliko je bilo radikalnih cistektomij, koliko pa transuretralnih resekcij, v RRS ni), 12 % jih je bilo poleg operacije dodatno še obsevanih in zdravljenih s kemoterapijo, 10 % pa je poleg kirurškega prejelo še obsevalno zdravljenje; še dodatnih 10 % je bilo zdravljenih s kombinacijo operacije, citostatikov in obsevanja; 7 % bolnikov je bilo zdravljenih z drugimi kombinacijami.

V obdobju 2001–2005 se je 40 % bolnikov začelo zdraviti v UKC Ljubljana, po 15 % v UKC Maribor in SB Celje, po 6 % v SB Novo mesto, SB Slovenj Gradec, SB Izola in SB Nova Gorica, 3 % v SB Murska Sobota in 2 % na OI Ljubljana.

Relativno preživetje bolnikov z rakom sečnega mehurja se v 15 letih ni bistveno povečalo; v zadnjem obdobju se je celo zmanjšalo (na 51 % v primerjavi z leti 1996–2000, ko je bilo 53 %) (Slika 2), bolj pri ženskah kot pri moških (Tabela 3). Stadij ob diagnozi je sicer napovedni dejavnik izida bolezni, saj je preživetje največje pri bolnikih z omejenim stadijem, vendar tudi pri teh bolnikih v zadnjem obdobju ni pomembnega izboljšanja (Slika 3): petletno relativno preživetje bolnikov z omejenim stadijem v letih 2001–2005 je bilo 65-odstotno. Napovedni dejavnik je tudi starost, saj je relativno preživetje najslabše pri starih 75 let in več, pri katerih se je v zadnjem obdobju tudi najbolj zmanjšalo; manjši napredek je le pri bolnikih, diagnosticiranih v starosti 50–74 let; vrednotenje preživetja pri mlajših pa ni zanesljivo, ker je primerov premalo (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 51 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 67-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom sečnega mehurja statistično značilno manjše od evropskega povprečja za 20 % (Slika 5).

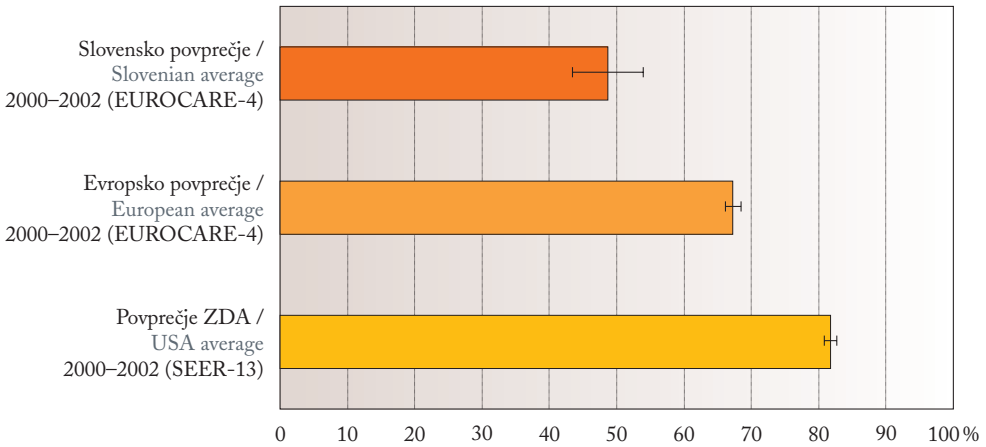
KLINIČNI KOMENTAR

Boris Sedmak

V opazovanem 15-letnem obdobju se je incidenca invazivnega raka mehurja večala. Kljub porastu deleža bolnikov z omejeno boleznijo se je petletno preživetje bolnikov v tem obdobju le malo povečalo. Podatki o načinih zdravljenja kažejo, da se je večal delež bolnikov, ki so se zdravili samo s kirurgijo, zmanjšal pa se je delež bolnikov, zdravljenih s kombiniranim zdravljenjem, kirurgijo, kemoterapijo in obsevanjem. Zavedati se moramo, da je radikalna cistektomija še vedno standardni način zdravljenja in da je pri invazivnem raku sečnega mehurja transuretralna resekcija kot edini način zdravljenja nezadostna. V poštev pride le kot diagnostični, ne pa kot terapevtski postopek. Le v izbranih primerih je možno zdraviti bolnika s transuretralno resekcijo mehurja in zdravljenje nadaljevati s kemo- in radioterapijo. Bolnike, ki so se zdravili z metodo ohranitvenega zdravljenja mehurja, je treba natančno slediti, za to pa so potrebni oprema in strokovno usposobljeno osebje.

Za boljšo napoved izida bolezni so zgodnja diagnostika ter pravilno in pravočasno zdravljenje ključnega pomena. Najpomembnejša preiskava za diagnozo raka sečnega mehurja je cistoskopija in nato endoskopska resekcija tumorja mehurja s patohistološko preiskavo tkiva. Za zamejitev bolezni uporabljamo UZ preiskavo, intravenozno urografijo, CT, MRI in bimanualno palpacijo v anesteziji med transuretralno resekcijo. Velik pomen ima dostopnost slikovnih preiskav, posebej CT in MRI. Čakanje na omenjeni preiskavi podaljšuje čas do začetka zdravljenja in slabša izid bolezni.

Indikacija za radikalno cistektomijo je mišično invazivni karcinom sečnega mehurja, opredeljen kot T2-T4a, N0–NX, M0, in obsežni površinski papilarni rak mehurja, ki ga ni mogoče zdraviti s konzervativnimi metodami. Večkratno ponavljanje transuretralnih resekcij mehurja



Slika 5: *Petletno relativno preživetje bolnikov z rakom sečnega mehurja (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of bladder cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 51% (Figure 2); patients surviving the first year may expect to survive five years in 67%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of bladder cancer patients in Slovenia is statistically significantly below the European average (Figure 5).

CLINICAL COMMENTARY

Boris Sedmak

In the observed 15-year period the incidence of invasive bladder cancer has increased. Despite the greater proportion of patients with localized disease, an increase in the 5-year survival of patients observed in that period was negligible. The data on treatment approach show that the proportion of patients treated by surgery alone was increasing while the proportion of those treated with a combination of surgery, chemotherapy and irradiation was decreasing. It should be kept in mind that radical cystectomy still represents a standard treatment and that in invasive bladder cancer transurethral resection as single modality treatment is insufficient. It can be used as a diagnostic but not also as a therapeutic procedure. In certain cases only, the patient may be treated with transurethral bladder resection followed by chemo- and radiotherapy. The patients treated by bladder preserving approach require close monitoring, which calls for adequate equipment and competent staff.

For better outcome of this disease, early diagnosis as well as correct and timely treatment is of essential importance. Cystoscopy is the most relevant procedure for the diagnosis of bladder cancer; the next is endoscopic resection of the bladder tumor with pathohistological examination of the resected tissue. Staging of the disease is performed by means of US, intravenous urography, CT scan, MRI and bimanual palpation under anesthesia during transurethral resection. The availability of imaging methods, particularly of CT and MRI, is of great importance. Too long wwaiting for the investigations mentioned, delays the beginning of treatment and adversely affects the prognosis.

Indications for radical cystectomy include muscle invasive carcinoma of the urinary bladder classified as T2-T4a, N0–NX, M0 and extensive superficial papillary bladder cancers, which

pri ugotovljenem mišično invazivnem raku sečnega mehurja in pri bolniku, kjer je cistektomija možna, je nedopustno. Pogosteje bi morali bolnike zdraviti kombinirano z neoadjuvantno kemoterapijo in cistektomijo. Pri teh bolnikih bi morali pozorno spremljati učinek kemoterapije in v primeru, da ta ni učinkovita, bolnika čim prej operirati. Bolnike z rakom sečnega mehurja bi bilo treba zdraviti interdisciplinarno. Radikalna cistekotomija in ustrezna izpeljava urina je obsežna operacija, za katero so potrebne velike izkušnje. Za boljše rezultate zdravljenja bi bilo treba bolnike obravnavati v večjih centrih. V opazovanem obdobju se je preživetje bolnikov pri omejeni bolezni izboljšalo, kar je verjetno posledica večjega števila radikalnih cistektomij. Slabše preživetje bolnikov pri razširjeni in še posebej pri razsejani bolezni je verjetno posledica tega, da ti bolniki niso v zadostnem številu zdravljeni s kemoterapijo in z obsevanjem.

VIRI
Literature

Babjuk M, Oosterlinck W, Sylvester R. Guidelines on TaT1 (Non-Muscle invasive) Bladder Cancer. European Association of Urology 2008.

Messing EM. Urotelial Tumors of the Bladder. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology. Philadelphia. Saunders, 2007: 2407–46.

Jones JS, Campbell SC. No-Muscle-Invasive Bladder Cancer (Ta, T1, CIS). In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology. Philadelphia. Saunders, 2007: 2447–68.

Schoenberg MP, Gonzalgo M, Management of invasive and Metastatic Bladder Cancer. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology. Philadelphia. Saunders, 2007: 2468–79.

Stenzl A, Cowan NC, Santis MD, Jakse G, Kuczyk M, Merseburger AS, et al. Guidelines on Bladder Cancer Muscle-invasive and Metastatic. European Association of Urology 2008.

KLINIČNI KOMENTAR
Tanja Čufer

Rak sečnega mehurja je srednje pogost rak, za katerim nekoliko pogosteje zbolevajo moški kot ženske. Incidenca bolezni tako pri nas kot v svetu počasi raste. Incidenca, pa tudi preživetje, sta odvisna tudi od tega, ali se prijavlja samo invazivni ali tudi neinvazivni, t. i. in situ rak mehurja. V večini evropskih registrov raka in pri nas se prijavljajo samo invazivni primeri raka, zato je za razliko od ZDA incidenca bolezni v Evropi nižja, slabše pa je tudi preživetje bolnikov. Pri nas v zadnjem desetletju žal ne opažamo padajočega trenda umrljivosti za tem rakom, kot ga opažajo ponekod v Evropi.

Preživetje bolnikov z rakom sečnega mehurja je pri nas slabo in se žal v zadnjih letih ni izboljšalo. Tudi to zadnje poročilo ne kaže večjega, ampak celo manjše petletno preživetje vseh bolnikov, zbolelih v obdobju 2001–2005, glede na tiste, zbolele v letih 1996–2000 (Slika 2). Medtem ko se preživetje bolnikov z rakom mehurja v Evropi izboljšuje, pri nas temu žal ni tako. Kar 15-odstotni zaostanek v petletnem preživetju, opazovan v raziskavi EUROCARE-3 pri bolnikih, zbolelih v letih 1990–1994, se je v obdobju 2000–2002 glede na izsledke EUROCARE-4 raziskave še povečal. Petletno relativno preživetje bolnikov z rakom sečnega mehurja je bilo pri diagnosticiranih v letih 2000–2002 v Evropi 68,9 %, v Sloveniji pa samo 48,0 %.

Pričujoče poročilo pokaže, da se je tako 1-, 3- kot 5-letno preživetje bolnikov, diagnosticiranih v letih 2001–2005, celo nekoliko zmanjšalo. Poslabšanje je opazno pri vseh stadijih bolezni, predvsem pri ženskah. Ker se delež bolnikov z odkrito boleznijo po različnih stadijih v zadnjem obdobju ni spremenil, je vzrok manjšega preživetja iskati v neustreznem zdravljenju. Delež bolnikov, zdravljenih z radikalno kirurgijo, je pri nas premajhen. Zgovorno je dejstvo, ki ga je v svojem magistrskem delu pokazala Urška Bizjak Ogrinc, da je bilo v letih 1987, 1992 in 1997 samo 6,6 % bolnikov (5 % stadija T2 in 16 % stadija T3) deležnih radikalne cistektomije. To je standardno zdravljenje mišično invazivnega raka sečnega mehurja, s katerim je mogoče ozdraviti okoli polovico bolnikov. V teh letih je 57 % bolnikov v okviru kirurškega zdravljenja imelo opravljeno samo TUR, ki za večino bolnikov ni najustreznejši način zdravljenja. Drugi način zdravljenja za izbrane bolnike z mišičnoinvazivnim rakom mehurja je ohranitveno zdravlje-

cannot be treated by conservative methods. Repeated transurethral resections of the urinary bladder in a confirmed muscle-invasive bladder cancer and when cystectomy is feasible, is intolerable. The patients should be treated more often with a combination of neoadjuvant chemotherapy and cystectomy. In these patients the effect of chemotherapy should be closely monitored and in the case that it turns out ineffective, the patient should be operated on as soon as possible. Bladder cancer patients should be treated by an interdisciplinary approach. Radical cystectomy with a suitable urostomy (urinary diversion) is a major surgical procedure that requires a lot of experience. For better treatment outcomes, the patients should be treated in bigger specialized centers. In the period under observation, the survival of patients with localized disease has improved, which is probably attributable to the higher number of radical cystectomies. Worse survival of patients with regional and particularly with disseminated disease is probably due to the fact that an insufficient number of patients were treated by chemotherapy and irradiation.

CLINICAL COMMENTARY

Tanja Čufer

The frequency of bladder cancer is moderate, with males being affected more often than females. The incidence in Slovenia as elsewhere in the world is slowly increasing. Both, the incidence as well as the survival rates depend on whether only invasive or also non-invasive, the so-called *in situ* bladder cancers are reported. In a majority of European cancer registries, and thus also in Slovenia, only invasive cancers are registered, and therefore – for the difference from the USA – the incidence in Europe is lower, but then the survival is lower too. In the last decade, unfortunately, no decreasing trend in the mortality for this cancer has been observed in Slovenia.

The survival rates of bladder cancer in Slovenia are poor and have unfortunately not improved in last years. According to the current report, 5-year survival of all patients diagnosed in the period 2001–2005 is even lower compared to those diagnosed in the period 1996–2000 (Figure 2). While the survival of bladder cancer patients in Europe is improving, in Slovenia it is unfortunately not so. A fifteen-percent lagging behind in 5-year survival revealed by EUROCARE-3 in patients diagnosed in the period 1990–1994 underwent a further increase in the period 2002–2002, as evident from the results of EUROCARE-4 study. While in Europe the relative survival of bladder cancer patients diagnosed in the period 2000–2002 was 68.9%, in Slovenia it was only 48.0%.

The current report shows that 1-, 2-, 3- as well as 5-year survival of patients diagnosed in the period 2001–2005 underwent a slight decrease compared to the previous period. The decrease is noted in all stages of the disease, particularly in women. Since in the last period the proportions of patients diagnosed with different stages of the disease have not changed, the cause for poor survival should be sought in inadequate treatment. In Slovenia, the proportion of patients treated by radical surgery is too low. A fact pointed out in the Master's thesis by Urška Bizjak Ogrinc speaks for itself: in the years 1987, 1992 and 1997 only 6.6% of patients (5% with T2 and 16% with T3 stage) underwent radical cystectomy, a standard therapy for muscle-invasive bladder cancer, which can cure approximately 50% of the affected patients. In those years, in 57% of patients surgery consisted of TUR alone, though in a majority of cases this method is not the best choice. Another treatment approach to a selected group of patients with muscle-invasive bladder cancer is bladder-preserving treatment by means of TUR, chemotherapy and irradiation. However, this treatment is suitable only for selected patients with muscle-invasive bladder cancer, and therefore the proportion of patients treated in this way in Slovenia as well as elsewhere in the world is low. Thus, in the years 1992 and 1997 only about 6% of patients with muscle-invasive cancer received such therapy.

The reason for poor survival of bladder cancer patients in Slovenia in last years is attributable to the sub-optimal surgery for muscle-invasive cancer, and therefore all the efforts should be directed into improving this treatment approach. So far, adjuvant therapy of this type of cancer with

nje s TUR, kemoterapijo in obsevanjem. To zdravljenje je primerno le za malo bolnikov z mišično invazivnim rakom, zato je delež tako zdravljenih bolnikov povsod po svetu, pa tudi pri nas, majhen. Pri nas je bilo tako zdravljenih v letih 1992 in 1997 le okoli 6 % bolnikov z mišično invazivnim rakom mehurja.

Razlog za slabo preživetje bolnikov z rakom sečnega mehurja v Sloveniji v zadnjih letih je gotovo iskati v suboptimalnem kirurškem zdravljenju mišičnoinvazinega raka, zato je treba vse moči usmeriti v izboljšanje tega zdravljenja. Dopolnilno zdravljenje tega raka s citostatiki zaenkrat še ni dalo prepričljivih rezultatov. To zdravljenje ima majhno dobrobit pri bolnikih s prizadetimi področnimi bezgavkami, a bistvenega izboljšanja preživetja z dopolnilno kemoterapijo, ki je danes na voljo, ni pričakovati. Treba pa je z ustrezno vodenim citostatskim zdravljenjem izboljšati preživetje bolnikov z razsejanim rakom sečnega mehurja, ki je s citostatskim zdravljenjem zazdravljiva bolezen. Pri nas premajhen delež bolnikov z razsejano boleznijo prejme ustrezno citostatsko zdravljenje.

Zaskrbljujoče je tudi, da je preživetje slabo predvsem pri mlajših od 50 let in pri starih 75 let in več. Tema dvema populacijama bo potrebno v prihodnosti posvetiti še večjo pozornost.

VIRI
Literature

Bizjak-Ogrinc U. Preživetje bolnikov z invazivnim rakom sečnega mehurja glede na stadij in način zdravljenja v Sloveniji v obdobju 1987–1997 v treh izbranih letih. [magistrska naloga]. Ljubljana: Univerza v Ljubljani; 2007.

Čufer T. Combined modality treatment with organ preservation in invasive bladder cancer = Kombinirano zdravljenje raka sečnega mehurja z možnostjo ohranitve organa. Radiol Oncol 2000; 34: 21–25.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18: 581–92.

Matos T, Čufer T, Červek J, Borštnar S, Kragelj B, Žumer-Pregelj M. Prognostic factors in invasive bladder carcinoma treated by combined modality protocol (organ-sparing approach). Int J Radiat Oncol Biol Phys. 2000; 46: 403–9.

cytostatics has not yielded any convincing results. This treatment can be slightly beneficial for patients with local lymph node involvement; however, no major improvement in the survival can be expected from the use of currently available adjuvant chemotherapy without radical local therapy. Nevertheless, it is necessary to improve the survival of patients with disseminated bladder cancer by means of systemic treatment, since this type of cancer can be effectively treated with cytostatics. In Slovenia, the proportion of patients with disseminated disease receiving chemotherapy is still too small.

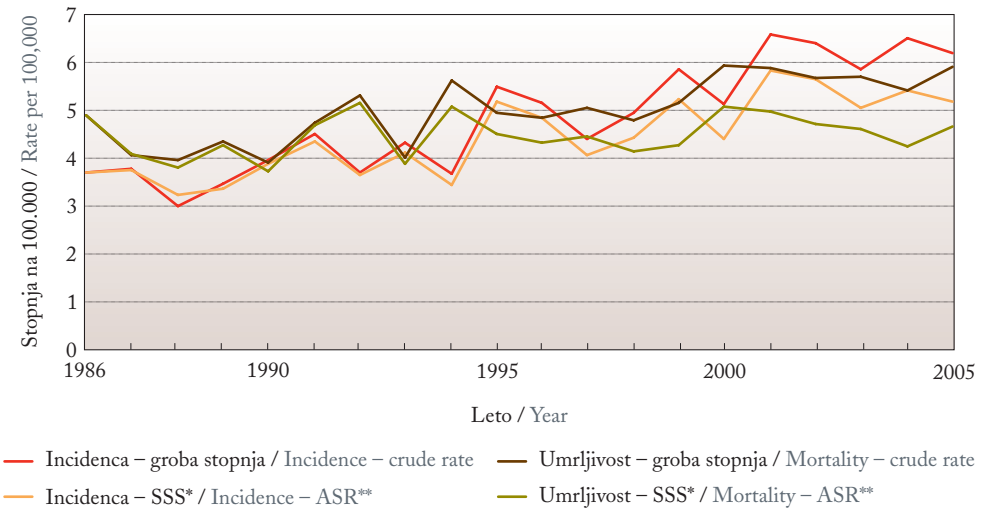
Furthermore, the fact that the survival is poor particularly in patients under 50 and over 75 years of age also raises concern. Therefore, more attention should be paid to these two population groups in the future.

MOŽGANI

MKB 10: C71

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom možganov zbolelo 1636 ljudi, od tega 878 moških in 758 žensk. Kot je razvidno s Slike 1, se incidenčne in umrljivostne stopnje večajo. Groba incidenčna stopnja se je večala za povprečno 3,7 % letno, starostno standardizirana pa za nekoliko manj, za 2,6 % letno. Groba in starostno standardizirana umrljivostna stopnja kažeta bolj počasen trend, čeprav so ti podatki zaradi težav pri šifriranju vzrokov smrti manj zanesljivi; večkrat je namreč iz prijav vzroka smrti nemogoče razlikovati med malignimi tumorji možganov in tumorji negotovega in nejasnega značaja, ki morfološko ne sodijo v skupino invazivnih rakov.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka možganov, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of brain cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1426 primerov; 69 primerov (4,2 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 141 mlajših od 20 let pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih.

V obdobju 2001–2005 je bilo mikroskopsko potrjenih 83 % primerov. Delež mikroskopsko potrjenih primerov se ves čas opazovanja zmanjšuje; v obdobju 1991–1995 je bil 88 %. Med mikroskopsko potrjenimi primeri je bilo v obdobju 2001–2005 82 % gliomov, pri 11 % histološka diagnoza ni bila opredeljena, redko pa so se pojavljali germinomi in sarkomi. Med gliomi je bilo približno

Tabela 1: *Število bolnikov z rakom možganov po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of brain cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	196	34,2	62,2	3,6	189	29,6	64,0	6,3
1996–2000	247	36,0	56,7	7,3	208	23,6	68,8	7,7
2001–2005	315	26,0	64,8	9,2	271	24,7	59,8	15,5

BRAIN

MKB 10: C71

EPIDEMIOLOGY

In the period 1991–2005, a total of 1636 persons were diagnosed with brain cancer, of these 878 males and 758 females. As evident from Figure 1, the incidence and mortality rates have been increasing. The crude mortality rate has been increasing by 3.7% and the age-standardized by 2.6% annually on average. The upward trend of crude and age-standardized mortality rates has been slower. However, these data are less reliable due to difficulties in coding the causes of death, as it is often not possible to distinguish between malignant brain tumors and tumors of uncertain origin, which morphologically do not belong into the group of invasive cancers, solely on the basis of death certificates.

The survival analysis included 1426 cases; 69 cases (4.2%) diagnosed only after death, were not considered in the analysis, 141 patients under 20 years of age are presented in the chapter on the survival of children and adolescents.

In the period 2001–2005, 83% of cancers were microscopically verified. The proportion of microscopically confirmed cases has been decreasing throughout the observation time; in the period 1991–1995 it was 88%. Among the microscopically confirmed cases in the period 2001–2005, 82% were gliomas while in 11% histological type was not precisely defined; germinomas and sarcomas were rare. Approximately two thirds of gliomas were classified as glioblastoma, 14% as astrocytoma and 10% as oligodendroglioma. Other types of glioma were rare.

Approximately 60% of patients were diagnosed at an age between 50 to 74 years, and a fourth at an age between 20 to 49 years. The proportion of those aged 75 years or older is the lowest, however it is increasing with time in both genders (Table 1). Brain cancer is generally detected at a localized stage (Table 2).

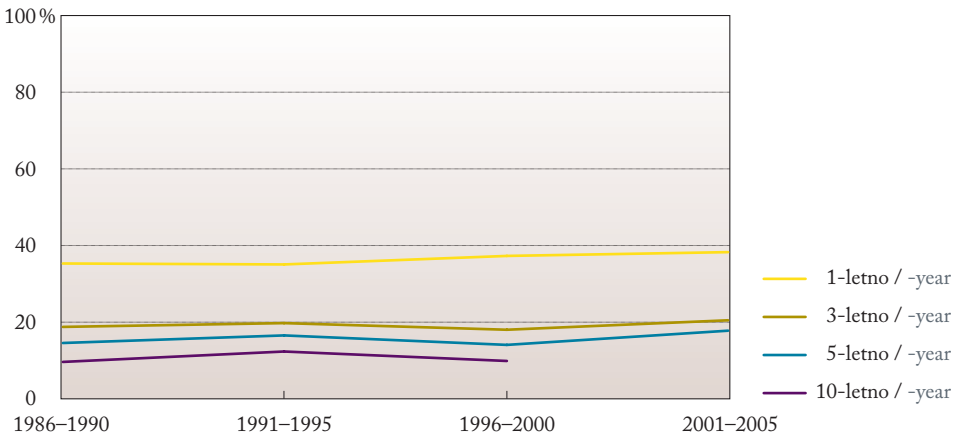
In the period 2001–2005, 21% of patients did not receive specific treatment. The proportion of untreated patients was increasing throughout the observation period; among those diagnosed in the period 1991–1995 there were 18% of patients without specific treatment. Among the patients receiving specific treatment in the period 2001–2005, 36% were treated by surgery alone, 30% received radio- and chemotherapy in addition to surgery, while 28% were only irradiated. Other combinations of treatment were used in less than 5% of the patients. In comparison with the previous periods, in the last one more patients received chemotherapy in addition to surgery and radiotherapy as part of their primary treatment.

In the period 2001–2005, the majority of patients (80%) started their treatment in the UMC Ljubljana, 18% in the UMC Maribor and 3% at the IO Ljubljana.

The relative survival rate of patients with brain cancer has not been changing significantly: in 15 years, the 5-year relative survival increased only by 1% (Figure 2); the survival in females is slightly better than in males (Table 3). The relevance of age at diagnosis is shown in Figure 3. The 5-year relative survival of patients diagnosed before 50 years of age is 45%, patients diagnosed

Tabela 2: *Število bolnikov z rakom možganov po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*
Table 2: *Number of brain cancer patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	196	99,5	0,5	0,0	0,0	189	97,4	2,6	0,0	0,0
1996–2000	247	95,5	2,4	0,4	1,6	208	99,0	1,0	0,0	0,0
2001–2005	315	99,4	0,3	0,3	0,0	271	97,0	2,6	0,4	0,0



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom možganov po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of brain cancer patients by period of diagnosis.*

dve tretjini tumorjev opredeljenih kot glioblastom, 14 % je bilo astrocitomov, 10 % pa oligodendrogliomov. Ostali gliomi so bili redki.

Približno 60 % zbolelih je bilo ob diagnozi starih 50–74 let, četrtina pa 20–49 let. Delež starih 75 let in več je najmanjši, vendar se pri obeh spolih s časom veča (Tabela 1).

Rak možganov je bolezen, ki je praviloma odkrita v omejenem stadiju (Tabela 2).

V obdobju 2001–2005 ni bilo specifično zdravljenih 21 % bolnikov. Delež nezdravljenih bolnikov se je skozi opazovano obdobje nekoliko povečal; med bolniki, zbolelimi v obdobju 1991–1995, jih 18 % ni bilo specifično zdravljenih. Med specifično zdravljenimi je bilo v letih 2001–2005 36 % bolnikov samo operiranih, pri 30 % je bila operaciji dodana še radio- in kemoterapija, 28 %

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom možganov po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of brain cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	36,7 (30,6–44,1)	18,4 (13,7–24,7)	13,3 (9,3–19,0)	32,3 (26,3–39,7)	19,0 (14,2–25,6)	16,9 (12,3–23,2)
1996–2000	37,2 (31,7–43,8)	17,4 (13,3–22,8)	13,0 (9,4–17,9)	35,6 (29,6–42,7)	16,3 (12,0–22,2)	12,5 (8,7–17,9)
2001–2005	37,1 (32,2–42,9)	18,7 (14,8–23,5)	14,0 (10,4–18,8)	37,6 (32,3–43,9)	19,7 (15,4–25,1)	18,2 (14,0–23,5)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	37,5 (29,9–45,1)	19,6 (12,9–26,3)	14,8 (8,4–21,2)	32,7 (25,2–40,2)	19,8 (13,0–26,6)	18,1 (11,4–24,8)
1996–2000	38,1 (31,4–44,8)	18,7 (12,9–24,6)	14,7 (9,1–20,4)	36,0 (28,8–43,3)	17,0 (10,9–23,2)	13,5 (7,6–19,3)
2001–2005	38,1 (32,2–44,0)	20,2 (14,9–25,4)	16,0 (10,5–21,5)	38,3 (31,9–44,6)	20,7 (15,0–26,5)	20,0 (14,1–25,9)

at an age between 50–74 years have 9% 5-year relative survival while those aged 75 years or older do not survive five years from diagnosis.

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 18% (Figure 2); patients surviving the first year may expect to survive five years in 44%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of brain cancer patients in Slovenia is below (statistically not significant) the European average (Figure 4).

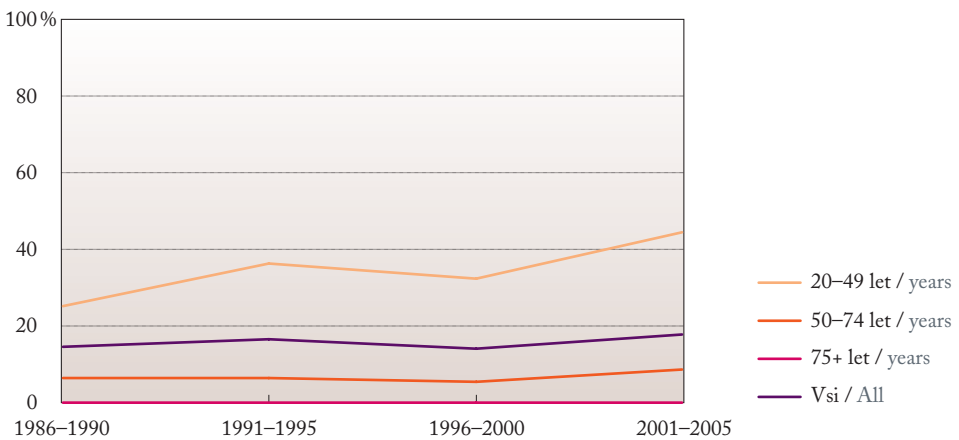
CLINICAL COMMENTARY

Uroš Smrdel

When reviewing tables and curves pertaining to patients with brain tumors, at a first glance, one cannot note any particular difference between the beginning and the end of the observation period. Most positive is an improved survival in the group of patients less than 50 years of age, observed after the year 2001. Improvement in survival in the last period, particularly after the inclusion of chemotherapy into treatment, has been reported by several authors. They also find the improvement to be the greatest in the group of younger patients.

However, considering still poor survival of patients with brain tumors, a few facts need to be pointed out. Besides on age and method of treatment, the survival depends on the histological type and grade of tumor differentiation (grade, G). Thus, for example, the median survival of patients with G2 astrocytoma is 7 years while the survival of patients with glioblastoma is only 16 months; the survival of patients with oligodendrogliomas is higher than in those with astrocytoma. In the group of primary brain tumors, glioblastoma is the most frequent, thus most significantly influencing the survival. After the year 2004, however, major changes occurred in the treatment of glioblastoma.

Considering the treatment of our patients, we need to call attention to the large proportion of surgical resection. While elsewhere biopsy is the most common method of tumor verification, in Slovenia the most frequent approach to diagnosis is still maximum surgical resection. Likewise, patients with progressive disease are relatively frequently subjected to reoperations, which are used less frequently in other countries. Throughout the observation period, radiotherapy remains indispensable in gliomas of high-grade malignancy. In recent period we note a moderate increase in the cumulative dose, mainly on the account of more radical treatment



Slika 3: *Petletno relativno preživetje bolnikov z rakom možganov po starosti in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of brain cancer patients by age and period of diagnosis.*

pa so samo obsevali. Ostale kombinacije zdravljenja so uporabili pri manj kot 5 % bolnikov. V zadnjih letih je v primerjavi s prejšnjimi obdobji več bolnikov v okviru prvega zdravljenja poleg operacije in radioterapije prejelo še kemoterapijo.

Večina bolnikov (80 %) je v obdobju 2001–2005 zdravljenje pričela v UKC Ljubljana, 18 % v UKC Maribor in 3 % na OI Ljubljana.

Relativno preživetje bolnikov z rakom možganov se bistveno ne spreminja; v 15 letih se je petletno relativno preživetje povečalo le za 1 % (Slika 2); nekoliko dlje preživijo ženske (Tabela 3). Kako pomembna je starost ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov, zbolelih pred 50. letom, je 45 %, bolniki, zboleli v starosti 50–74 let, imajo petletno relativno preživetje 9 %, medtem ko stari 75 let in več ne preživijo petih let po diagnozi.

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 18 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 44-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom možganov statistično neznačilno manjše od evropskega povprečja (Slika 4).

KLINIČNI KOMENTAR

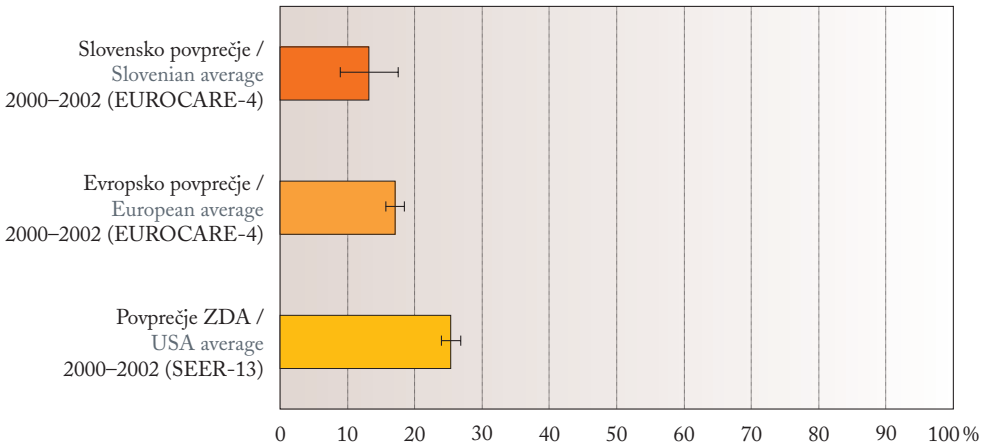
Uroš Smrdel

Ko pregledujem tabele in krivulje bolnikov z možganskimi tumorji, na prvi pogled ne vidim pomembne razlike med začetkom in koncem opazovanega obdobja. Najbolj pozitivno je izboljšanje preživetja skupine bolnikov, mlajših od 50 let, po letu 2001. Izboljšanje preživetja v zadnjem obdobju, predvsem po vključitvi kemoterapije v zdravljenje, opisujejo številni avtorji. Tudi ti ugotavljajo, da je izboljšanje največje v skupini mlajših bolnikov.

Glede na še vedno slabo preživetje bolnikov s tumorji možganov, pa je potrebno poudariti še nekaj dejstev. Preživetje se pri bolnikih poleg starosti in načina zdravljenja razlikuje tudi glede na histološko vrsto in stopnjo diferenciacije (gradus, G) tumorja. Tako je npr. srednje preživetje bolnikov z astrocitomom G2 7 let, bolnikov z glioblastomom pa le 16 mesecev; preživetje bolnikov z oligodendroglialnimi tumorji je večje kot tistih z astrocitomi. V skupini primarnih možganskih tumorjev je glioblastom najpogostejši in tudi najpomembneje vpliva na preživetje. Ravno pri glioblastomu pa je prišlo po letu 2004 do največjih sprememb v načinu zdravljenja.

Če pogledamo način zdravljenja naših bolnikov, moramo najprej opozoriti na velik delež kirurških resekcij. Medtem ko je drugod zelo pogost način verifikacije biopsija, pa je v Sloveniji maksimalna kirurška odstranitev še vedno najpogostejši način, ki privede do diagnoze. Ravno tako so pri bolnikih, pri katerih pride do napredovanja bolezni, razmeroma pogoste ponovne operacije, ki so drugod redkejše. Radioterapija ostaja v celotnem obdobju stalnica pri visoko malignih gliomih. V tem času sicer opažamo zmerno povečanje skupnega odmerka, predvsem na račun bolj radikalnih zdravljenj, pomembnejša pa je sprememba načina obsevanja z bolj natančno določitvijo obsevalnih polj. Odprto pa ostaja vprašanje zgodnje ali odložene radioterapije pri nizko malignih gliomih. Kemoterapija se je v večji meri pridružila zdravljenju po letu 2001 in to predvsem v obliki dodatnega zdravljenja; pred letom 2001 se je kemoterapija pri glioblastomih uporabljala predvsem paliativno ob napredovanju tumorja. S hkratno kemo- in radioterapijo smo pričeli zdraviti bolnike leta 2004; do konca leta 2005 je bilo zdravljenih okrog 30 bolnikov, kar predstavlja v skupnem številu le 2 % in v obdobju 2001 do 2005 5 % bolnikov. Že prej smo začeli uporabljati kemoterapijo pri anaplastičnih oligodendrogliomih, vendar ti predstavljajo le manjši del vseh primarnih možganskih tumorjev. Tako kemoterapija pri tej skupini ni pomembno vplivala na preživetje. Pri razmeroma majhnem deležu bolnikov je bilo zdravljenje le podporno; večina teh bolnikov se je zdravila tudi operativno.

Za konec naj še dodam, da se pri bolnikih z možganskimi tumorji terapevtske možnosti širijo, čeprav je populacijsko preživetje v Sloveniji še vedno majhno. Terapevtski nihilizem, ki je



Slika 4: *Petletno relativno preživetje bolnikov z rakom možganov (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 4: *5-year relative survival of brain cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

schedules, however, the most important change has occurred in the irradiation technique using more accurate determination of irradiated fields. However, the issue of early or postponed radiotherapy in gliomas of low-grade malignancy remains unresolved. Chemotherapy started to be used in the treatment more regularly after the year 2001, particularly in the form of adjuvant therapy; before 2001, chemotherapy was used only with palliative intent in advanced glioblastomas. Simultaneous chemo- and radiotherapy was introduced into the treatment in 2004; by the end of 2005, there were approximately 30 patients treated in this way, which represents only 2% of the total and in the period 2001–2005, 5% of patients. Chemotherapy for the treatment of anaplastic oligodendrogliomas started to be used even earlier, however the latter type represents only a minor proportion of all primary brain tumors. Thus, chemotherapy in this group has not significantly influenced the survival. A relatively small proportion of patients received only supportive therapy; the majority of these patients also underwent surgery.

Finally, let me add that in patients with brain tumors therapeutic options are expanding, although the population-based survival in Slovenia is still low. The therapeutic nihilism that used to prevail as regards the treatment of brain tumors has now been replaced by the search of prognostic factors predicting a better treatment outcome. Further development, particularly in the direction of searching for molecular targets and treatment optimization, would probably contribute to further improvement of survival, at least in patients with a good performance status.

prej prevladoval pri zdravljenju možganskih tumorjev, je sedaj zamenjalo iskanje napovednih dejavnikov, ki obetajo večjo uspešnost zdravljenja. Z dodatnim razvojem, predvsem v smeri iskanja molekularnih tarč in optimiziranja zdravljenja, pa bi verjetno, vsaj pri bolnikih v dobrem stanju zmogljivosti, lahko uspeli še dodatno izboljšati preživetje.

VIRI
Literature

Barbagallo GM, Jenkinson MD, Brodbelt AR. 'Recurrent' glioblastoma multiforme, when should we reoperate? Br J Neurosurg 2008; 22: 452–5.

Brandes AA, Tosoni A, Franceschi E, Reni M, Gatta G, Vecht C. Glioblastoma in adults. Crit Rev Oncol Hematol 2008; 67: 139–52.

Brandes AA, Tosoni A, Vastola F, Pasetto LM, Coria B, Danieli D, et al. Efficacy and feasibility of standard procarbazine, lomustine, and vincristine chemotherapy in anaplastic oligodendroglioma and oligoastrocytoma recurrent after radiotherapy. A Phase II study. Cancer 2004; 101: 2079–85.

Newton HB. Glioblastoma multiforme. Curr Treat Options Neurol 2008; 10: 285–94.

Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 2008; 62: 564–76.

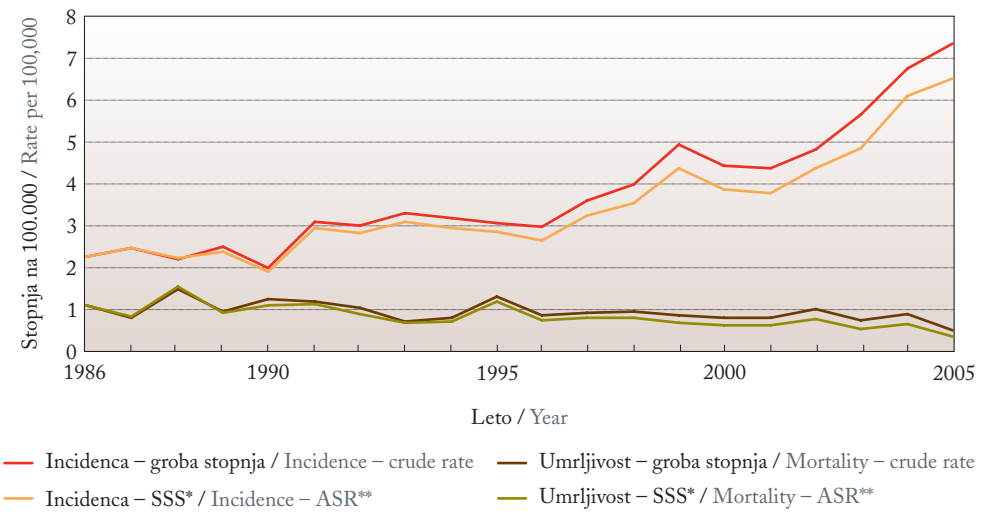
Stupp R, Mason WP, van den Bent MJ, Mason WP, Weller M, Mirimanoff RO, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987–96.

ŠČITNICA

MKB 10: C73

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom ščitnice zbolelo 1316 ljudi, od tega 312 moških in 1004 ženske. Kot je razvidno s Slike 1, se časovni trendi incidenčnih in umrljivostnih stopenj razlikujejo. Groba incidenčna stopnja je bila med letoma 1991 in 1995 stabilna, od 1996 naprej pa se povečuje za 9,0 % letno. Umrljivostna stopnja se pri bolnikih z rakom ščitnice zmanjšuje za povprečno 2,6 % letno. Ker so bolniki z rakom ščitnice ob diagnozi redko starejši od 75 let (Tabela 1), sta obe starostno standardizirani meri praktično enaki grobim stopnjam.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja raka ščitnice, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of thyroid cancer, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1241 primerov; 27 primerov (2,2 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 48 mlajših od 20 let pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih.

V obdobju 2001–2005 so bili mikroskopsko potrjeni vsi primeri, le trije niso imeli mikroskopske potrditve v desetletju 1991–2000. V celotnem obdobju je imelo 67 % bolnikov papilarni karcinom, 10 % folikularnega, po 7 % anaplastičnega in karcinom Hürtlovih celic ter 5 % medularnega. Drugih opredeljenih histoloških vrst je bilo manj kot 1 %. Delež papilarnega karcinoma

Tabela 1: *Število bolnikov z rakom ščitnice po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of thyroid cancer patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	70	45,7	51,4	2,9	235	44,7	41,7	13,6
1996–2000	95	35,8	54,7	9,5	284	44,7	43,7	11,6
2001–2005	122	38,5	54,9	6,6	435	45,3	45,3	9,4

THYROID

ICD 10: C73

EPIDEMIOLOGY

In the period 1991–2005, a total of 1316 persons were diagnosed with cancer of the thyroid, of these 312 males and 1004 females. As evident from Figure 1, the trends in incidence and mortality rates differ from each other. Thus in the years 1991–1995 crude incidence rate was stable, while from 1996 on it has been increasing by 9.0% annually on average. Crude mortality rate was decreasing by 2.6% annually. Since thyroid cancer patients are hardly ever older than 75 years at diagnosis (Table 1), both age-standardized rates are practically the same as crude rates.

The survival analysis included 1241 cases; 27 patients (2.2%) diagnosed only after death, were not considered in the analysis, 48 patients under 20 years of age are presented in the chapter on the survival of children and adolescents.

In the period 2001–2005, all the cases were microscopically verified, while in the decade from 1991–2000 only three cases lacked microscopic confirmation. In the total observation period, papillary carcinoma was found in 67% of patients, follicular in 10%, anaplastic and Hürthle-cell carcinoma in 7% each, and medullary carcinoma in 5% of patients. Other identified histological types represented less than 1% of cases. The proportion of papillary carcinoma has been increasing all the time; in the last period this histological type represented already 75% of all thyroid cancers. Although in different periods the number of patients diagnosed with follicular and anaplastic carcinomas has not changed significantly, in the last period their proportion among all thyroid cancers was smaller due to a higher total number of these cancers.

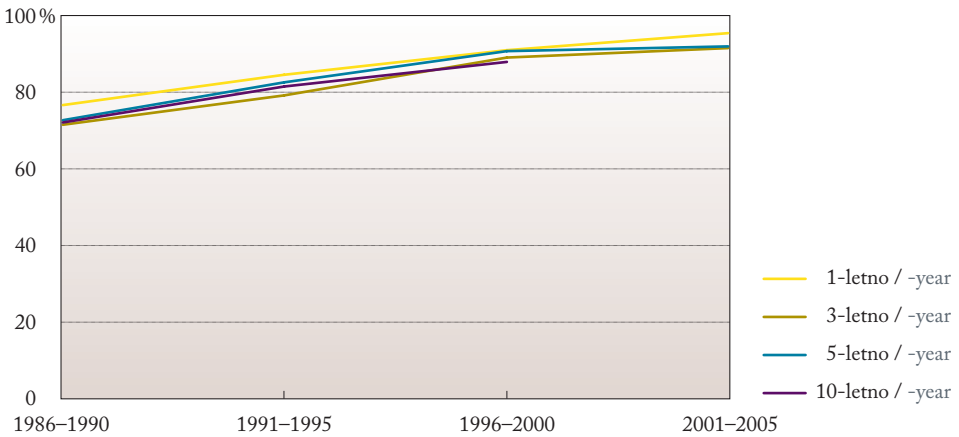
More than half of male patients are at an age between 50 and 74 years, with few males developing the disease aged 75 years or older. In females, the proportion of those aged between 50 and 74 years is roughly the same as the proportion of those aged between 20 and 50 years. Approximately 10% of patients are aged 75 years or older (Table 1). The proportions in individual age groups did not change significantly with time.

The proportion of patients with localized stage has been increasing throughout the observation period. In the last period 59% of male and 69% of female patients were diagnosed with localized thyroid cancer (Table 2). The proportions of patients with disseminated, regional and undefined stages have decreased on the account of a higher proportion of those with localized disease; in the last period there were less than 1% of patients with undefined stage.

In the years 2001–2005, 2% of patients did not receive specific treatment. The proportion of untreated patients was decreasing throughout the duration of analysis; among those diagnosed in the period 1991–1995 there were 9% of patients without specific treatment. In the period 2001–2005, 92% of patients with specific treatment underwent surgery. Two thirds of surgically treated patients also received radioiodine and hormonal treatment while 23% of them had only postoperative hormonal therapy.

Tabela 2: *Število bolnikov z rakom ščitnice po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*
Table 2: *Number of thyroid cancer patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	70	38,6	45,7	12,9	2,9	235	56,2	30,6	11,5	1,7
1996–2000	95	50,5	36,8	11,6	1,1	284	60,6	29,9	8,1	1,4
2001–2005	122	59,0	32,0	8,2	0,8	435	69,2	21,8	8,0	0,9



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom ščitnice po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of thyroid cancer patients by period of diagnosis.*

se ves čas povečuje. V zadnjem obdobju je ta histološka vrsta predstavljala že 75 % vseh rakov ščitnice. Čeprav se število zbolelih s folikularnim in anaplastičnim karcinomom v različnih obdobjih ni bistveno spreminjalo, pa je zaradi večjega skupnega števila njihov delež med vsemi raki ščitnice v zadnjem obdobju manjši.

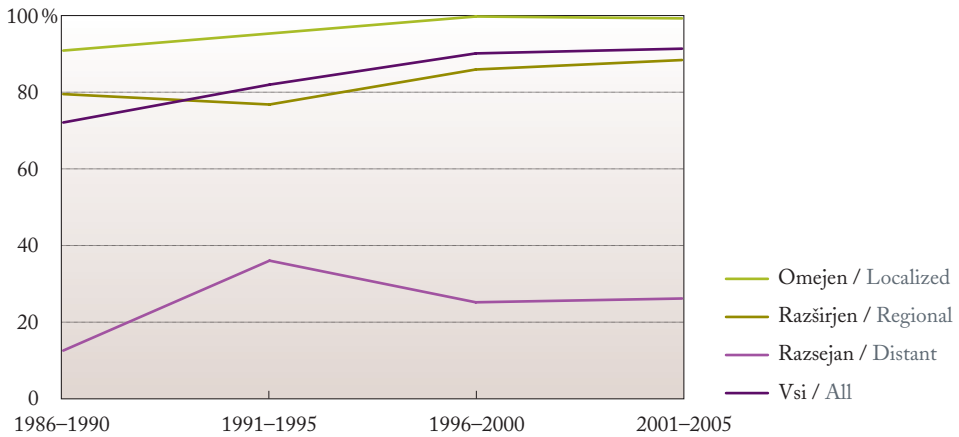
Več kot polovica zbolelih moških je stara med 50 in 74 let, redki moški zbolijo po 75. letu. Pri ženskah je delež starih od 50 do 74 let približno enak deležu starih 20–49 let. Približno 10 % bolnic je starih 75 let in več (Tabela 1). Deleži v posameznih starostnih skupinah se s časom niso bistveno spreminjali. Ves čas opazovanja pa se je večal delež bolnikov z omejenim stadijem bolezni. V zadnjem obdobju je bilo z omejenim rakom ščitnice odkritih 59 % moških in 69 % žensk (Tabela 2). Na račun večjega deleža raka v omejenem stadiju so se zmanjšali deleži

Tabela 3: *Opazovano in relativno preživetje bolnikov z rakom ščitnice po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of thyroid cancer patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	81,4 (72,8–91,1)	70,0 (60,0–81,6)	70,0 (60,0–81,6)	82,6 (77,8–87,6)	76,6 (71,4–82,2)	75,3 (70,0–81,0)
1996–2000	84,2 (77,2–91,9)	77,9 (70,0–86,7)	75,8 (67,6–84,9)	90,1 (86,7–93,7)	87,0 (83,1–91,0)	84,2 (80,0–88,5)
2001–2005	92,6 (88,1–97,4)	85,7 (79,7–92,3)	80,3 (72,9–88,6)	93,8 (91,6–96,1)	89,3 (86,4–92,3)	86,0 (82,4–89,7)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	83,0 (73,2–92,8)	74,3 (62,0–86,6)	77,0 (64,2–89,7)	84,2 (79,1–89,3)	81,4 (75,4–87,3)	82,7 (76,4–89,0)
1996–2000	86,6 (78,7–94,5)	85,0 (75,4–94,6)	86,3 (75,9–96,7)	91,4 (87,8–95,0)	91,0 (86,8–95,2)	90,2 (85,5–94,9)
2001–2005	94,3 (89,5–99,2)	91,4 (84,4–98,3)	90,2 (80,9–99,5)	94,7 (92,4–97,0)	92,4 (89,3–95,5)	91,5 (87,6–95,5)



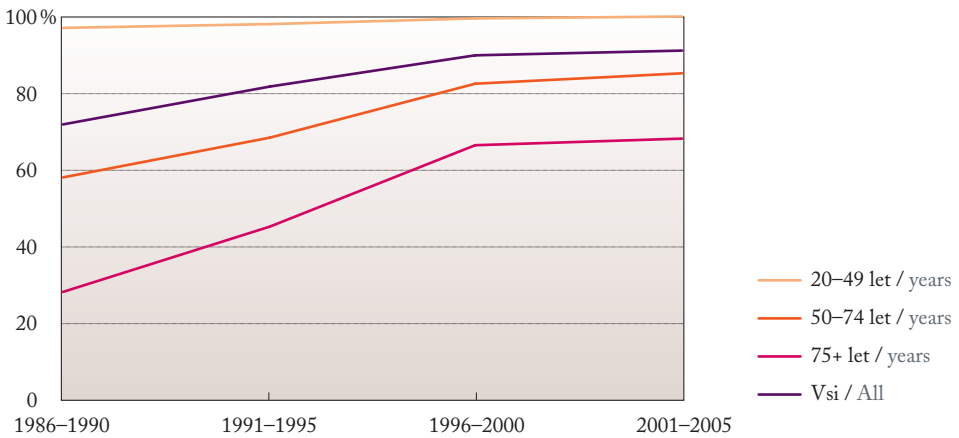
Slika 3: *Petletno relativno preživetje bolnikov z rakom ščitnice po stadiju in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of thyroid cancer patients by stage and period of diagnosis.*

In the period 2001–2005, 73% started their treatment at the IO Ljubljana, 17% in the UMC Ljubljana and 7% in the UMC Maribor. Individual patients started their treatment in GH of Izola, Slovenj Gradec and Jesenice. Practically all patients (98%), irrespective of their initial treatment hospital, were in the course of their primary treatment referred to the IO Ljubljana.

The relative survival rate of patients with thyroid cancer has been gradually increasing: in 15 years, the 5-year relative survival increased by 9% (Figure 2), in males slightly more than in females (Table 3). The relevance of stage at diagnosis is shown in Figure 3. In the last two periods, 5-year relative survival of patients with localized stage has reached 100%. The survival of patients with regional disease has been increasing throughout the observation period as well, the 5-year relative survival in those diagnosed between the years 2001–2005 being 88%. Age is a prognostic factor as well, since in the last period all the patients under 50 years of age survived five years, while 68% of those aged 75 years or older survived five years (Figure 4).

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 91% (Figure 2). Patients surviving the first year may expect to survive five years in 96%.



Slika 4: *Petletno relativno preživetje bolnikov z rakom ščitnice po starosti in obdobju postavitve diagnoze.*

Figure 4: *5-year relative survival of thyroid cancer patients by age and period of diagnosis.*

bolnikov z razsejanim in razširjenim stadijem ter bolnikov brez določenega stadija; zadnjih je bilo v obdobju 2001–2005 manj kot 1 %.

V obdobju 2001–2005 ni bilo specifično zdravljenih 2 % bolnikov. Delež nezdravljenih bolnikov se je v celotnem obdobju analize zmanjševal; med bolniki, zbolelimi v obdobju 1991–1995, jih je bilo brez specifičnega zdravljenja 9 %. Med specifično zdravljenimi je bilo v letih 2001–2005 operiranih 92 % bolnikov. Med njimi sta bili dve tretjini bolnikov zdravljeni še z radiojodom in s hormoni, 23 % jih je po operaciji prejelo le hormonska zdravila.

V obdobju 2001–2005 je 73 % bolnikov pričelo zdravljenje na OI Ljubljana, 17 % v UKC Ljubljana ter 7 % v UKC Maribor. Posamezne bolnike so pričeli zdraviti še v SB Izola, SB Slovenj Gradec in SB Jesenice. Skoraj vsi bolniki (98 %) so bili, ne glede na bolnišnico pričetka zdravljenja, v okviru prvega zdravljenja obravnavani tudi na OI Ljubljana.

Relativno preživetje bolnikov z rakom ščitnice se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 9 % (Slika 2), pri moških nekaj več kot pri ženskah (Tabela 3). Kako pomemben je stadij ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov z omejenim stadijem je v zadnjih dveh obdobjih 100 %. Ves čas se povečuje tudi preživetje bolnikov z razširjenim stadijem; zboleli v letih 2001–2005 so imeli petletno relativno preživetje 88 %. Napovedni dejavnik je tudi starost, saj so v zadnjem obdobju vsi mlajši od 50 let preživeli pet let, pri starih 75 let in več pa je petletno relativno preživetje 68 % (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 91 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 96-odstotno petletno relativno preživetje.

Rak ščitnice je ena redkih rakavih bolezni, pri kateri je petletno relativno preživetje slovenskih bolnikov, zbolelih v obdobju 2000–2002, statistično značilno večje od povprečja evropskih držav, zajetih v raziskavo EUROCARE-4 (Slika 5).

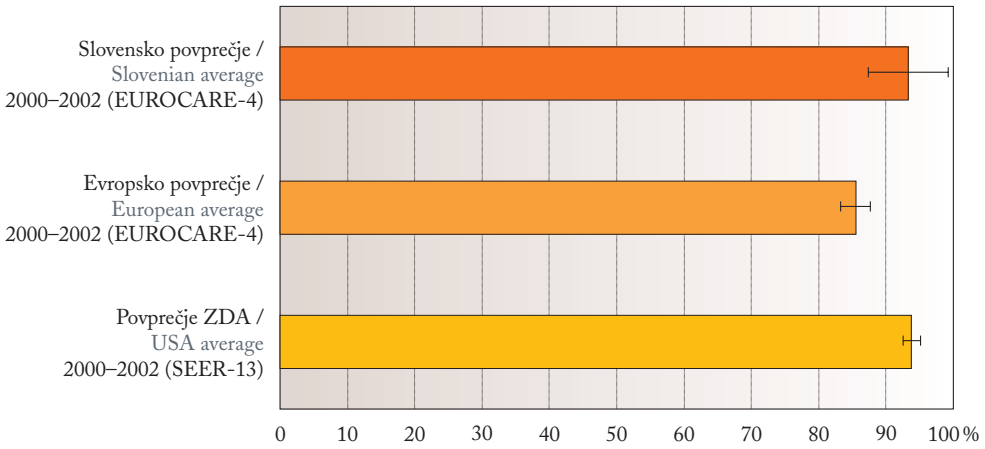
KLINIČNI KOMENTAR

Nikola Bešić

Tako kot povsod po svetu tudi v Sloveniji incidenca raka ščitnice raste. Najverjetneje je vzrok za to boljša in zgodnejša diagnostika, saj se veča število ultrazvočnih preiskav ščitnice in ultrazvočno vodenih tankoigelnih aspiracijskih biopsij. Ta omogoča odkrivanje raka, še preden je lahko klinično prepoznan. Zato se je zelo povečala incidenca papilarnega mikrokarcinoma ščitnice. Tudi naši bolniki s papilarnim mikrokarcinomom imajo zelo dobro napoved izida bolezni; petletno preživetje teh bolnikov je bilo 99 %, desetletno pa 98 %. Sedaj bolnike z rakom ščitnice odkrijemo v zgodnejših stadijih (Tabela 2). Na to kaže tudi manjša povprečna velikost tumorja. Med našimi bolniki s citološko postavljenim sumom za folikularnega raka je bil v obdobju od 1988–1993 povprečni premer tumorja 4,2 cm, v obdobju od 1994–1999 3,7 cm in v obdobju od 2000–2004 samo še 3,3 cm.

Razen zgodnejšega diagnosticiranja raka ščitnice je izboljšanje napovedi izida za bolnike, zdravljene v obdobju 1996–2005, v primerjavi s prejšnjim obdobjem najverjetneje posledica dodatnega jodiranja kuhinjske soli v Sloveniji. V letih 1953–1998 je bilo soli dodano 10 mg kalijevega jodida na kilogram soli, od leta 1998 pa je kilogram soli jodiran s 25 mg kalijevega jodida. Dodatno jodiranje soli je spremenilo delež podtipov raka ščitnice. Več je takšnih z ugodnejšo napovedjo izida.

Na dobro preživetje bolnikov zanesljivo vpliva tudi učinkovito zdravljenje. Razveseljivo je, da skoraj vse bolnike z rakom ščitnice operirajo le na treh oddelkih samo kirurgi z izkušnjami s kirurgijo ščitnice. Zato se pri večini bolnikov opravi optimalni poseg – totalna ali skoraj totalna tiroidektomija. Vse nadaljnje zdravljenje in sledenje bolnikov izvajamo na OI Ljubljana, kjer zdravljenje poteka multidisciplinarno. Seveda sledimo vsem novostim pri diagnostiki in zdravljenju. Že od leta 2001 uporabljamo rhTSH pri bolnikih, ki zaradi slabega splošnega stanja ali spremljajočih bolezni ne bi mogli dobiti radiojoda ob hormonskem premoru. Zadnjih nekaj



Slika 5: *Petletno relativno preživetje bolnikov z rakom ščitnice (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of thyroid cancer patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

Thyroid cancer is one of the few cancer diseases in which 5-year relative survival of patients in Slovenia is statistically significantly above the average in other European countries included in EUROCARE-4 study for patients diagnosed in 2000–2002 study (Figure 5).

CLINICAL COMMENTARY

Nikola Bešić

As elsewhere in the world, in Slovenia too the incidence of thyroid cancer is increasing. Most probably, the reason for that is better and earlier diagnosis, as the number of ultrasonographies of the thyroid and US-guided fine-needle aspiration biopsies has been increasing, thus facilitating cancer detection before the disease becomes clinically evident. Therefore, a marked increase has been observed in the incidence of papillary microcellular carcinoma of the thyroid. Our patients with papillary microcarcinoma also have a very favorable prognosis, their 5-year survival being 99% and 10-year survival 98%. Nowadays, thyroid cancer patients are diagnosed at an earlier stage (Table 2), which is evident from their smaller average tumor size. In the period 1988–1993, an average tumor diameter in patients with cytologically suspected follicular cancer was 4.2 cm, in the period 1994–1999 3.7 cm, whereas in the period 200–2004 it was only 3.3 cm.

Apart from earlier diagnosis of thyroid cancer, better prognosis of patients treated in the period 1996–2005 – as compared to the preceding period – is most probably attributable to the iodizing of table salt in Slovenia. In the years 1953–1998, 10 mg of potassium iodide were added per one kilogram of salt, whereas from 1998 on the iodization level has been 25 mg of potassium iodide per kg of salt. Additional iodization of table salt has brought about a change in the proportion of thyroid cancer subtypes, those with a favorable diagnosis being more frequent.

Better survival of patients is certainly influenced by an effective treatment. It is encouraging that almost all thyroid cancer patients are operated on exclusively in three specialized departments by surgeons-experts in thyroid surgery, and therefore most patients undergo an optimal procedure, i. e. total or near-total thyroidectomy. Any further treatment and patient follow up is performed at the IO Ljubljana, using multidisciplinary team approach. Of course, all advances

let uporabljamo rhTSH tudi za ablacijo ostanka ščitnice z radiojodom in za testiranje kopičenja radiojoda, kar bolnikom zelo zmanjša težave, ki so jih imeli zaradi hipotiroze. Zaradi večjega deleža bolnikov s prognostično ugodnim papilarnim mikrokarcinomom se je zvečal delež bolnikov, ki jih ni potrebno zdraviti z radiojodom. Ti bolniki morajo namesto zavornega zdravljenja s ščitničnimi hormoni jemati hormone le v nadomestnih odmerkih.

VIRI
Literature

Bešić N, Žgajnar J, Hočevar M, Frković-Grazio S. Is patient's age a prognostic factor for follicular thyroid carcinoma in the TNM classification system? Thyroid 2005; 15: 439–48.

Bešić N, Sešek M, Perič B, Žgajnar J, Hočevar M. Predictive factors of carcinoma in 327 patients with follicular neoplasm of the thyroid. Med Sci Monitor 2008; 14: CR 459–67.

Bešić N. Zavorno in nadomestno zdravljenje s ščitničnimi hormoni. Onkologija 2008; 12: 33–4.

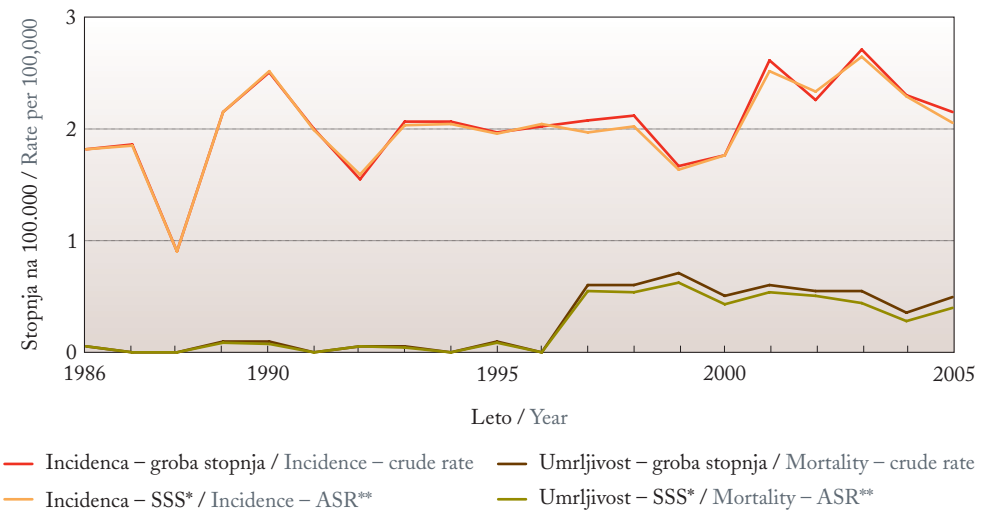
in diagnosis and treatment are considered, and thus ever since 2001 recombinant human TSH has been used in patients in whom the use of radio-iodine during hormonal pause is not possible due to their poor general condition or concomitant diseases. In the last few years rhTSH has also been used for radioiodine ablation of residual thyroid tissue as well as for testing radioiodine uptake, which significantly alleviates hypothyroidosis-related difficulties. Due to a greater proportion of patients with prognostically favorable papillary microcarcinoma, the proportion of patients not requiring radioiodine treatment has been increased accordingly. Instead of suppressive therapy with thyroid hormones, these patients need to receive only supplementary doses of hormones.

HODGKINOV LIMFOM

MKB 10: C81

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za Hodgkinovim limfomom (HL) zbolelo 633 ljudi, od tega 333 moških in 300 žensk. Kot je razvidno s Slike 1, se je groba incidenčna stopnja povečevala od leta 1991 v povprečju za 1,8 % letno. Podatkov o umrljivosti do leta 1997 ni mogoče interpretirati, saj do tedaj HL kot vzroka smrti niso ustrezno šifrirali. Med letoma 1999 in 2005 se je groba umrljivostna stopnja zmanjševala povprečno za 2,9 % letno, starostno standardizirana pa za 4,3 %.



Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja Hodgkinovega limfoma, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of Hodgkin's lymphoma, Slovenia 1986–2005.*

V analizo preživetja je vključenih 509 primerov; 10 bolnikov (1,6 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 114 otrok in mladostnikov pa obravnavamo v poglavju o preživetju pri otrocih in mladostnikih. Vsi tumorji bolnikov, vključenih v analizo, so bili mikroskopsko potrjeni.

Približno dve tretjini bolnikov zbolita pred 50. letom, večina ostalih do 74. leta, manj kot 10 % bolnikov pa je ob postavitvi diagnoze starih 75 let ali več (Tabela 1). Razen povečanega deleža najstarejših žensk se deleži v posameznih starostnih skupinah s časom niso bistveno spreminjali. V vseh treh obdobjih je bila najmanjšemu deležu bolnikov diagnoza postavljena v začetnem

Tabela 1: *Število bolnikov s Hodgkinovim limfomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of Hodgkin's lymphoma patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	80	62,5	30,0	7,5	67	68,7	25,4	6,0
1996–2000	86	68,6	27,9	3,5	72	65,3	22,2	12,5
2001–2005	108	63,9	30,6	5,6	96	66,7	20,8	12,5

HODGKIN's LYMPHOMA

ICD 10: C81

EPIDEMIOLOGY

In the period 1991–2005, a total of 633 persons were diagnosed with Hodgkin's lymphoma (HL), of these 333 males and 300 females. As evident from Figure 1, the incidence rate has been increasing since 1991, by 1.8% annually on average. Mortality data till 1997 cannot be analyzed because until then HL as cause of death had not been coded appropriately. In the period between 1999 and 2005 the crude mortality rate in patients with HL was decreasing by 2.9% and age-standardized by 4.3% annually on average.

The survival analysis included 509 cases; 10 patients (1.6%) diagnosed only after death, were not considered in the analysis; 114 children and adolescents are presented in the chapter on the survival of children and adolescents.All tumors of the patients under analysis were microscopically confirmed.

Approximately two thirds of the patients were diagnosed before 50 years of age, most of the remaining ones up to the age of 74 years, while less than 10% of patients aged 75 years or older at diagnosis (Table 1). Except for the increased proportion of females in the oldest age group, the proportions in individual age groups did not change significantly with time.

In all three periods the smallest proportion of patients were diagnosed in the initial stage. In last years, the proportion of patients diagnosed in the second stage has increased significantly. The increase is more apparent in females and is a consequence of the decreasing proportion of patients with the disease diagnosed in the third and fourth stages (Table 2).

In the period 2001–2005, 7% of patients did not receive specific treatment. Nearly half of them were older than 80 years. The proportion of untreated patients has remained approximately the same throughout the period under analysis. Among the patients receiving specific treatment in the period 2001–2005, 55% were treated by chemotherapy and irradiation, 33% received only chemotherapy, while the rest were treated with other combinations of therapeutic modalities.

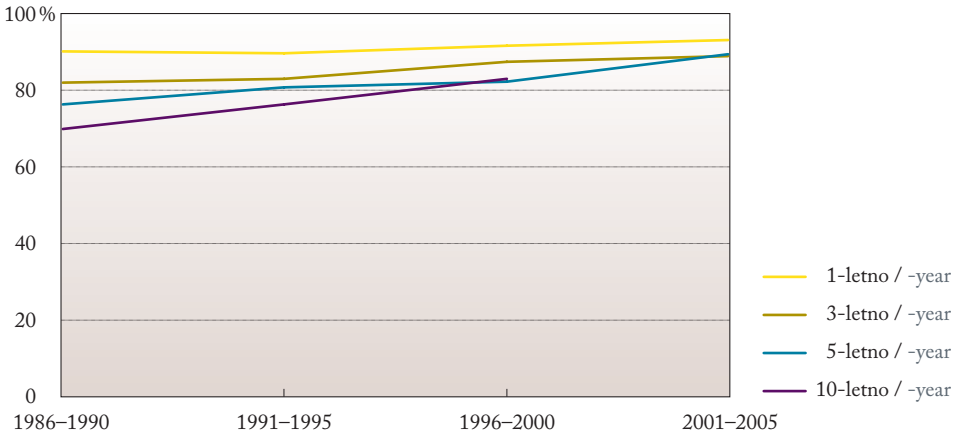
Nearly all patients with HD received their specific treatment at the IO Ljubljana; in the period 2001–2005 there were only 7 patients treated in the UMC Ljubljana, UMC Maribor and GH Izola.

The relative survival has been gradually increasing; in 15 years, the 5-year relative survival increased by 9% (Figure 2), the increase being approximately the same in both genders (Table 3). The survival of patients diagnosed in the first and second stage is very good; in the period 2001–2005 it was 96% in both cases. In the last 15 years the 5-year relative survival of patients with the third and fourth stage has not changed significantly, being approximately 80% (Figure 3). In patients with HL, age at diagnosis is also an important prognostic factor of survival. In the period 2001–2005, the 5-year relative survival of patients less than 50 years of age was 96%,

Tabela 2: *Število bolnikov s Hodgkinovim limfomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of Hodgkin's lymphoma patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	N	I (%)	II (%)	III + IV (%)	Neznan (%)	N	I (%)	II (%)	III + IV (%)	Neznan (%)
1991–1995	80	16,3	30,0	53,8	0,0	67	13,4	35,8	47,8	3,0
1996–2000	86	16,3	30,2	48,8	4,7	72	13,9	40,3	41,7	4,2
2001–2005	108	14,8	37,0	46,3	1,9	96	10,4	51,0	33,3	5,2



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov s Hodgkinovim limfomom po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of Hodgkin's lymphoma patients by period of diagnosis.*

stadiju. Značilno se je v zadnjih letih večal delež bolnikov z boleznijo, ugotovljeno v drugem stadiju. Povečanje je bolj očitno pri ženskah in je posledica tega, da se zmanjšuje delež bolnikov, pri katerih je bolezen ugotovljena v tretjem in četrtem stadiju (Tabela 2).

V obdobju 2001–2005 ni bilo specifično zdravljenih 7 % bolnikov. Skoraj polovica med njimi je bila starejša od 80 let. Delež nezdravljenih bolnikov ostaja skozi vse obdobje analize približno enak. V letih 2001–2005 je bilo s kombinacijo kemoterapije in obsevanja zdravljenih 55 % od vseh specifično zdravljenih, 33 % jih je prejelo le kemoterapijo, ostali pa so bili zdravljeni z drugimi kombinacijami zdravljenj.

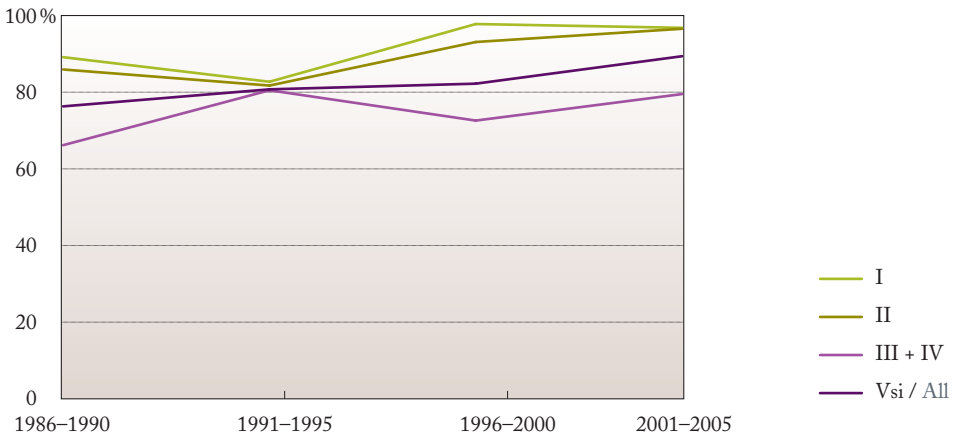
Skoraj vsi bolniki so bili specifično zdravljeni na OI Ljubljana, v obdobju 2001–2005 je bilo le 7 bolnikov zdravljenih v UKC Ljubljana in UKC Maribor ter v SB Izola.

Tabela 3: *Opazovano in relativno preživetje bolnikov s Hodgkinovim limfomom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of Hodgkin's lymphoma patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	88,8 (82,1–96,0)	77,5 (68,9–87,2)	73,8 (64,7–84,1)	88,1 (80,6–96,2)	82,1 (73,4–91,8)	77,6 (68,2–88,3)
1996–2000	93,0 (87,8–98,6)	83,7 (76,3–91,9)	75,6 (67,0–85,2)	87,5 (80,2–95,5)	84,7 (76,8–93,5)	79,2 (70,3–89,1)
2001–2005	92,6 (87,8–97,7)	84,1 (77,4–91,3)	82,9 (76,0–90,5)	90,6 (85,0–96,6)	86,5 (79,9–93,6)	83,9 (76,7–91,8)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	90,3 (82,9–97,6)	81,3 (71,1–91,5)	80,5 (69,2–91,7)	88,7 (80,6–96,9)	84,0 (74,1–93,9)	81,1 (70,0–92,2)
1996–2000	94,0 (88,4–99,6)	86,7 (78,2–95,2)	80,0 (69,8–90,2)	88,5 (80,5–96,6)	88,1 (79,0–97,2)	84,4 (73,8–95,1)
2001–2005	93,8 (88,6–98,9)	87,5 (80,0–95,0)	88,8 (80,7–96,9)	92,0 (85,9–98,1)	90,6 (83,1–98,1)	90,3 (81,9–98,8)



Slika 3: *Petletno relativno preživetje bolnikov s Hodgkinovim limfomom po stadiju in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of Hodgkin's lymphoma patients by stage and period of diagnosis.*

of patients aged 50–74 years it was 80% while the survival of those aged 75 years and older was near to 60% (Figure 4).

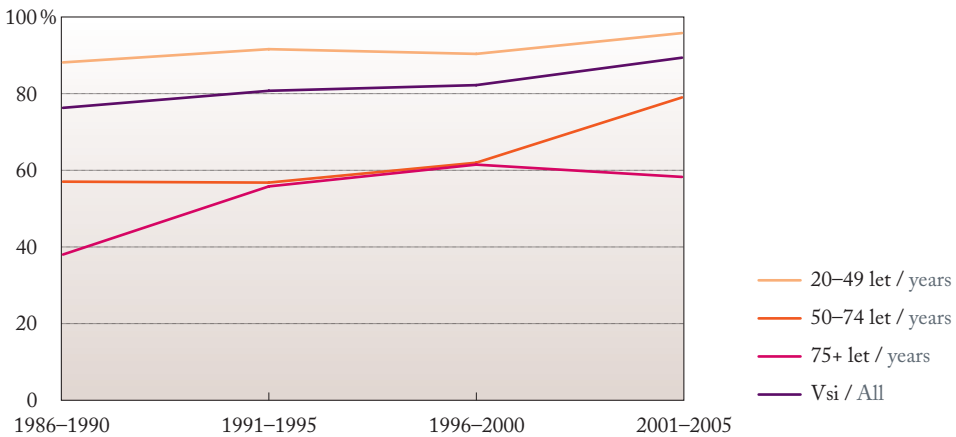
The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 90% (Figure 2); patients surviving the first year may expect to survive five years in 95%.

According to the results of EUROCARE-4 study for patients diagnosed in 2000–2002, the survival of Hodgkin's lymphoma patients in Slovenia is above (statistically not significant) the European average (Figure 5).

CLINICAL COMMENTARY

Barbara Jezeršek Novaković

In the period 1991–2005, the 5-year relative survival of patients with HL increased from 81% to 90%, which is attributed to better diagnostics as well as to better treatment and an individualized approach to every patient. Patients with HL are treated prevailingly at the IO Ljubljana



Slika 4: *Petletno relativno preživetje bolnikov s Hodgkinovim limfomom po starosti in obdobju postavitve diagnoze.*

Figure 4: *5-year relative survival of Hodgkin's lymphoma patients by age and period of diagnosis.*

Relativno preživetje se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 9 % (Slika 2), povečanje je približno enako pri obeh spolih (Tabela 3). Zelo dobro je preživetje bolnikov, odkritih v prvem in drugem stadiju; v obdobju 2001–2005 je v obeh primerih 96 %. Petletno relativno preživetje bolnikov s tretjim in četrtim stadijem se v zadnjih 15 letih ni bistveno spremenilo in je približno 80 % (Slika 3). Pomemben napovedni dejavnik preživetja bolnikov s HL je tudi starost ob diagnozi. Petletno relativno preživetje mlajših od 50 let je bilo v obdobju 2001–2005 96 %, bolnikov, starih 50–74 let 80 %, starih 75 let in več pa skoraj 60 % (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 90 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 95-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov s Hodgkinovim limfomom statistično neznačilno večje od evropskega povprečja (Slika 5).

KLINIČNI KOMENTAR

Barbara Jezeršek Novaković

Petletno relativno preživetje bolnikov s HL se je v obdobju od 1991–2005 povečalo z 81 % na 90 %, kar pripisujemo tako boljši diagnostiki kot boljšemu zdravljenju in individualiziranemu pristopu k vsakemu bolniku. Bolniki s HL se zdravijo pretežno na OI Ljubljana (96 % vseh, ki so bili zdravljeni), kar se odraža z zelo dobrim preživetjem bolnikov v primerjavi z bolniki v ostalih evropskih državah. Bolniki, ki so obravnavani na OI Ljubljana, se namreč zdravijo po enotnih sodobnih doktrinarnih načelih, tako glede diagnostičnega kot terapevtskega pristopa, hkrati pa pri izbiri najprimernejšega zdravljenja upoštevamo individualne značilnosti posameznega bolnika. Preseneča dokaj visok odstotek bolnikov (7 %), ki naj bi ne bili deležni zdravljenja; podatki kažejo, da gre večinoma za starejše bolnike, verjetno s številnimi pridruženimi boleznimi.

Novost v zdravljenju bolnikov s HL v obravnavanem obdobju je zdravljenje s citostatsko shemo BEACOPP (poleg standardne sheme ABVD) od leta 1997, ki daje boljše rezultate zdravljenja pri razsejani bolezni. Citostatskemu zdravljenju sledi obsevanje prizadetih področij v primeru omejene in razširjene bolezni in obsevanje samo ostanka bolezni v primeru razsejane bolezni. Natančnejšo zamejitev bolezni pred pričetkom zdravljenja in natančnejšo določitev ostanka bolezni pri razsejani obliki je omogočila tudi uvedba preiskave PET CT v rutinsko obravnavo bolnikov s HL.

Skupno petletno relativno preživetje se je v obdobju 1991–2005 večalo predvsem pri bolnikih z omejeno, pa tudi z razširjeno boleznijo. Pri bolnikih z razsejano boleznijo pa je bilo preživetje v obdobju 2001–2005 praktično enako kot v obdobju 1991–1995. Ob tem je potrebno omeniti, da se je v celotnem opazovanem obdobju zmanjševal delež bolnikov z omejeno in razsejano boleznijo predvsem na račun bolnikov z razširjeno boleznijo, kjer pa je podaljšanje preživetja najbolj izrazito.

Petletno relativno preživetje bolnikov, starih 75 let in več, se je v obdobju po letu 1991 le malo spreminjalo; preživetje se je večalo predvsem pri mlajših, starih 20–49 let in 50–74 let, kar je posledica odločnejšega in učinkovitejšega zdravljenja ter boljše diagnostike.

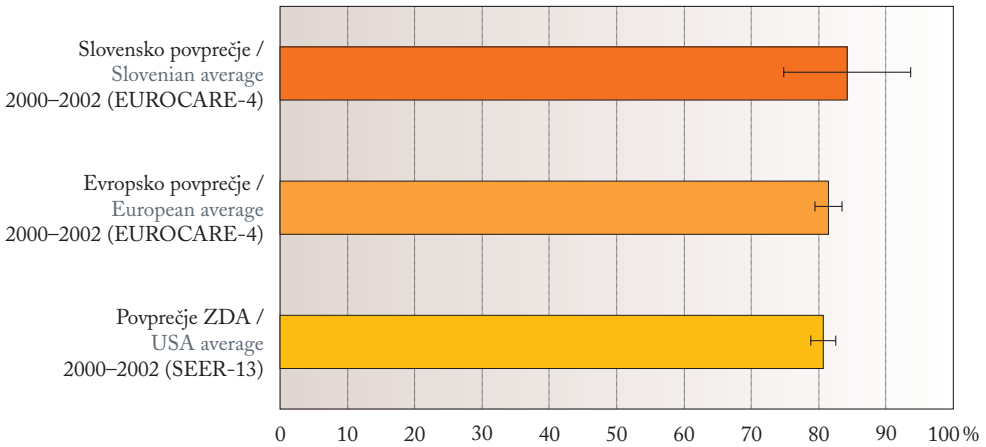
VIRI

Literature

Canellos GP, Lister TA, Sklar JL, eds. The lymphomas. 2nd edition. Philadelphia: W. B. Saunders Company; 2006.

Dalla-Favera R, Gaidano G. Lymphomas. In: DeVita VTJr, Hellman S, Rosenberg SA, eds. Cancer Principles and Practice of Oncology. 7th edition. Philadelphia: Lippincott Williams and Wilkins; 2005.

Jezeršek-Novaković B, ed. Smernice za obravnavo bolnikov z malignimi limfomi. Ljubljana: Onkološki inštitut Ljubljana; 2008.



Slika 5: *Petletno relativno preživetje bolnikov s Hodgkinovim limfomom (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of Hodgkin's lymphoma patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

(96% of all treated patients), which is reflected in their very good survival as compared to the patients in other European countries. Namely, the patients referred to the IO Ljubljana are treated according to the uniform up-to-date doctrinary principles in terms of diagnostic as well as therapeutic approach, while in selecting the treatment of choice, individual characteristics of every individual patient are taken into account. Surprising is a relatively high percentage of patients (7%) who are presumably left untreated; the data show that these are generally older patients, possibly with numerous concomitant diseases.

A novelty in the treatment of patients with HL in the period under analysis is treatment with cytostatics according to BEACOPP schedule (besides the standard ABVD schedule) used since 1997, which is found to be more effective in the cases with disseminated disease. Cytostatic treatment is followed by irradiation of the affected areas in the case of localized and regional disease, whereas in a disseminated stage irradiation is limited to the residual disease. The introduction of PET CT examination into the routine management of patients with HL facilitated more accurate staging of the disease before the beginning of treatment as well as more accurate assessment of the residual disease in a disseminated stage.

In the period 1991–2005, overall 5-year relative survival was increasing particularly in patients with localized and also in those with regional disease. In the period 2001–2005, the survival of patients with disseminated disease was practically the same as in the period 1991–1995. However, it should be pointed out that throughout the observation period the proportion of patients with localized and disseminated disease has been decreasing mainly on the account of patients with regional disease in whom an increase in survival is most apparent.

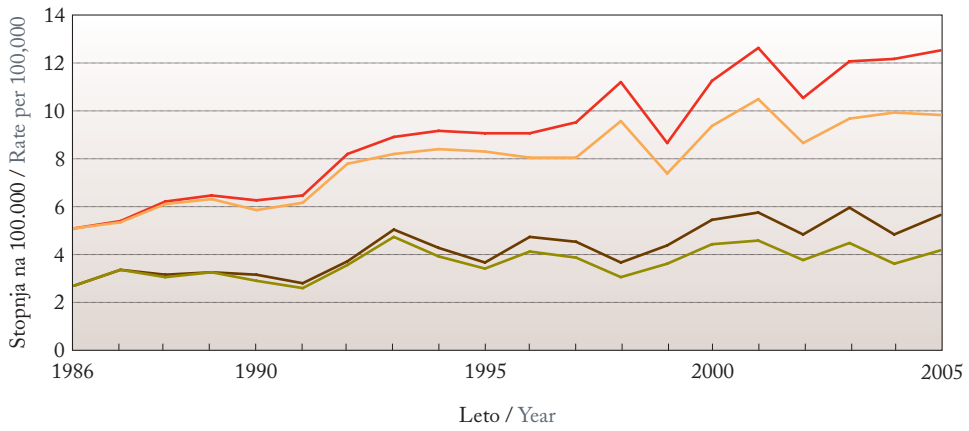
In the period since 1991, the 5-year relative survival of patients aged 75 years or older has not undergone any particular change; the survival showed an upward trend only in younger age groups, i. e. 20–49 years and 50–74 years, as a result of more radical and effective treatment and better diagnostics.

NE-HODGKINOV LIMFOM

MKB 10: C82–C85

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za ne-Hodgkinovim limfomom (NHL) zbolelo 3068 ljudi, 1472 moških in 1596 žensk. Kot je razvidno s Slike 1, sta se obe incidenčni in umrljivostni stopnji v opazovanem obdobju povečevali. Ker so NHL pogostejši pri starejših (Tabela 1), je večanje bolj očitno pri obeh grobih stopnjah. Incidenca se je večala bolj kot umrljivost, v povprečju za 3,7 % letno; umrljivost se je večala v povprečju za 3,2 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja ne-Hodgkinovega limfoma, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of non-Hodgkin's lymphoma, Slovenia 1986–2005.*

V analizo preživetja je vključenih 2924 primerov; 49 bolnikov (1,6 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 95 otrok in mladostnikov pa obravnavamo v posebnem poglavju. Od vseh bolnikov le eden ni imel mikroskopsko potrjene bolezni; 1773 tumorjev je bilo nodalnega, 1151 pa ekstranodalnega izvora.

Celotno skupino bolnikov z NHL smo glede na histološko vrsto limfoma razdelili v štiri podvrste: indolentne (MKB-O-3: 9670–9673, 9689, 9691–9699), agresivne (MKB-O-3: 9678, 9680–9687, 9727–9729), T-celične (MKB-O-3: 9702–9705, 9709–9714, 9717–9719) in

Tabela 1: *Število bolnikov z ne-Hodgkinovim limfomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of non-Hodgkin's lymphoma patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	390	23,3	56,2	20,5	409	17,6	55,3	27,1
1996–2000	455	20,9	62,2	16,9	505	19,0	53,5	27,5
2001–2005	537	22,9	54,0	23,1	628	14,8	53,0	32,2

NON-HODGKIN LYMPHOMA

ICD 10: C82-C85

EPIDEMIOLOGY

In the period 1991–2005, a total of 3068 persons were diagnosed with non-Hodgkin lymphoma (NHL), of these 1472 males and 1596 females. As evident from Figure 1, in the observed time period both incidence and mortality rates have been increasing. NHL being more frequent in the elderly (Table 1), the increase is more apparent in both crude rates. The incidence has been increasing more rapidly than the mortality, by 3.7% vs. 3.2% annually on average, respectively.

The survival analysis included 2924 cases; 49 patients (1.6%) diagnosed only after death, were not considered in the analysis; 95 children and adolescents are presented in a separate chapter. Of all the patients, only one did not have microscopically verified disease; 1773 tumors were of nodal and 1151 of extranodal origin.

According to histological type of lymphoma, the whole group of NHL patients was divided into four subgroups: indolent (ICD-O-3: 9670–9673, 9689, 9691–9699), aggressive (ICD-O-3: 9678, 9680–9687, 9727–9729), T-cell (ICD-O-3: 9702–9705, 9709–9714, 9717–9719) and undetermined (ICD-O-3: 9590, 9591). T-cell NHL with 240 patients (8%) represented the smallest group while undetermined and indolent NHL were present in a similar percentage: 839 cases of the former (29%) and 804 cases of the latter (28%). More than one third of all NHL are aggressive – 1041 cases (36%). In the earlier periods, the number of undetermined NHL was the highest, however, later on, by a more accurate histological classification, their number decreased significantly. In recent years, the majority of NHL patients present with aggressive and indolent NHL subtype (Figure 2).

Approximately half of the patients are diagnosed at an age between 50–74 years (Table 1). The proportions in individual age groups did not change significantly with time. Likewise, there was no great difference in age at diagnosis when individual subgroups of NHL were compared with each other, except in the undetermined NHL, which are in the last period considerably less frequent in young patients and more frequent in patients aged 75 years and older.

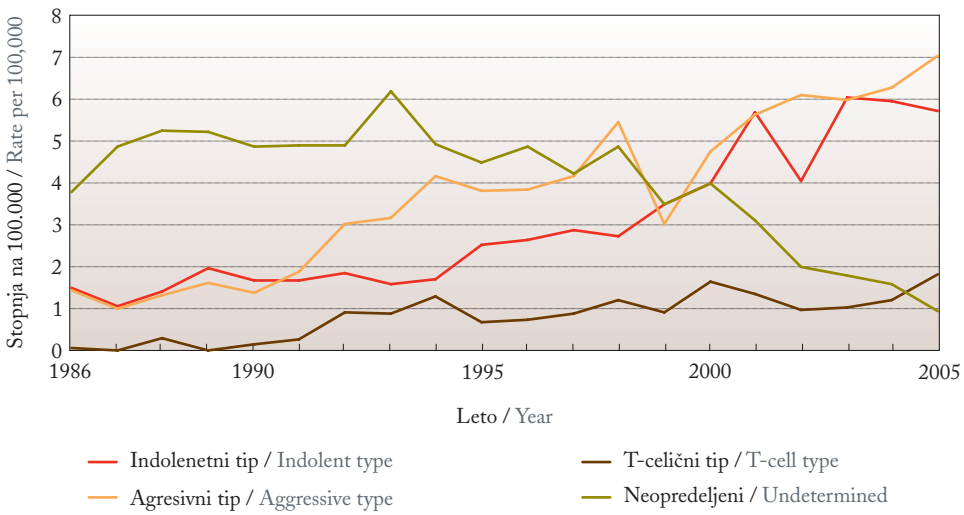
Almost half of the patients had the disease diagnosed in the first and the second stage, their proportion decreasing slightly in the last period while the proportion of patients with the third and the fourth stage, and surprisingly also the proportion of those with undefined stage at diagnosis, have increased (Table 2). Most frequently the stage was not determined in undefined NHL (in nearly one third of cases); in T-cell and aggressive NHL the stage was not determined in less than 10% of patients.

In the years 2001–2005, 19% of patients did not receive specific treatment. Almost a half of the untreated patients were those with undefined NHL, one third had indolent NHL and very few (less than 5%) untreated patients had T-cell NHL. Also, patients under 50 years of age and those with stage I and stage II at diagnosis very rarely remain without specific treatment. The proportion of untreated patients has remained approximately the same throughout the

Tabela 2: *Število bolnikov z ne-Hodgkinovim limfomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of non-Hodgkin's lymphoma patients by sex and period of diagnosis with their proportions by stage.*

	Moški / Males					Ženske / Females				
Obdobje / Period	N	I (%)	II (%)	III + IV (%)	Neznan (%)	N	I (%)	II (%)	III + IV (%)	Neznan (%)
1991–1995	390	27,4	23,6	38,5	10,5	409	29,8	22,0	36,2	12,0
1996–2000	455	24,4	26,4	37,1	12,1	505	27,1	21,0	38,4	13,5
2001–2005	537	22,9	20,9	41,2	15,1	628	24,7	19,4	41,1	14,8



Slika 2: *Groba incidenčna stopnja štirih histoloških podvrst ne-Hodgkinovega limfoma, Slovenija 1986–2005.*

Figure 2: *Crude incidence rate of four hystological subgroups of non-Hodgkin's lymphoma, Slovenia 1986–2005.*

neopredeljene (MKB-O-3: 9590, 9591). Z 240 bolniki (8 %) je bila najmanjša skupina s T-celičnimi NHL, neznanih in indolentnih NHL je bilo približno enako: 839 primerov prvih (29 %) in 804 primerov drugih (28 %). Več kot tretjina med vsemi NHL je agresivnih – 1041 primerov (36 %). V začetnih obdobjih je bilo največ neopredeljenih NHL, a se je njihovo število s kasnejšo bolj natančno histološko opredelitvijo bistveno zmanjšalo. Zadnja leta je med bolniki z NHL največ tistih z agresivnimi in indolentnimi NHL (Slika 2).

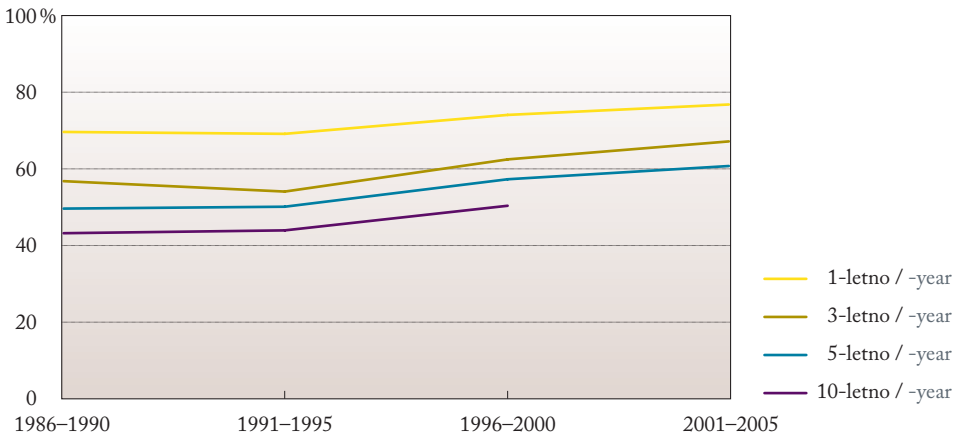
Približno polovica bolnikov zboli v starosti 50–74 let (Tabela 1). Deleži v posameznih starostnih skupinah se z leti niso bistveno spreminjali. Prav tako ni velike razlike v starosti ob diagnozi,

Tabela 3: *Opazovano in relativno preživetje bolnikov z ne-Hodgkinovim limfomom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of non-Hodgkin's lymphoma patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	67,2 (62,7–72,0)	48,5 (43,7–53,7)	41,3 (36,7–46,5)	65,5 (61,1–70,3)	47,4 (42,8–52,5)	40,3 (35,9–45,4)
1996–2000	70,3 (66,3–74,7)	55,8 (51,4–60,6)	45,5 (41,1–50,3)	72,7 (68,9–76,7)	55,8 (51,7–60,3)	49,3 (45,1–53,9)
2001–2005	74,1 (70,5–77,9)	58,2 (54,1–62,5)	46,8 (42,3–51,8)	73,9 (70,5–77,4)	61,0 (57,3–65,0)	51,8 (47,6–56,3)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	70,2 (65,2–75,3)	55,3 (49,4–61,3)	51,5 (45,1–58,0)	68,0 (63,0–72,9)	53,1 (47,4–58,8)	48,8 (42,7–55,0)
1996–2000	73,2 (68,7–77,7)	63,1 (57,7–68,5)	56,2 (50,2–62,1)	75,0 (70,9–79,1)	61,5 (56,6–66,5)	58,4 (53,0–63,8)
2001–2005	77,2 (73,3–81,2)	66,2 (61,2–71,2)	58,8 (52,5–65,0)	76,4 (72,8–80,1)	67,9 (63,5–72,3)	62,5 (57,0–67,9)

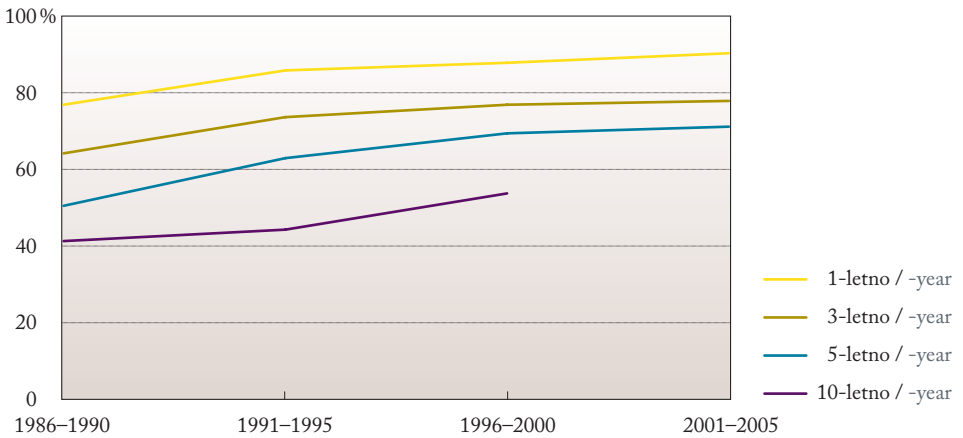


Slika 3: *Deset-, pet-, tri- in enoletno relativno preživetje vseh bolnikov z ne-Hodgkinovim limfomom po obdobju postavitve diagnoze.*

Figure 3: *10-, 5-, 3- and 1-year relative survival of all non-Hodgkin's lymphoma patients by period of diagnosis.*

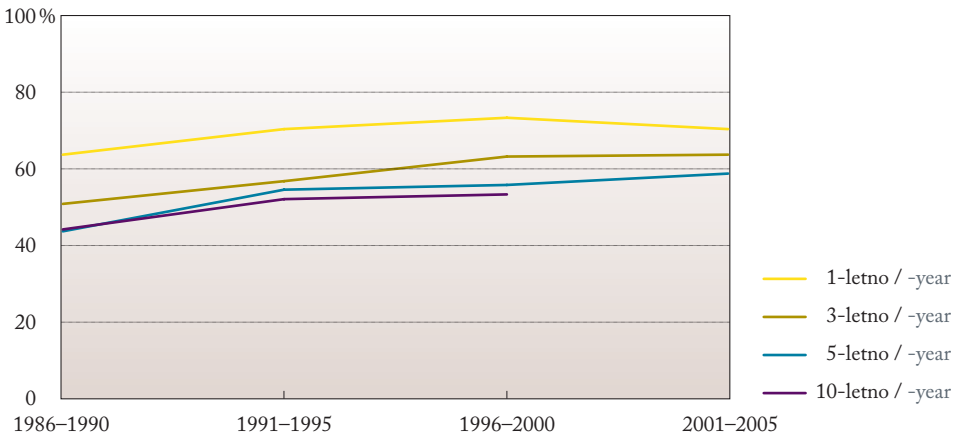
study period. Among the patients receiving specific treatment in the period 2001–2005, 80% were treated by chemotherapy, slightly over a half of them also had radiotherapy and/or surgery in addition. Radiotherapy alone was used in 9% and surgery alone in 6% of patients. Additional 14% of patients underwent surgery in combination with other treatment modalities. In the period 2001–2005, 14% of the treated patients received rituximab as part of their primary treatment; in the previous two periods there were only 4% such patients. Among all the rituximab-treated patients two thirds had aggressive NHL while 26% of the patients had indolent NHL.

In the period 2001–2005, a half of specifically treated patients started their treatment at the IO Ljubljana, 13% in the UMC Ljubljana, 6% in the UMC Maribor, and the remaining ones in lesser proportions in practically all general hospitals of Slovenia. Of those that started their



Slika 4: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z indolentnim ne-Hodgkinovim limfomom po obdobju postavitve diagnoze.*

Figure 4: *10-, 5-, 3- and 1-year relative survival of indolent non-Hodgkin's lymphoma patients by period of diagnosis.*



Slika 5: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z agresivnim ne-Hodgkinovim limfomom po obdobju postavitve diagnoze.*

Figure 5: *5-year relative survival of aggressive non-Hodgkin's lymphoma patients by period of diagnosis.*

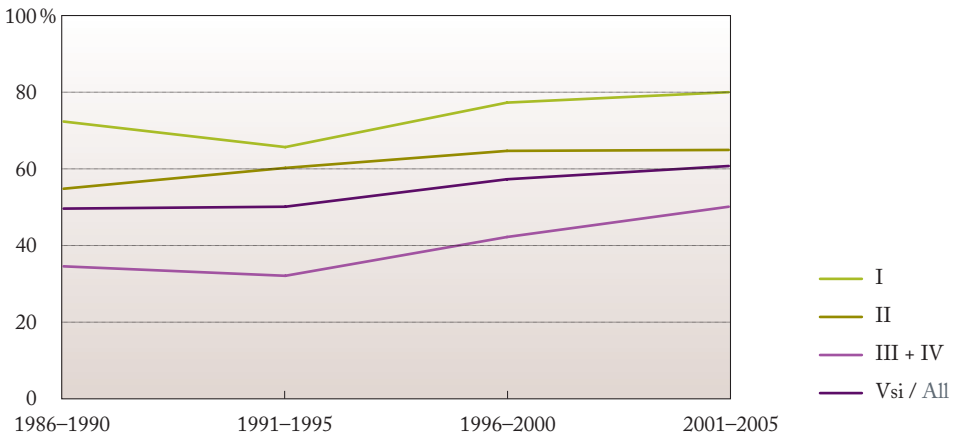
če med seboj primerjamo posamezne podvrste NHL, razen pri neopredeljenih NHL, ki jih je v zadnjem obdobju bistveno manj pri mladih, več pa pri starih 75 let in več.

Pri približno polovici bolnikov je bila bolezen odkrita v prvem in drugem stadiju bolezni; njihov delež se je v zadnjem obdobju nekoliko zmanjšal, povečal pa se je delež bolnikov s tretjim in četrtim stadijem ter, presenetljivo, delež tistih, ki jim stadij ob diagnozi ni bil določen (Tabela 2). Najpogosteje stadij ni določen pri neopredeljenih NHL (pri skoraj tretjini primerov), pri T-celičnih in agresivnih NHL pa je bilo brez določenega stadija manj kot 10 % bolnikov.

V letih 2001–2005 ni bilo specifično zdravljenih 19 % bolnikov. Skoraj polovica med nezdravljenimi so bolniki z neopredeljenimi NHL, ena tretjina jih je imela indolentni NHL, zelo malo (manj kot 5 % zbolelih) pa ni bilo zdravljenih bolnikov s T-celičnimi NHL. Zelo redko ostanejo brez specifičnega zdravljenja tudi mlajši od 50 let in bolniki s prvim in drugim stadijem ob diagnozi. Delež nezdravljenih bolnikov ostaja v celotnem obdobju analize približno enak. Med specifično zdravljenimi je bilo v letih 2001–2005 80 % bolnikov zdravljenih s kemoterapijo, dobra polovica med njimi je bila še dodatno zdravljena z obsevanjem in/ali operativno. Samo obsevanih je bilo 9 % bolnikov, samo operiranih pa 6 %. V kombinaciji z drugimi načini zdravljenja je bilo operiranih še dodatnih 14 % bolnikov. Med leti 2001–2005 je v okviru prvega zdravljenja rituksimab prejelo 14 % zdravljenih, v prejšnjih dveh obdobjih pa le 4 %. Med vsemi, ki so bili zdravljeni z rituksimabom, je kar dve tretjini bolnikov z agresivnim NHL, 26 % bolnikov pa je imelo indolentni NHL.

Polovica specifično zdravljenih je v obdobju 2001–2005 z zdravljenjem pričela na OI Ljubljana, 13 % v UKC Ljubljana, 6 % v UKC Maribor, ostali pa v manjših deležih praktično v vseh slovenskih splošnih bolnišnicah. Od tistih, ki zdravljenja niso pričeli na OI Ljubljana, jih je bilo tja po začetku zdravljenja preusmerjenih več kot polovica; v sklopu prvega zdravljenja je kar 80 % bolnikov z NHL prejelo vsaj del terapije na OI Ljubljana.

Relativno preživetje bolnikov z NHL se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 11 % (Slika 3), za 14 % pri ženskah in za 7 % pri moških (Tabela 3). Najboljše preživetje imajo bolniki z indolentnim NHL (Slika 4); petletno relativno preživetje pri bolnikih z indolentnim NHL je 78 %. Izboljšanje relativnih preživetij v zadnjih letih pri bolnikih z agresivnim NHL prikazuje Slika 5. Petletna relativna preživetja so pri obeh spolih podobna, v zadnjem obdobju 59 %. Preučevanje relativnega preživetja pri bolnikih s T-celičnimi



Slika 6: *Petletno relativno preživetje vseh bolnikov z ne-Hodgkinovim limfomom po stadiju in obdobju postavitve diagnoze.*

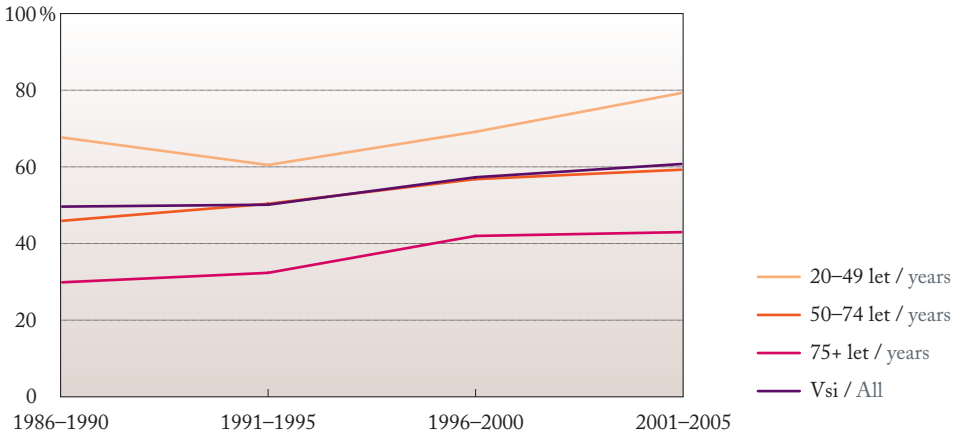
Figure 6: *5-year relative survival of all non-Hodgkin's lymphoma patients by stage and period of diagnosis.*

treatment elsewhere, more than half were later referred to the IO Ljubljana, so that as many as 80% of all patients with NHL received at least a part of their primary treatment at the IO Ljubljana.

The relative survival of patients with NHL has been gradually increasing; in 15 years, the 5-year relative survival increased by 11% (Figure 3), 14% in females and 7% in males (Table 3). The best survival is observed in patients with indolent NHL (Figure 4); 5-year relative survival in patients with indolent NHL is 78%. An improvement in the relative survival observed in patients with aggressive NHL in recent years is presented in Figure 5. 5-year relative survival rates are comparable in both genders, in the last period being 59%. The analysis of relative survival in patients with T-cell and undefined NHL is unreliable due to a very small number of patients with these two subtypes in individual periods. The relevance of stage at diagnosis is shown in Figure 6. In the last period, patients diagnosed in stage I had 80% 5-year relative survival while the rate in those with stages III and IV was only 50%. In comparison with the period 1991–1995, the survival of patients with all stages has increased. When analyzing the influence of stage on the survival of patients with indolent and aggressive NHL, the results are similar, however, the average survivals in all stages are slightly lower in aggressive and slightly higher in indolent NHL. In patients with NHL, age at diagnosis is also an important prognostic factor of survival. In the period 2001–2005, the 5-year relative survival of patients less than 50 years of age was 80%, of patients aged 50–74 years it was 60% and of those aged 75 years and older it was 43% (Figure 7). A similar association with age is also established in the survival of patients with indolent and aggressive NHL.

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 60% (Figure 3); patients surviving the first year may expect to survive five years in 77%. The expectancy of survival after one year is even higher in patients with aggressive NHL: after having survived the first year, these patients have 81% 5-year relative survival. In patients with indolent NHL an increase in the survival after the first year is less obvious (their 5-year relative survival increases from 71% to 77%).

According to the EUROCARE-4 study results for those diagnosed in the period 2000–2002, the survival of patients with NHL in Slovenia is above (statistically not significant) the European average (Figure 8).



Slika 7: *Petletno relativno preživetje vseh bolnikov z ne-Hodgkinovim limfomom po starosti in obdobju postavitve diagnoze.*

Figure 7: *5-year relative survival of all non-Hodgkin's lymphoma patients by age and period of diagnosis.*

in neopredeljenimi NHL je nezanesljivo, saj je bilo število bolnikov pri teh dveh podvrstah v posameznih obdobjih zelo majhno. Kako pomemben je stadij ob diagnozi, kaže Slika 6. Bolniki, ki jim je bila diagnoza postavljena v prvem stadiju, so v zadnjem obdobju imeli petletno relativno preživetje 80 %, tisti s tretjim ali četrtim stadijem pa le 50 %. V primerjavi z obdobjem 1991–1995 se je večalo preživetje bolnikov vseh stadijev. Pri analizi vpliva stadija na preživetje pri bolnikih z indolentnimi in agresivnimi NHL so rezultati podobni, seveda pa so preživetja v povprečju pri vseh stadijih nekoliko manjša pri agresivnih in nekoliko večja pri indolentnih NHL. Pomemben napovedni dejavnik preživetja bolnikov z NHL je tudi starost ob diagnozi. Petletno relativno preživetje mlajših od 50 let je bilo v obdobju 2001–2005 80 %, starih med 50 in 74 let 60 %, pri starih 75 let in več pa je bilo 43 % (Slika 7). Podobno je s starostjo povezano tudi preživetje bolnikov z indolentnimi in agresivnimi NHL.

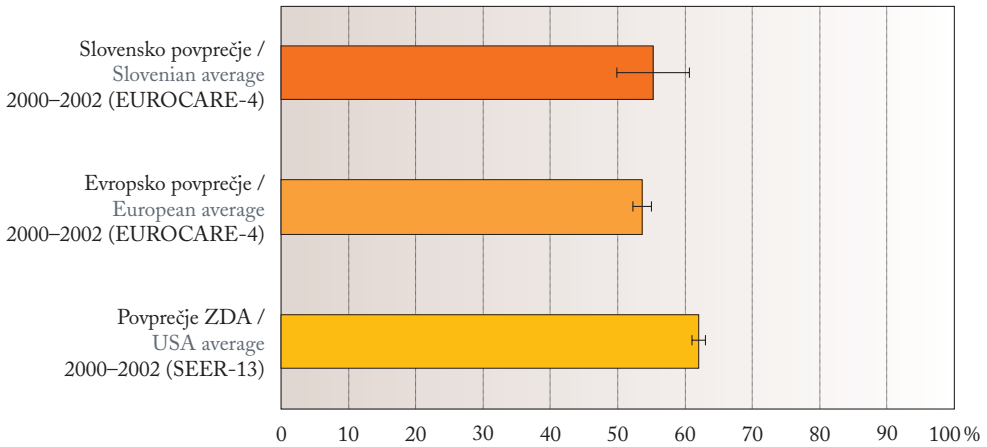
Petletno relativno preživetje vseh zbolelih z NHL v obdobju 2001–2005 je bilo 60 % (Slika 3); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 77-odstotno petletno relativno preživetje. Še bolj se po enem letu poveča verjetnost preživetja bolnikov z agresivnimi NHL: po preživetem prvem letu imajo ti bolniki 81-odstotno petletno relativno preživetje. Pri bolnikih z indolentnimi NHL je izboljšanje preživetja po preživetem prvem letu manj očitno (petletno relativno preživetje se poveča z 71 na 77 %).

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z NHL statistično neznačilno večje od evropskega povprečja (Slika 8).

KLINIČNI KOMENTAR

Barbara Jezeršek Novaković

Izboljšanje preživetja bolnikov z NHL v prvi vrsti pripisujemo boljšemu zdravljenju; precej večji delež bolnikov v tem obdobju je bil namreč zdravljen z monoklonskim protitelesom proti CD20 determinanti, rituksimabom. Ta je registriran za indukcijsko zdravljenje B-celičnih CD20 pozitivnih limfomov (difuznih velikoceličnih B, folikularnih in drugih indolentnih B-celičnih limfomov) ter za vzdrževalno zdravljenje po ponovitvi folikularnih in drugih indolentnih B-celičnih limfomov po uspešnem indukcijskem zdravljenju. V ZDA je v uporabi od leta 1997, v Sloveniji od leta 1998, v širši uporabi pa od leta 2000. Zdravljenje z rituksimabom je po letu 2000 prispevalo k izboljšanju preživetja bolnikov tako z indolentnimi kot agresivnimi B-celičnimi NHL, kar je v skladu z opažanji Sehna s sodelavci, ki poroča o 55-odstotnem 4-letnem pre-



Slika 8: *Petletno relativno preživetje bolnikov z ne-Hodgkinovim limfomom* (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 8: *5-year relative survival of of non-Hodgkin's lymphoma patients* (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

* Nabor MKB10 kod v študiji EUROCARE-4 je nekoliko drugačen kot smo ga uporabili pri ostalih analizah predstavljenih v tem poglavju: v študiji EURCARE-4 so v analizo vključene tudi tudi levkemije celic T pri odraslih (MKB10: C915).

* The ICD10 code selection in EUROCARE-4 study is slightly different in comparison to the selection applied in other analysis in this chapter: in EUROCARE-4 study the adult T-cell leukemia (ICD10: C915) is included.

CLINICAL COMMENTARY

Barbara Jezeršek Novaković

The improved survival of patients with NHL is mainly attributed to better treatment; namely, a considerably greater proportion of patients in this period were treated with rituximab, a monoclonal antibody against CD20 determinant. This medication is registered for the induction therapy of B-cell CD20-positive lymphomas (diffuse large B-cell, follicular and other indolent B-cell lymphomas) as well as for maintenance therapy after the recurrence of follicular and other indolent B-cell lymphomas following a successful induction therapy. In the U. S. A. it has been in use since 1997, in Slovenia since 1998, but used more widely since 2000. After the year 2000, the treatment with rituximab has contributed to the improved survival of patients with indolent as well as aggressive B-cell NHL, which is consistent with the findings of Sehn and co-workers who reported on 55% 4-year survival of patients with diffuse large B-cell lymphoma in a prognostically unfavorable group after treatment with rituximab and chemotherapy (after treatment with chemotherapy alone the 5-year survival of such patients is only 32%).

Patients with NHL are most frequently treated at the IO Ljubljana, however, the proportion of patients with NHL treated at that institute (80%) is considerably lower than that of patients with HL (96%), which is reflected in a worse survival of NHL patients as compared to those with HL. Namely, the patients referred to the IO Ljubljana are treated according to the uniform up-to-date doctrinary principles in terms of diagnostic as well as therapeutic approach, which is not the case in patients treated at other hospitals.

In an additional analysis we compared certain characteristics of a group of 938 patients diagnosed in the period 2001–2005, who had their primary treatment at the IO Ljubljana, with the survival in a group of 227 patients diagnosed in the same period, who were treated elsewhere. The median survival of patients treated at the IO Ljubljana was 5 years, while the survival of those treated at other hospitals was only 10 months. The median age at diagnosis of patients treated at the IO Ljubljana was 61 years, while the age of those treated elsewhere was 71 years.

življenju bolnikov z difuznim velikoceličnim B-limfomom v slabi prognostični skupini po zdravljenju z rituksimabom in kemoterapijo (po zdravljenju samo s kemoterapijo je petletno preživetje takih bolnikov samo 32 %).

Bolniki z NHL se najpogosteje zdravijo na OI Ljubljana, odstotek bolnikov z NHL, ki je v obravnavi na tem inštitutu (80 %), pa je precej nižji kot pri bolnikih s Hodgkinovim limfomom (96 %), kar se zrcali tudi s slabšim preživetjem bolnikov z NHL v primerjavi s Hodgkinovim limfomom. Bolniki, ki so obravnavani na OI Ljubljana, se namreč zdravijo po enotnih sodobnih doktrinarnih načelih tako glede diagnostičnega kot terapevtskega pristopa, česar ne moremo trditi za obravnavo bolnikov v drugih zdravstvenih ustanovah.

V dodatni analizi smo primerjali nekatere značilnosti skupine 938 bolnikov, zbolelih v letih 2001–2005, ki so se zdravili na OI Ljubljana v okviru prvega zdravljenja, s preživetjem skupine 227 zbolelih v istem obdobju, ki se v okviru prvega zdravljenja niso zdravili v tej ustanovi. Srednje preživetje bolnikov, zdravljenih na OI Ljubljana, je bilo 5 let, zdravljenih v drugih bolnišnicah pa le 10 mesecev. Povprečna starost zdravljenih na OI Ljubljana je bila 61 let, zdravljenih drugod pa 71 let. Pri drugod zdravljenih bolnikih stadij ni bil določen pri 48 %, pri 34 % je bil razsejan (stadij III in IV), pri 10 % razširjen (stadij II) in pri 8 % omejen (stadij I); v skupini zdravljenih na OI Ljubljana pa stadij ni bil določen pri 7 %, pri 43 % je bil razsejan (stadij III in IV), pri 23 % razširjen (stadij II) in pri 27 % omejen (stadij I). Ker na preživetje pomembno vplivajo stadij, starost in zdravljenje, smo te napovedne dejavnike vključili v multivariatni Coxov preživetveni model (Tabela 4). S tem smo želeli stvarno oceniti vpliv izbora bolnišnice prvega zdravljenja na izid bolezni. Rezultat je zaskrbljujoč, saj prvo zdravljenje bolnika zunaj OI Ljubljana tudi v multivariatni analizi ostaja dejavnik tveganja smrti bolnika; bolniki, ki v okviru prvega zdravljenja niso zdravljeni na OI Ljubljana, imajo 2,5-krat večje relativno tveganje smrti v primerjavi s tistimi, ki so zdravljeni v tej ustanovi.

Presenetljivo je, da se je v obdobju 2001–2005 glede na prejšnja obdobja povečal delež bolnikov z razsejano boleznijo (stadij III in IV) in zmanjšal delež tistih z omejeno (stadij I); to je posledica boljše diagnostike in s tem natančnejše zamejitve bolezni.

Petletno relativno preživetje bolnikov, starih 75 let in več, se je v obdobju po letu 1991 večalo. V istem obdobju se je tudi povečal delež bolnikov z NHL, ki so zboleli starejši, tj. v skupini s sicer najmanjšim petletnim preživetjem. Preživetje bolnikov v tej starosti je slabše že zaradi številnih spremljajočih bolezni, značilnih za to življenjsko obdobje; prav zaradi teh pa je treba prilagoditi zdravljenje in zmanjšati odmerke citostatikov, kar pomeni slabšo kakovost zdravljenja. V starostnih skupinah bolnikov, starih 20–49 let in 50–74 let, pa se je od leta 1991 do 2005 preživetje stalno izboljševalo v skladu z odločnejšim in učinkovitejšim zdravljenjem.

VIRI
Literature

Canellos GP, Lister TA, Sklar JL, eds. The lymphomas. 2nd edition. Philadelphia: W. B. Saunders Company; 2006.

Dalla-Favera R, Gaidano G. Lymphomas. In: DeVita VTJr, Hellman S, Rosenberg SA, eds. Cancer Principles and Practice of Oncology. 7th edition. Philadelphia: Lippincott Williams and Wilkins; 2005.

Jezeršek-Novaković B, ed. Smernice za obravnavo bolnikov z malignimi limfomi. Ljubljana: Onkološki inštitut Ljubljana; 2008.

Molina A. A decade of rituximab: Improving survival outcomes in Non-Hodgkin's lymphoma. Annu Rev Med 2008; 59: 237–50.

Shipp M, Harrington D, Anderson J. A predictive model for aggressive non-Hodgkin's lymphomas. N Engl J Med 1993; 329: 987–94.

Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, et al. The revised International Prognostic Index is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007; 109: 1857–61.

Tabela 4: *Multivariatna analiza tveganja smrti bolnikov z NHL v Sloveniji, zbolelih v obdobju 2001–2005.*
Table 4: *Multivariate analysis of the risk of death in NHL patients in Slovenia, diagnosed in the period 2001–2005.*

Napovedni dejavnik / Prognostic factor	Relativno tveganje / Relative risk	95-odstotni interval zaupanja / 95% confidence interval
V okviru prvega zdravljenja se JE bolnik zdravil na OIL / Patient DID receive primary treatment at IOL	1,0	
V okviru prvega zdravljenja se bolnik NI zdravil na OIL / Patient DID NOT receive primary treatment at IOL	2,5	2,00–3,10
Starost / Age 20–49	1,0	
Starost / Age 50–74	2,2	1,60–3,00
Starost / Age 75+	4,7	3,40–6,52
Stadij / Stage I + II	1,0	
Stadij / Stage III + IV	1,7	1,40–2,00
Stadij neznan / Stage unknown	0,8	0,60–1,10

In patients treated elsewhere, the stage was not determined in 48%, disseminated (stage III and IV) in 34%, regional (stage II) in 10% and localized (stage I) in 8%; in the group treated at the IO Ljubljana, the stage was not determined in 7%, was found to be disseminated (stage III and IV) in 43%, regional (stage II) in 23% and localized (stage I) in 27%. Because survival is significantly influenced by stage, age and treatment, these prognostic factors were included into a multivariate Cox's survival model (Table 4). Thus we wanted to assess the influence of primary treatment hospital choice on the outcome of the disease controlling for different prognostic factors. The results raise concern since also in the multivariate analysis the primary treatment outside the IO Ljubljana remains associated with the risk of death; the patients who do not receive their primary treatment at the IO Ljubljana have 2.5 fold higher relative risk of death in comparison with those treated at the IO Ljubljana.

It is surprising that – with respect to the pervious periods – in the period 2001–2005 the proportion of patients with disseminated disease increased (stage III and IV) while the proportion of those with localized disease (stage I) decreased as a result of better diagnostics and thus more accurate staging of the disease.

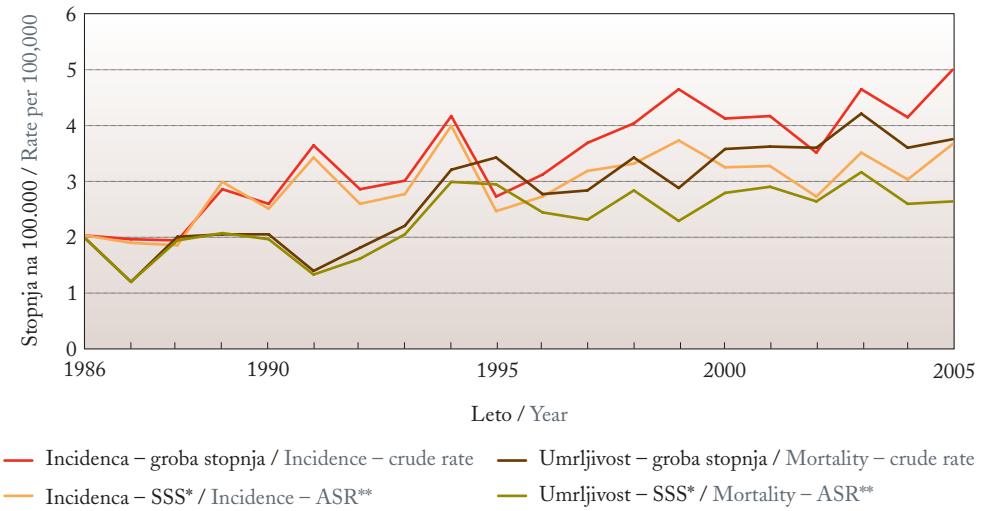
In the period after 1991, the 5-year relative survival of patients aged 75 years and older has been increasing. In the same period, the proportion of NHL patients diagnosed at an advanced age, i. e. in the group with the lowest 5-year survival, has increased too. If for no other reasons, the survival of patients in that age group is worse because of numerous concomitant diseases characteristic for old age; these require adjustment of therapy and a reduced dosage of cytostatics, which entails a lower quality of treatment. In the age groups 20–49 and 50–74 years, in the period from 1991 to 2005, the survival has been steadily increasing along with the use of more radical and effective treatment.

PLAZMOCITOM

MKB 10: C90

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za plazmocitomom zbolelo 1178 ljudi, 527 moških in 651 žensk. Kot je razvidno s Slike 1, se časovni trendi incidenčnih in umrljivostnih stopenj razlikujejo. Incidenca se veča za povprečno 2,9 % letno, umrljivost pa se po velikem skoku med letoma 1991 in 1994 veča povprečno za 2,4 % letno. Incidenca in umrljivost se večata predvsem zaradi staranja prebivalstva, saj se starostno standardizirani stopnji v opazovanem obdobju skoraj nista povečali.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja plazmocitoma, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of plasmacytoma, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1145 primerov; 33 primerov (2,8 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

Mikroskopsko potrjenih je bilo v vseh letih opazovanja 99 % primerov.

V letih 2001–2005 je bilo približno dve tretjini moških in dobra polovica žensk ob diagnozi starih 50–74 let. Bolezen je redka pri mlajših od 50 let, v zadnjem obdobju se je povečal delež žensk, starih 75 let in več (Tabela 1).

Tabela 1: *Število bolnikov s plazmocitomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of plasmacytoma patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	146	6,8	69,2	24,0	181	6,6	68,0	25,4
1996–2000	175	6,9	68,0	25,1	214	4,7	66,8	28,5
2001–2005	195	10,3	67,7	22,1	234	4,7	59,8	35,5

PLASMACYTOMA

ICD 10: C90

EPIDEMIOLOGY

In the period 1991–2005, a total of 1178 persons were diagnosed with plasmacytoma, of these 527 males and 651 females. As evident from Figure 1, the time trends in incidence and mortality rates differ from each other. While the incidence rate has been increasing by 2.9% annually on average, the mortality – after a rapid increase in the period 1991–1994 – has been increasing by 2.4% annually on average. Both, incidence and mortality rates are increasing particularly owing to population aging, since the age-standardized rates have remained almost unchanged in the observation period.

The survival analysis included 1145 cases; 33 patients (2.8%) diagnosed only after death, were not considered in the analysis.

In all the years under observation 99% of cases were microscopically confirmed.

In the period 2001–2005, approximately two thirds of males and a good half of females were aged 50–74 years at diagnosis. The disease rarely occurs in persons under 50 years of age; in the last period the proportion of female patients aged 75 years and older has increased (Table 1).

Plasmacytoma typically appears in a diffuse disseminated form (Table 2). Out of 1445 patients at diagnosis 1118 (89%) had diffuse plasmacytoma, 43 (4%) solitary plasmacytoma of the bone, 36 (3%) solitary plasmacytoma of other organs and 6 (0.5%) plasma-cell leukemia. In 41 patients the type of plasmacytoma was not determined.

In the years 2001–2005, 27% of patients did not receive specific treatment. The proportion of untreated patients was decreasing throughout the study period; among those diagnosed in the period 1991–1995 there were 40% of patients without specific treatment. Among the patients receiving specific treatment in the period 2001–2005, 39% were treated with a combination of cytostatics and corticosteroids, 16% with cytostatics alone, while 12% received radiotherapy in addition to cytostatics or a combination of cytostatics and corticosteroids; 6% patients were only irradiated. Other combinations of treatment were used in less than 5% of the patients. Hematopoietic stem-cell transplantation was performed in 5% of patients. Compared to the period 1991–1995, in last years significantly more patients have been treated with cytostatics and corticosteroids and much less with cytostatics or irradiation as single modality treatment.

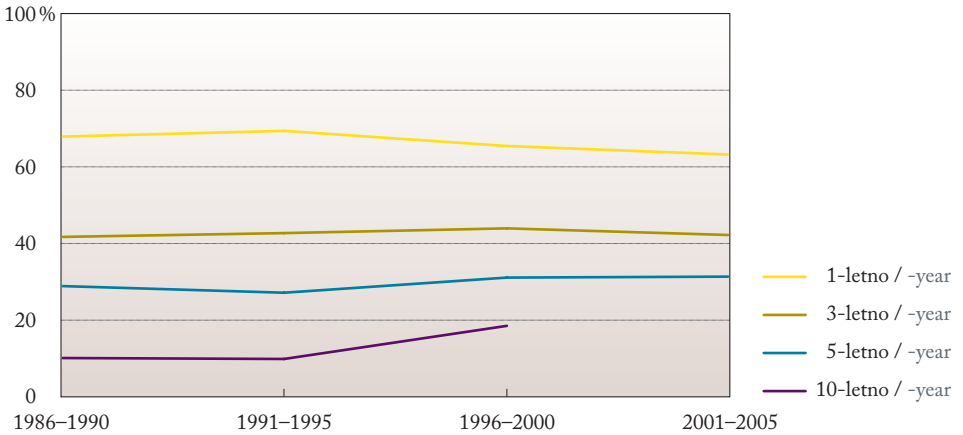
In the period 2001–2005, less than half of patients (45%) started their treatment in the UMC Ljubljana, 17% in the UMC Maribor, 13% at the IO Ljubljana and 10% in the GH Celje. Individual patients also started their treatment in the general hospitals of Nova Gorica, Murska Sobota, Slovenj Gradec, Novo mesto, Izola and Jesenice.

The relative survival rate of patients with plasmacytoma has been gradually increasing: in 15 years, the 5-year relative survival increased by 4% (Figure 2), in males slightly more than in females (Table 3). The relevance of age at diagnosis is shown in Figure 3: the 5-year relative survival

Tabela 2: *Število bolnikov s plazmocitomom po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 2: *Number of plasmacytoma patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	146	1,4	0,7	97,9	0,0	181	0,0	0,0	100,0	0,0
1996–2000	175	4,0	0,6	94,9	0,6	214	0,9	0,5	98,6	0,0
2001–2005	195	3,6	0,5	93,8	2,1	234	0,9	0,0	98,7	0,4



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov s plazmocitomom po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of plasmacytoma patients by period of diagnosis.*

Plazmocitom se tipično pojavlja v razsejani, difuzni obliki (Tabela 2). Med 1445 bolniki jih je imelo ob diagnozi 1118 (89 %) difuzni plazmocitom, 43 (4 %) solitarni plazmocitom kosti, 36 (3 %) solitarni plazmocitom drugih organov in 6 (0,5 %) plazmocitno levkemijo. Pri 41 bolnikih vrsta plazmocitoma ni bila določena.

V letih 2001–2005 ni bilo specifično zdravljenih 27 % bolnikov. Delež nezdravljenih bolnikov se je v celotnem obdobju analize zmanjševal; med bolniki, zbolelimi v obdobju 1991–1995, jih je bilo brez specifičnega zdravljenja 40 %. Med specifično zdravljenimi je bilo v letih 2001–2005 39 % bolnikov zdravljenih s kombinacijo citostatikov in kortikosteroidov, 16 % jih je prejelo le citostatike, po 12 % pa jih je poleg citostatikov ali kombinacije citostatikov in kortikosteroidov bilo še obsevanih; samo obsevanih je bilo 6 % bolnikov. Druge kombinacije zdravljenja so

Tabela 3: *Opazovano in relativno preživetje bolnikov s plazmocitomom po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 3: *Observed and relative survival of plasmacytoma patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	64,4 (57,1–72,6)	43,2 (35,8–52,0)	22,6 (16,7–30,5)	68,5 (62,1–75,6)	33,1 (27,0–40,8)	21,0 (15,8–27,9)
1996–2000	59,4 (52,6–67,2)	38,3 (31,7–46,2)	24,6 (19,0–31,9)	65,4 (59,3–72,1)	38,8 (32,8–45,9)	25,2 (20,0–31,8)
2001–2005	62,6 (56,1–69,7)	40,1 (33,7–47,7)	28,0 (21,8–35,9)	59,0 (53,0–65,6)	34,9 (29,2–41,7)	23,0 (17,7–29,8)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	67,7 (59,1–76,4)	50,5 (40,2–60,9)	29,7 (19,3–40,1)	70,8 (63,4–78,1)	36,8 (28,3–45,3)	25,2 (17,0–33,4)
1996–2000	62,5 (54,4–70,7)	44,8 (35,5–54,0)	32,2 (22,7–41,7)	67,7 (60,8–74,7)	43,2 (35,3–51,1)	30,4 (22,5–38,3)
2001–2005	65,3 (57,8–72,8)	46,1 (37,4–54,9)	35,7 (25,5–45,8)	61,1 (54,2–68,0)	39,2 (31,6–46,9)	27,9 (19,7–36,2)

of patients diagnosed before 50 years of age is 52%, patients diagnosed at an age between 50–74 years had 37% 5-year relative survival while the survival of those aged 75 years and older has decreased to 9% in the last period.

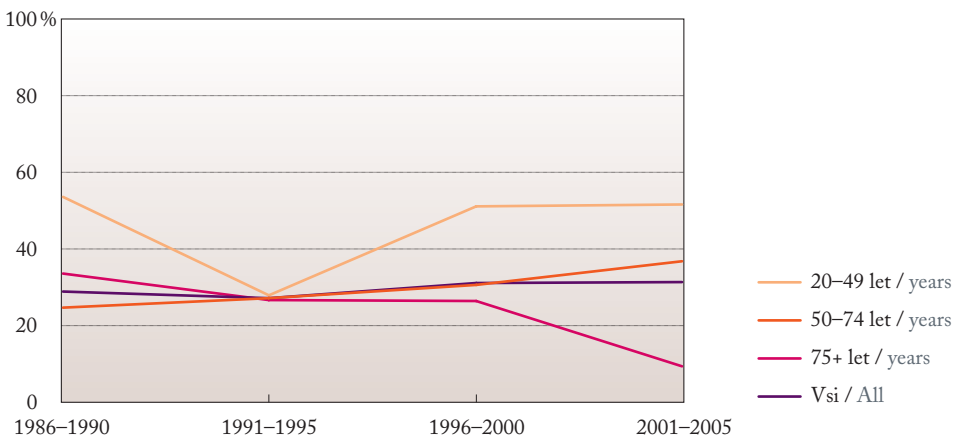
The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 31% (Figure 2); patients surviving the first year may expect to survive five years in 48%.

According to the EUROCARE-4 study results for those diagnosed in the period 2000–2002, the survival of patients with plasmacytoma in Slovenia is statistically significantly below the European average (Figure 4).

CLINICAL COMMENTARY

Samo Zver

There is no reasonable explanation for the fact that in the period 2001–2005 27% of patients with diffuse plasmacytoma were left without specific treatment. Perhaps the doctors have overlooked that specific therapy also includes monotherapy with corticosteroids (this applies to the era before the use of biological agents), which are often the treatment of choice in elderly patients in poor clinical condition (e. g., concomitant extensive pneumonia, acute renal failure or amyloidosis at the time of diagnosis). Equal survival in all the periods under analysis is explainable by an equal treatment approach to diffuse plasmacytoma being used in all time periods. All this time, advances were made only in symptomatic treatment, e. g. by means of new antibiotics, bisphosphonates, erythropoietin and analgesics. In Slovenia, a substantial increase in the number of patients treated by autologous hematopoietic stem-cell transplantation (HSCT) was observed only after the year 2000, while tandem autologous HSCT has been used since 2003. Only in the middle of the last observation period the age limit for autologous HSCT increased from previous 55 years to current 70 years. Moreover, all biological agents (with the exception of few cases of treatment with thalidomide) finally expected to contribute towards a significant increase in the survival of patients with diffuse plasmacytoma, in Slovenia likewise elsewhere in the world have become widely available (outside clinical studies) only after the year 2005. Thus, the best treatment results achieved in all time periods in patients less than 50 years of age are understandable, since this was the very age group that was the first to be treated by autologous HSCT. It is difficult to explain, why the oldest group of patients has had worse results in the last observation period.



Slika 3: *Petletno relativno preživetje bolnikov s plazmocitomom po starosti in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of plasmacytoma patients by age and period of diagnosis.*

uporabili pri manj kot 5 % zbolelih. Petim odstotkom bolnikov so presadili krvotvorne matične celice. V primerjavi z obdobjem 1991–1995 je bilo v zadnjih letih bistveno več bolnikov zdravljenih s citostatiki in kortikosteroidi, bistveno manj pa jih je prejelo le citostatike ali pa samo obsevanje.

Manj kot polovica bolnikov (45 %) je v obdobju 2001–2005 zdravljenje začela v UKC Ljubljana, 17 % v UKC Maribor, 13 % na OI Ljubljana in 10 % v SB Celje. Posamezne bolnike so pričeli zdraviti še v splošnih bolnišnicah v Novi Gorici, Murski Soboti, Slovenj Gradcu, Novem mestu, v Izoli in na Jesenicah.

Relativno preživetje bolnikov s plazmocitomom se le postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 4 % (Slika 2), pri moških nekoliko več kot pri ženskah (Tabela 3). Kako pomembna je starost ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov, zbolelih pred 50. letom, je 52 %, bolniki, zboleli v starosti 50–74 let imajo petletno relativno preživetje 37 %, medtem ko se je preživetje starih 75 let in več v zadnjem obdobju zmanjšalo na 9 %.

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 31 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 48-odstotno petletno relativno preživetje.

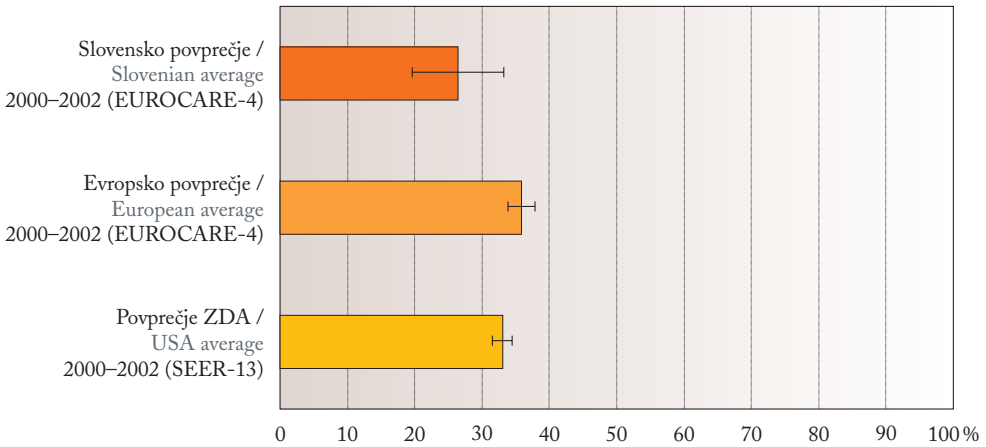
Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov s plazmocitomom statistično značilno manjše od evropskega povprečja (Slika 4).

KLINIČNI KOMENTAR

Samo Zver

Za podatek, da specifičnega zdravljenja v obdobju 2001–2005 ni bilo deležnih 27 % bolnikov z difuznim plazmocitomom, ni moč najti prave razlage. Morda so zdravniki spregledali, da k specifičnemu zdravljenju sodi tudi monoterapija s kortikosteroidi (gre za obdobje pred biološkimi zdravili), ki so pogosto zdravilo izbire pri starejših bolnikih v slabem kliničnem stanju (npr. ob postavitvi diagnoze bolezni in sočasni obsežni pljučnici, akutni ledvični odpovedi ali pridruženi amiloidozi). Enako preživetje v vseh analiziranih obdobjih je razložljivo z enakim načinom zdravljenja difuznega plazmocitoma v vseh obdobjih. Ves ta čas se je izboljševalo le simptomatsko ukrepanje, npr. z novimi antibiotiki, bisfosfonati, eritropoetini in s protibolečinskimi zdravili. Šele po letu 2000 je v Sloveniji začelo občutneje naraščati število bolnikov, zdravljenih z avtologno presaditvijo krvotvornih matičnih celic (PKMC), tandemsko avtologno PKMC pa izvajamo od leta 2003. Šele nekje v sredini zadnjega opazovanega obdobja se je dvignila tudi starostna meja za zdravljenje z avtologno PKMC s 55 let na zdaj okoli 70 let. Tudi vsa biološka zdravila (z izjemo nekaj primerov zdravljenja s talidomidom), od katerih si po dolgih letih obetamo značilno povečanje preživetja bolnikov z difuznim plazmocitomom, so v Sloveniji, kot tudi drugod po svetu, postala širše dostopna (zunaj kliničnih raziskav) šele po letu 2005. Najboljši rezultati zdravljenja pri bolnikih, mlajših od 50 let, v vseh obdobjih so razumljivi, saj smo prav to starostno skupino pričeli najprej zdraviti z avtologno PKMC. Zakaj ima v zadnjem obdobju najstarejša skupina bolnikov slabše rezultate, je težko pojasniti.

Difuzni plazmocitom je neozdravljiva bolezen, lahko pa jo za daljše obdobje zazdravimo. Najbolj učinkovit način zdravljenja je tandemska (dvojna) avtologna PKMC, ki jo v Sloveniji opravljamo od leta 2003. Zdravljenje poteka na Kliničnem oddelku za hematologijo UKC Ljubljana, zdravimo pa vse bolnike v Sloveniji, ki so za zdravljenje primerni. Lastna analiza zdravljenih bolnikov v štiriletnem obdobju (2003–2006) je pokazala povprečno preživetje 50,2 meseca, srednje preživetje pa v opazovanem obdobju še ni bilo doseženo. Naši rezultati zdravljenja z avtologno PKMC so povsem primerljivi z rezultati zdravljenja v ostalih velikih evropskih in ameriških centrih. Preživetje po PKMC verjetno lahko še dodatno povečamo z vzdrževalnim zdravljenjem ali zdravljenjem ponovitve bolezni po PKMC z novimi biološkimi zdravili (talidomid, bortezomib, lenalidomid).



Slika 4: *Petletno relativno preživetje bolnikov s plazmocitomom (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 4: *5-year relative survival of plasmacytoma patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

Diffuse plasmacytoma is an incurable disease, though treatment may result in a long-term remission. The most effective treatment is tandem autologous HSCT, which has been performed in Slovenia since 2003. The treatment is carried out at the Department of Hematology of the UMC Ljubljana in all patients assessed as suitable candidates for this type of treatment. Our own analysis of patients treated in the four-year period from 2003 to 2006 has revealed an average survival of 50.2 months, while the median survival in the period under observation has not been reached yet. Our treatment results obtained by autologous HSCT are fully comparable with the results of treatment in other large European and American centers. Post-HSCT survival could possibly be further improved by maintenance therapy or by treatment of recurrences following HSCT using new biological agents (thalidomide, bortezomib and lenalidomide).

The fact is that diffuse plasmacytoma is prevailingly a disease of the elderly (Table 1). The provisional age limit for autologous HSCT is 70 years. For many years, AP (melphalan, prednisolone) and VAD (vincristine, pharmarubicin, dexamethason) schedules were the standards of treatment in elderly patients. In patients treated with AP and VAD, the median survival probability is 33.4 months (own data). In recent years, patients over 70 years of age and those who are not candidates for autologous HSCT due to concomitant diseases are treated with new biological agents, such as thalidomide, bortezomib and lenalidomide. As a rule, the treatment is started in the case of AP or VAD failure (2nd or 3rd line therapy) and is combined with corticosteroids. More detailed analyses of the survival of patients treated subsequently also with thalidomide and/or bortezomib and lenalidomide are still underway. The reason for that is mainly in the short observation period and a small number of patients included in the analysis. It seems, however, that every new therapeutic approach may extend the survival for another 4–6 months.

Elderly patients with disseminated plasmacytoma are treated in a majority of Slovenian general hospitals. The latter information is important in view of the fact that in a majority of peripheral Slovenian hospitals access to new biological drugs (thalidomide, lenalidomide, bortezomib and finally also arsenic trioxide) is difficult if not straightforward impossible. The main obstacle is the extremely high price of new biological drugs and well-known financial problems of hospitals. Only by providing an equal access to up-to-date therapeutic modalities for

Dejstvo je, da je difuzni plazmocitom predvsem bolezen starejših ljudi (Tabela 1). Okvirna starostna meja za zdravljenje z avtologno PKMC je 70 let. Standard zdravljenja pri starejših bolnikih sta vrsto let predstavljali shemi AP (melfalan, prednizolon) in VAD (vinkristin, farmarubicin, deksametazon). Pri bolnikih, zdravljenih z AP in VAD, je verjetnost srednjega preživetja 33,4 meseca (lastni podatki). Bolnike, ki so starejši od 70 let, in tiste, ki zaradi spremljajočih bolezenskih stanj niso kandidati za avtologno PKMC, zdravimo v zadnjih letih z novejšimi biološkimi zdravili, kot so talidomid, bortezomib in lenalidomid. Z zdravljenjem praviloma začenjamo v primeru neučinkovitosti AP ali VAD (zdravljenje drugega ali tretjega reda) in ga kombiniramo s kortikosteroidi. Natančnejše analize preživetja bolnikov, zdravljenih naknadno še z talidomidom in/ali bortezomibom in/ali lenalidomidom, so še v teku. Razlog je predvsem kratko obdobje opazovanja in tudi manjše število vključenih bolnikov. Zdi pa se, da z vsakim novim načinom zdravljenja lahko še dodatno podaljšamo življenje za 4–6 mesecev.

Starejši bolniki z diseminiranim plazmocitom se zdravijo v večini slovenskih bolnišnic. Slednje je pomemben podatek, saj je dostop do novih bioloških zdravil (talidomid, lenalidomid, bortezomib in nenazadnje tudi arzenov trioksid) v večini območnih slovenskih bolnišnic otežen, če ne celo nemogoč. Ovira je seveda izjemno visoka cena novih bioloških zdravil in znane spremljajoče finančne težave bolnišnic. Samo pri enaki dostopnosti sodobnih terapevtskih sredstev za vse starejše bolnike v Sloveniji (pa tudi tiste z relapsom bolezni po avtologni PKMC) si lahko obetamo tudi izboljšanje preživetja na populacijski ravni. Obstaja pa še en problem. Kar nekaj slovenskih bolnišnic nima zaposlenega hematologa, kar nedvomno vpliva na zgodnje odkrivanje difuznega plazmocitoma in kasneje tudi na zdravljenje bolnikov s to boleznijo.

VIRI
Literature

Kabaklić A, Černelč P. Ocena uspešnosti enajstletnega zdravljenja starejših bolnikov z diseminiranim plazmocitomom. Zdrav Vestn 2008; 77: I-81–85.

Zver A, Zver S, Mlakar U, Zupan IP, Pretnar J. Zdravljenje bolnikov z diseminiranim plazmocitomom s tandemsko avtologno presaditvijo krvotvornih matičnih celic v Sloveniji. Zdrav Vestn 2008; 77: I-75–80.

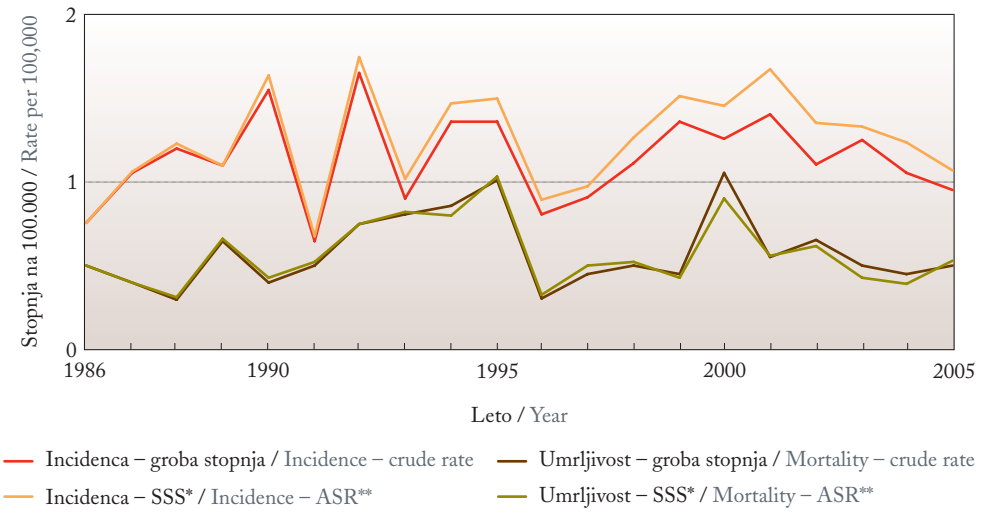
all elderly patients in Slovenia (as well as for those with recurrence after autologous HSCT) we may hope to improve the survival at the population level. However, there is yet another problem: quite a few Slovenian hospitals lack a qualified haematologist, which undoubtedly affects early detection of diffuse plasmacytoma and subsequently also the treatment of patients with this disease.

AKUTNA LIMFOBLASTNA LEVKEMIJA

MKB 10: C91.0

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za akutno limfoblastno levkemijo (ALL) zbolelo 417 ljudi, 235 moških in 182 žensk. Kot je razvidno s Slike 1, se incidenca veča; groba stopnja za povprečno za 0,8 % letno, starostno standardizirana pa za povprečno 1,4 % letno. Umrljivost se manjša, groba stopnja za povprečno 2,1 %, starostno standardizirana pa za povprečno 2,8 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja akutne limfoblastne levkemije, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of acute lymphoblastic leukaemia, Slovenia 1986–2005.*

V analizo preživetja je vključenih 156 primerov; 5 primerov (1,2 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 256, mlajših od 20 let ob diagnozi, pa obravnavamo v poglavju o otroških levkemijah.

Vsi v analizo vključeni primeri so bili mikroskopsko potrjeni.

Tabela 1: *Število bolnikov z akutno limfoblastno levkemijo po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of acute lymphoblastic leukaemia patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	24	50,0	41,7	8,3	30	33,3	53,3	13,3
1996–2000	21	47,6	42,9	9,5	22	45,5	40,9	13,6
2001–2005	34	50,0	41,2	8,8	25	20,0	64,0	16,0

ACUTE LYMPHOBLASTIC LEUKEMIA

ICD 10: C91.0

EPIDEMIOLOGY

In the period 1991–2005, a total of 417 persons were diagnosed with acute lymphoblastic leukemia (ALL), of these 235 males and 182 females. As evident from Figure 1, the incidence rate is increasing. The estimated annual percentage increase in crude incidence rate was 0.8% and in age standardized rate 1.4%. The mortality rate is decreasing, the estimated annual percentage decrease in crude mortality rate was 2.1% and 2.8% in age-standardized rate.

The survival analysis included 156 cases; 5 cases (1.2%) diagnosed only after death, were not considered in the analysis; 256 patients under 20 years of age at diagnosis are presented in the chapter on childhood leukemias.

All cases under analysis were microscopically confirmed.

Half of the male patients are younger than 50 years at diagnosis; patients aged 75 years and older are rare. Approximately two thirds of female patients are aged 50–74 years at diagnosis, while the proportions of younger and older patients are approximately equal (Table 1).

In the years 2001–2005, 20% of patients did not receive specific treatment. The proportion of untreated patients was decreasing throughout the duration of analysis; among those diagnosed in the period 1991–1995 there were 61% of patients without specific treatment. Among the patients receiving specific treatment in the period 2001–2005, 81% were treated by cytostatics with or without corticosteroids, 10% were irradiated in addition to chemotherapy. Irradiation alone was used in 6% of patients; a combination of cytostatics, corticosteroids and irradiation or treatment with corticosteroids alone was applied in less than 5% of patients.

In the period 2001–2005, 83% started their treatment in the UMC Ljubljana, 10% at the IO Ljubljana, while 3 patients were treated respectively in general hospitals of Brežice, Celje and Izola (one in each).

The relative survival of patients with ALL has been gradually increasing: in 15 years, the 5-year relative survival increased by 10% (Figure 2), in females slightly more than in males (Table 2). The relevance of age at diagnosis is shown in Figure 3: the 5-year relative survival of patients diagnosed before 50 years of age is 41%, patients diagnosed at an age between 50–74 years had 7% 5-year relative survival in the last period, while those aged 75 years and more do not survive five years from diagnosis.

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 23% (Figure 2); patients surviving the first year may expect to survive five years in 50%.

According to the results of EUROCARE-4 study of patients diagnosed in 2000–2002, the survival of Slovenian patients with ALL is above (statistically not significant) the European average (Figure 4).

CLINICAL COMMENTARY

Mojca Modic

Acute lymphoblastic leukemia is a childhood disease. In childhood it has a very favorable prognosis and its biological course is totally different than in adults. In adult patients unfavorable cytogenetic changes in the bone marrow are prevailing (30% of patients present with Philadelphia chromosome); besides patient age, number of leukocytes at diagnosis and immunological type, these changes are one of the most relevant prognostic factors. The majority of adult patients

Med moškimi je polovica zbolelih ob diagnozi mlajša od 50 let, bolniki, stari 75 let in več, pa so redki. Približno dve tretjini žensk je ob diagnozi starih od 50 do 74 let, medtem ko je delež mlajših in starejših približno enak (Tabela 1).

V letih 2001–2005 ni bilo specifično zdravljenih 20 % bolnikov. Delež nezdravljenih se je vse obdobje analize zmanjševal; med bolniki, zbolelimi v obdobju 1991–1995, jih je bilo brez specifičnega zdravljenja 61 %. Med specifično zdravljenimi je bilo v letih 2001–2005 81 % bolnikov zdravljenih s citostatiki s kortikosteroidi ali brez, 10 % pa je bilo poleg citostatikov še obsevanih. Samo obsevanih je bilo 6 % bolnikov, kombinacijo citostatikov, kortikosteroidov in obsevanja ali pa samo zdravljenje s kortikosteroidi je prejelo manj kot 5 % bolnikov.

V obdobju 2001–2005 se je 83 % bolnikov pričelo zdraviti v UKC Ljubljana, 10 % na OI Ljubljana, po 1 bolnik pa v splošnih bolnišnicah v Brežicah, Celju in Izoli.

Relativno preživetje bolnikov z ALL se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 10 % (Slika 2), pri ženskah nekoliko več kot pri moških (Tabela 2). Kako pomembna je starost ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov, zbolelih pred 50. letom, je 41 %, bolniki, stari 50–74 let, so imeli v zadnjem obdobju petletno relativno preživetje 7 %, medtem ko bolniki, stari 75 let in več, ne živijo pet let po diagnozi.

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 23 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 50-odstotno petletno relativno preživetje.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z ALL statistično neznačilno večje od evropskega povprečja (Slika 4).

KLINIČNI KOMENTAR

Mojca Modic

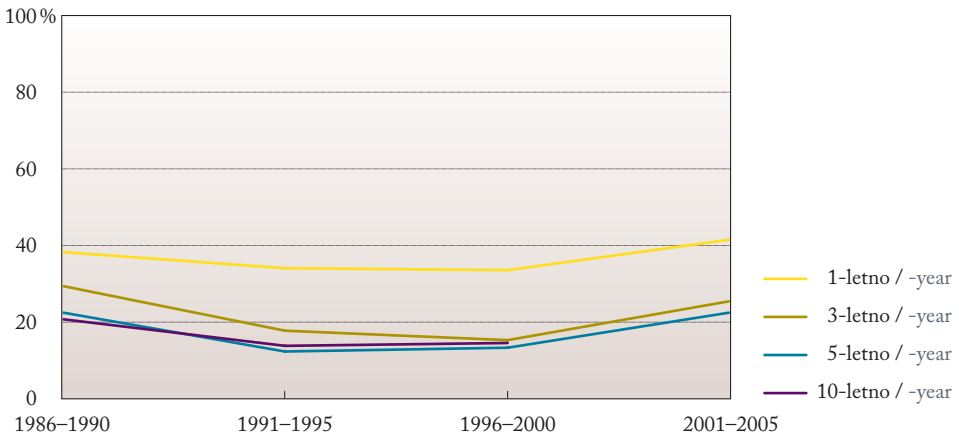
Akutna limfoblastna levkemija je bolezen otrok. V otroški dobi ima zelo ugoden izid in je biološko povsem drugačna bolezen kot pri odraslih. Pri odraslih bolnikih prevladujejo neugodne citogenetske spremembe v kostnem mozgu (30 % bolnikov ima kromosom Philadelphia), ki so poleg starosti bolnika, števila levkocitov ob odkritju bolezni in imunološkega tipa eden

Tabela 2: *Opazovano in relativno preživetje bolnikov z akutno limfoblastno levkemijo po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 2: *Observed and relative survival of acute lymphoblastic leukaemia patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	37,5 (22,4–62,9)	20,8 (9,6–45,4)	12,5 (4,3–36,0)	30,0 (17,4–51,8)	13,3 (5,4–33,2)	10,0 (3,4–29,3)
1996–2000	42,9 (26,2–70,2)	28,6 (14,5–56,2)	23,8 (11,1–51,2)	22,7 (10,5–49,1)	0,0	0,0
2001–2005	41,2 (27,6–61,5)	26,5 (15,1–46,4)	20,6 (10,6–39,8)	40,0 (24,7–64,6)	20,0 (9,1–43,8)	20,0 (9,1–43,8)

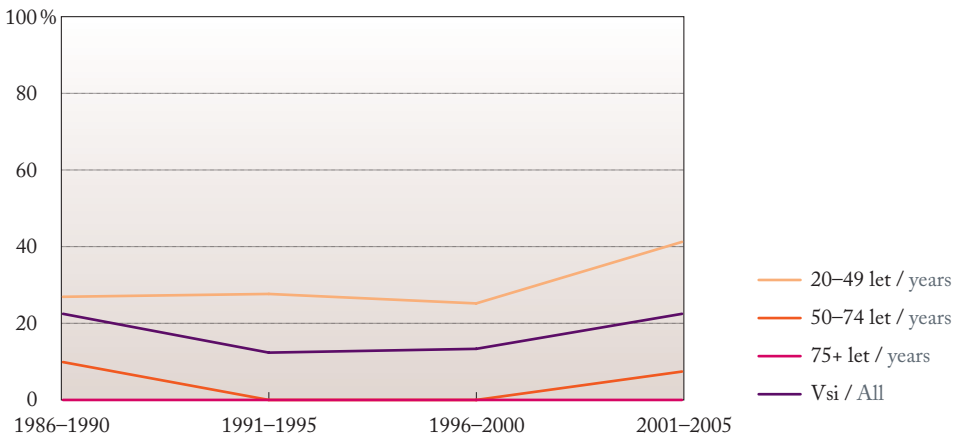
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	38,3 (12,4–64,3)	22,4 (0,0–48,8)	14,0 (0,0–40,3)	30,6 (8,3–52,8)	14,2 (0,0–35,3)	11,0 (0,0–32,2)
1996–2000	44,1 (16,0–72,3)	31,3 (1,1–61,6)	27,8 (0,0–59,7)	23,3 (0,0–50,3)	0,0	0,0
2001–2005	42,1 (21,3–63,0)	28,0 (7,0–49,1)	23,1 (1,5–44,6)	40,8 (15,6–65,9)	21,0 (0,0–46,0)	22,0 (0,0–48,1)



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z akutno limfoblastno levkemijo po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of acute lymphoblastic leukaemia patients by period of diagnosis.*

with ALL, intended to undergo an intensive cytostatics treatment and afterwards either related or unrelated allogeneic or autologous stem cell transplantation, are referred to the Department of Hematology of the UMC Ljubljana. This is the only center for stem cell transplantation in Slovenia. In order to achieve remission in these patients a combination of cytostatics, such as daunorubicin, cytosinarabinosid, vincristine, L-asparaginase and dexamethason, is used. In patients – candidates for stem-cell transplantation, a prophylaxis of the central nervous system with cranial irradiation and intrathecal injections of cytosar and methotrexate is considered. Patients older than 65 years, in whom intensive cytostatics therapy is not feasible, are treated at hematology department of other Slovenian general hospitals. In these patients, a symptomatic treatment with transfusions, low doses of corticosteroids, purinethol, methotrexate or alkeran is chosen instead. New antibiotics, antimycotics, cytokines and immunosuppressive medications contributed to an increase in the survival of these patients in last years. But nevertheless, the mortality of patients older than 65 years, particularly due to other septic infections and



Slika 3: *Petletno relativno preživetje bolnikov z akutno limfoblastno levkemijo po starosti in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of acute lymphoblastic leukaemia patients by age and period of diagnosis.*

najpomembnejših napovednih dejavnikov. Večina odraslih bolnikov z ALL, pri katerih se odločimo za intenzivno citostatsko zdravljenje in kasnejšo sorodno ali nesorodno alogenično ali avtologno presaditev krvotvornih matičnih celic, pride na hematološki oddelek UKC Ljubljana. To je tudi edini center za presaditev krvotvornih matičnih celic v Sloveniji. Pri teh bolnikih uporabljamo za doseganje remisije kombinacije citostatikov, kot so daunorubicin, citozinarabinozid, vinkristin, L-asparaginaza in deksametazon. Pri bolnikih, pri katerih se ne odločamo za presaditev, pride v poštev profilaksa centralnega živčnega sistema z obsevanjem glave in intratekalnimi injekcijami citozarja ter metotreksata. Bolniki, starejši od 65 let, pri katerih intenzivno citostatsko zdravljenje ne prihaja v poštev, se zdravijo na hematoloških oddelkih v drugih bolnišnicah po Sloveniji. Pri njih se pogosto odločajo za simptomatsko zdravljenje s transfuzijami, nizkimi odmerki kortikosteroidov, purinetola, metotreksata ali alkerana. Zaradi novih antibiotikov, antimikotikov, citokinov in imunosupresivnih zdravil se preživetje bolnikov v zadnjih letih povečuje. Še vedno pa je umrljivost bolnikov, starejših od 65 let, velika, predvsem zaradi septičnih okužb in sočasnih bolezni srca ter pljuč. V retrospektivni analizi bolnikov, zdravljenih pri nas v letih 2000–2007, se je izkazalo, da smo pri 41 bolnikih z ALL v starosti od 17 do 68 let s protokolom UKALL XII dosegli remisijo bolezni pri 81 %; petletno preživetje teh bolnikov je bilo 48 %. V tej skupini bolnikov smo kasneje naredili 5 sorodnih alogeničnih presaditev, 4 nesorodne alogenične presaditve in 9 avtolognih presaditev krvotvornih matičnih celic.

VIRI
Literature

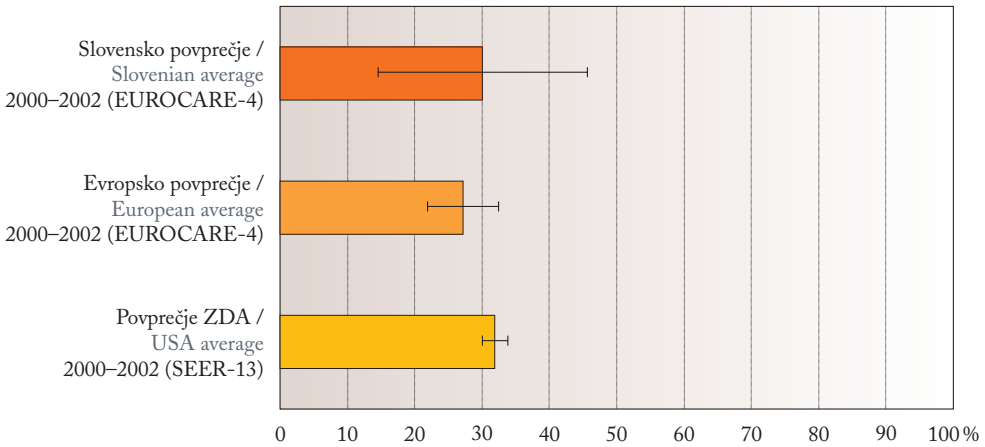
Hoelzer D, Thiel E, Loffler H, Buchner T, Ganser A, Heilet G, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblasic leukemia in adults. Blood 1988; 86: 123–31.

Modic M. Zdravljenje akutne limfoblastne levkemije odraslih s protokolom UKALL XII. Med Razgl 2000; 39 S5: 109–16.

Modic M, Skerget M. Uspeh zdravljenja akutne limfoblastne levkemije odraslih s protokolom UKALL XII na Hematološkem oddelku v Ljubljani. Zdrav Vestn 2008; 77: I-37–42.

Moorman AV, Harrison CJ, Buck GAN, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblasic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical research Council (MRC) UKALL XII/Eastern Cooperative Oncology Group (ECOG) 2993 Trial. Blood 2007; 105: 3189–97.

Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richardset SM, et al. Induction therapy for adults with acute lymphoblasic leukaemia: results of more than 1500 patients from the international ALL trial: MRC UKALL-XII/ECOG E2993. Blood 2005; 103: 3760–7.



Slika 4: *Petletno relativno preživetje bolnikov z akutno limfoblastno levkemijo (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 4: *5-year relative survival of acute lymphoblastic leukaemia patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

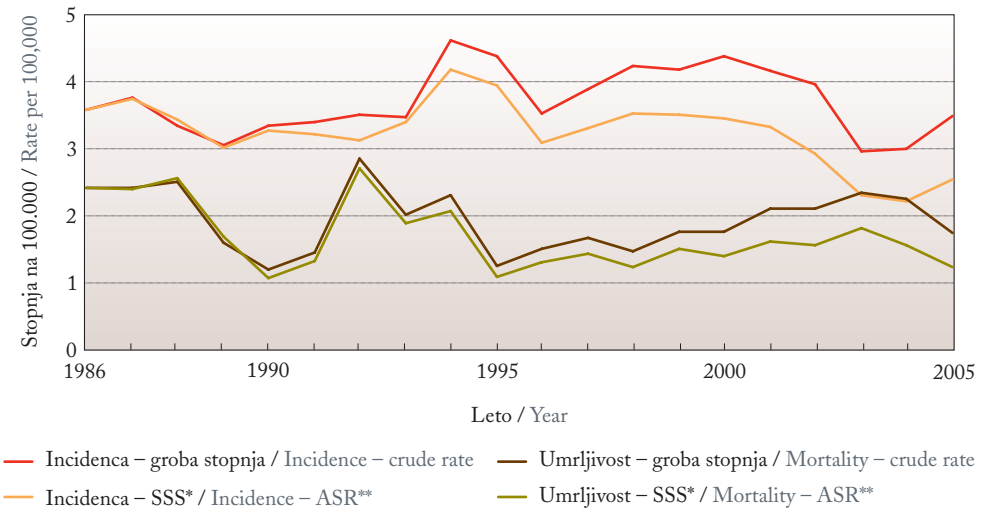
concomitant cardiac and pulmonary diseases, is still high. A retrospective analysis of patients treated in Slovenia in the years 2000–2007 showed that the use of UKALL XII protocol in 41 ALL patients aged 17–68 years resulted in a remission of the disease in 81%, while 5-year survival of these patients was 48%. Afterwards, 5 related allogeneic transplantations, 4 unrelated allogeneic transplantations and 9 autologous transplantations of stem cells were performed in this group of patients.

KRONIČNA LIMFOCITNA LEVKEMIJA

MKB 10: C91.1

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za kronično limfocitno levkemijo (KLL) zbolelo 1174 ljudi, 660 moških in 514 žensk. Kot je razvidno s Slike 1, se časovni trendi incidenčnih in umrljivostnih stopenj razlikujejo. Groba umrljivostna stopnja kaže rastoč trend; veča se povprečno za 0,8 % letno. V celotnem obdobju se incidenčni stopnji manjšata, groba incidenčna stopnja za 0,7 % povprečno letno. Takšno zmanjševanje incidence je nekoliko presenetljivo in je verjetno posledica po eni strani pomanjkljivosti v registraciji številnih nezdravljenih bolnikov s KLL, po drugi strani pa tudi natančnejše diagnostike, ki je omenjena v kliničnem komentarju.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja kronične limfocitne levkemije, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of chronic lymphocytic leukaemia, Slovenia 1986–2005.*

Tabela 1: *Število bolnikov s kronično limfocitno levkemijo po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of chronic lymphocytic leukaemia patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	208	5,3	64,4	30,3	178	5,1	62,4	32,6
1996–2000	238	8,4	68,9	22,7	163	5,5	58,9	35,6
2001–2005	196	8,2	62,2	29,6	155	4,5	46,5	49,0

CHRONIC LYMPHOCYTIC LEUKEMIA

ICD 10: C91.1

EPIDEMIOLOGY

In the period 1991–2005, a total of 1174 persons were diagnosed with chronic lymphocytic leukemia (CLL), of these 660 males and 514 females. As evident from Figure 1, the time trends in incidence and mortality rates differ from each other. Crude mortality rate has an increasing trend; it is increasing by 0.8% annually on average. Incidence rates have been decreasing throughout the observation period however, the crude rate by 0.7% annually on average. Such a downward trend in the incidence is somewhat surprising and is probably attributable to lacking registration of a number of untreated patients with CLL on the one hand and to more accurate diagnostics, as mentioned in the clinical comment, on the other.

The survival analysis included 1138 cases; 36 patients (3.1%) diagnosed only after death, were not considered in the analysis.

All cases under analysis were microscopically confirmed.

The disease rarely occurs in persons under 50 years of age. Almost two thirds of male patients are aged 50–74 years at diagnosis, the rest of them are mostly aged 75 years and older. In females, in the last period there was a significant increase in the proportion of those diagnosed in the oldest age group, so that currently approximately half of all patients are aged 50–74 years at diagnosis, while the other half are aged 75 years and older (Table 1).

The course of disease being benign, patients with CLL are rarely given specific treatment; in the period 2001–2005 25% of patient received such treatment. The proportion of untreated patients has remained approximately the same throughout the period under analysis. Among the patients receiving specific treatment in the period 2001–2005, 49% received cytostatics and corticosteroids, 31% cytostatics alone, while 20% were treated only by radiotherapy or by radio- and chemotherapy.

In the period 2001–2005, 31% of patients started their treatment at the IO Ljubljana, 20% in GH Celje, 17% in the UMC Ljubljana and 13% in the UMC Maribor. Individual patients were also treated in the general hospitals of Novo mesto, Slovenj Gradec, Murska Sobota and Nova Gorica.

The relative survival rate of patients with CLL has been increasing at a slow rate: in 15 years, the 5-year relative survival increased by 2% (Figure 2), in males more than in females (Table 2). Age is a prognostic factor as well, since the 5-year relative survival in patients aged 75 years and more is lower than in younger patients (Figure 3).

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 62% (Figure 2); patients surviving the first year may expect to survive five years in 72%.

According to the results of EUROCARE-4 study of patients diagnosed in 2000–2002, the survival of patients with CLL in Slovenia is below (statistically not significant) the European average (Figure 5).

CLINICAL COMMENTARY

Peter Černelč

Chronic lymphocytic leukemia is a disease that is treated at the IO Ljubljana as well as at the UMC Ljubljana, UMC Maribor and at smaller regional hospitals. The fact that patients are treated in different places throughout the country slightly affects the treatment results. A decrease in the number of patients was to a certain extent expected since new diagnostic methods enable

V analizo preživetja je vključenih 1138 primerov; 36 primerov (3,1 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti.

Vsi v analizo vključeni primeri so bili mikroskopsko potrjeni.

Bolezen je redka pri mlajših od 50 let. Pri moških je skoraj dve tretjini bolnikov ob diagnozi starih 50–74 let, večina ostalih pa 75 let in več. Pri ženskah se je v zadnjem obdobju bistveno povečal delež zbolelih v najstarejši starostni skupini, tako da je sedaj približno polovica vseh bolnic ob diagnozi stara 50–74 let, polovica pa je stara 75 let in več (Tabela 1).

Ker je potek bolezni benigen, so bolniki s KLL le redko specifično zdravljeni; v letih 2001–2005 je bilo specifično zdravljenih 25 % bolnikov. Delež nezdravljenih ostaja v celotnem obdobju analize približno enak. Med specifično zdravljenimi je bilo v letih 2001–2005 49 % bolnikov zdravljenih s citostatiki in kortikosteroidi, 31 % je prejelo samo citostatike, ostalih 20 % pa je bilo samo obsevanih ali pa so bili zdravljeni z radio- in kemoterapijo.

V obdobju 2001–2005 se je 31 % bolnikov pričelo zdraviti na OI Ljubljana, 20 % v SB Celje, 17 % v UKC Ljubljana in 13 % v UKC Maribor. Posamezne bolnike so zdravili še v splošnih bolnišnicah v Novem mestu, Slovenj Gradcu, Murski Soboti in v Novi Gorici.

Relativno preživetje bolnikov s KLL se le počasi veča; v 15 letih se je petletno relativno preživetje povečalo za 2 % (Slika 2), bolj pri moških kot pri ženskah (Tabela 2). Napovedni dejavnik je tudi starost, saj je petletno relativno preživetje starih 75 let in več manjše od preživetja mlajših bolnikov (Slika 3).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 62 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 72-odstotno petletno relativno preživetje.

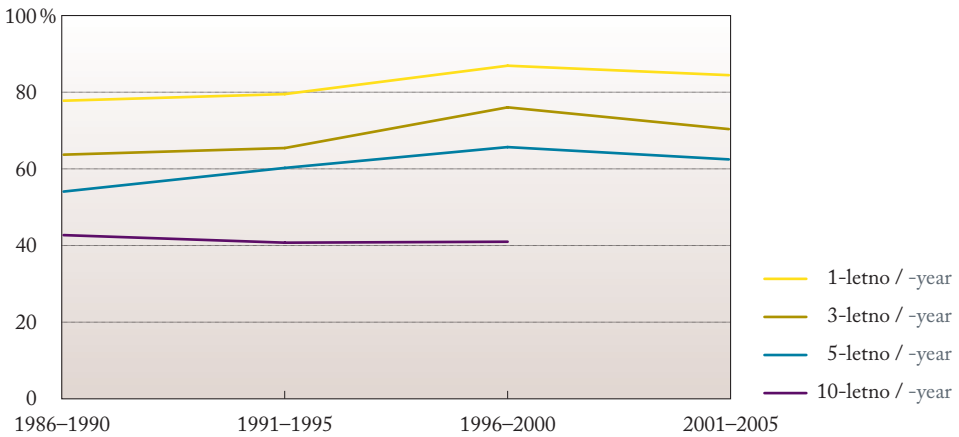
Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov s KLL statistično neznačilno manjše od evropskega povprečja (Slika 4).

Tabela 2: *Opazovano in relativno preživetje bolnikov s kronično limfocitno levkemijo po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 2: *Observed and relative survival chronic lymphocytic leukaemia patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	74,0 (68,3–80,2)	49,0 (42,7–56,3)	39,4 (33,3–46,7)	77,0 (71,0–83,4)	62,9 (56,2–70,4)	52,8 (46,0–60,7)
1996–2000	81,5 (76,7–86,6)	66,8 (61,1–73,1)	52,1 (46,1–58,9)	84,7 (79,3–90,4)	63,8 (56,8–71,6)	49,7 (42,6–58,0)
2001–2005	80,6 (75,3–86,3)	59,0 (52,4–66,4)	44,5 (37,3–53,0)	79,4 (73,2–86,0)	61,0 (53,8–69,3)	50,8 (42,9–60,1)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	78,6 (72,0–85,2)	58,9 (50,2–67,7)	54,0 (44,1–63,9)	80,5 (73,8–87,3)	72,4 (63,7–81,0)	66,9 (56,9–76,9)
1996–2000	85,4 (80,1–90,7)	77,7 (70,4–85,0)	67,7 (58,9–76,5)	88,5 (82,5–94,4)	73,4 (64,4–82,4)	63,0 (52,5–73,6)
2001–2005	85,2 (79,2–91,3)	70,2 (61,4–79,1)	59,9 (48,4–71,5)	83,1 (76,1–90,0)	70,7 (61,2–80,2)	65,5 (53,5–77,6)

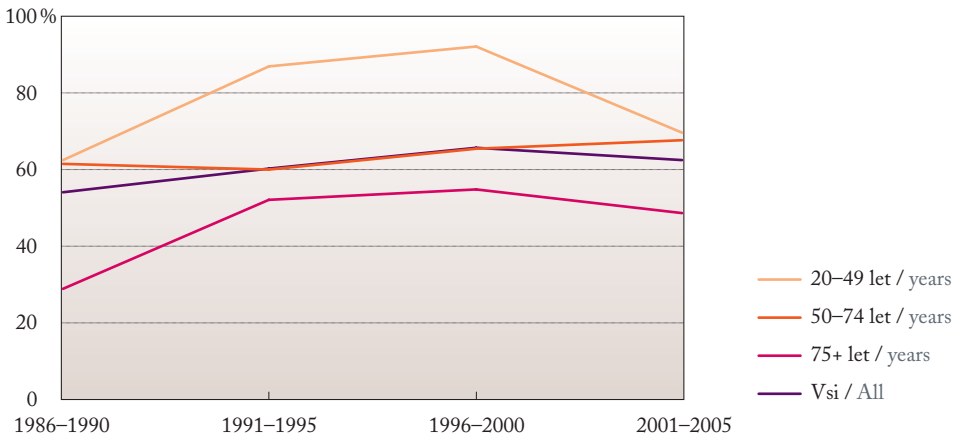


Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov s kronično limfocitno levkemijo po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of chronic lymphocytic leukaemia patients by period of diagnosis.*

us to differentiate CLL from other lymphomas more accurately. But nevertheless, the complete diagnosis for differentiation of CLL from other lymphomas is not carried out until progression of the disease, since 50–60% of patients are detected incidentally because of absolute lymphocytosis in the blood, which in most cases does not require treatment.

Despite some new medications for the treatment of CLL, such as alemtusumab and rituximab in combination with chemotherapy, their influence on the survival of patients is not reflected in the present survival analyses, since they have been used only in recent years. As for the medications used so far, such as fludarabin in combination with other cytostatics, they are known to influence the patients' quality of life, but their impact on their survival is negligible.



Slika 3: *Petletno relativno preživetje bolnikov s kronično limfocitno levkemijo po starosti in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of chronic lymphocytic leukaemia patients by age and period of diagnosis.*

KLINIČNI KOMENTAR

Peter Černelč

Kronična limfocitna levkemija je bolezen, ki jo zdravijo onkologi na OI Ljubljana in hematologi, ki delujejo v UKC Ljubljana, UKC Maribor in v manjših bolnišnicah. Dejstvo, da bolnike obravnavajo na več mestih v državi, praviloma nekoliko poslabša uspešnost zdravljenja. Zmanjšanje števila bolnikov je bilo do neke mere pričakovano, saj lahko z novejšo diagnostiko natančneje razmejimo KLL od drugih limfomov. Kljub temu pa celotne diagnostike za razmejitev KLL od drugih limfomov do napredovanja bolezni ne izvajamo, saj 50–60 % bolnikov odkrijemo slučajno zaradi absolutne limfocitoze v krvi, ki je pri večini ni treba zdraviti.

Kljub temu, da je nekaj novih zdravil za zdravljenje KLL, kot sta alemtuzumab in rituksimab v kombinaciji s kemoterapijo, njihovega vpliva na preživetje bolnikov še ni zaznati pri tokratnih prikazih preživetja, saj jih uporabljamo šele zadnja leta. Za doslej uporabljena zdravila, kot sta fludarabin v kombinaciji z drugimi citostatiki, pa je znano, da vpliva predvsem na kakovost življenja, neznatno pa na preživetje.

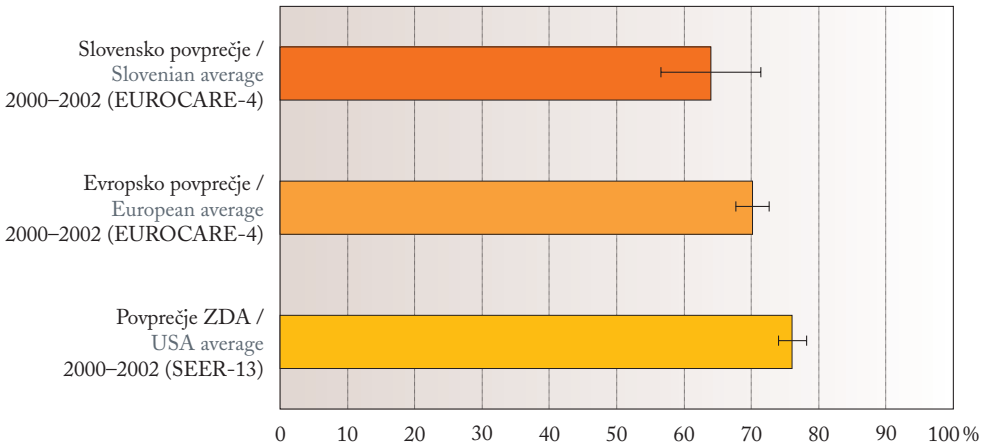
Zaenkrat je najpomembnejši dejavnik, ki vpliva na večje preživetje, predvsem starejših bolnikov s KLL, ki imajo sočasno še druge bolezni, simptomatično zdravljenje zapletov, v prvi vrsti okužb, ki jih je potrebno začeti zdraviti takoj, že v osnovnem zdravstvu.

VIRI

Literature

Černelč P, Modic M. Pomen novejših bioloških kazalcev za oceno prognoze pri bolnikih s kronično limfocitno levkemijo. In: Križman I, ed. Interna medicina 2005 – novosti in aktualnosti: zbornik predavanj. Ljubljana: Slovensko zdravniško društvo, Združenje internistov; 2005.

Pajič T, Černelč P. Ugotavljanje mutacijskih sprememb v variabilnih genih preurejenih genov za težko verigo imunoglobulina pri bolnikih s kronično limfocitno levkemijo. Zdrav Vestn 2008; 77 Suppl 1: I-69–I-74.



Slika 4: *Petletno relativno preživetje bolnikov s kronično limfocitno levkemijo (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 4: *5-year relative survival of chronic lymphocytic leukaemia patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

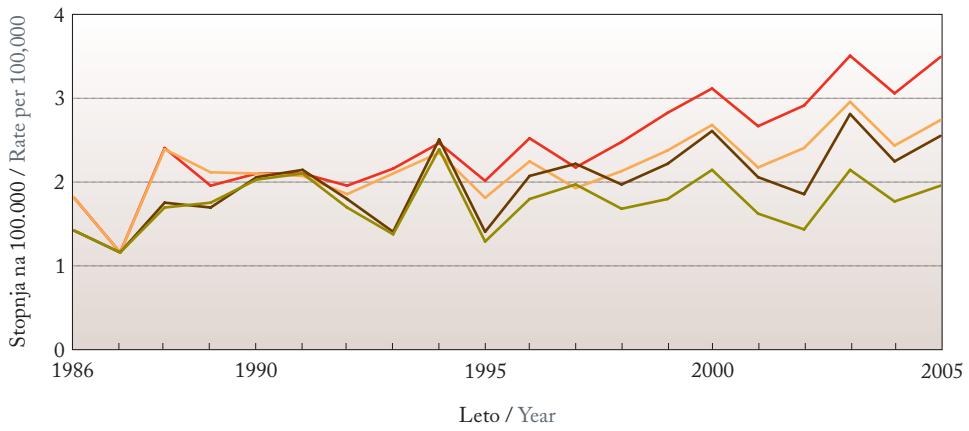
For the time being, the most important factor influencing a better survival – particularly in elderly patients with CLL and concomitant other diseases – is symptomatic treatment for complications, particularly infections, which should be started at once, already at the primary healthcare level.

AKUTA MIELOIČNA LEVKEMIJA

MKB 10: C92.0, C92.4, C92.5, C93.0, C94.0, C94.2, C94.4, C94.5, C95.0

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za akutno mieloično levkemijo (AML) zbolelo 813 ljudi, 417 moških in 396 žensk. Kot je razvidno s Slike 1, je časovni trend incidenčnih in umrljivostnih stopenj rastoč. Groba incidenčna stopnja raste za povprečno 4,0 % letno, groba umrljivostna stopnja pa povprečno za 2,3 % letno. Ker je AML pretežno bolezen starejših (Tabela 1), je trend rasti obeh starostno standardiziranih stopenj počasnejši; starostno standardizirana incidenčna stopnja raste povprečno letno za 2,4 %, umrljivostna pa le za 0,3 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja akutne mieloične levkemije, Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of acute myeloic leukaemia, Slovenia 1986–2005.*

V analizo preživetja je vključenih 736 primerov; 28 primerov (3,4 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 49 mlajših od 20 let ob diagnozi pa obravnavamo v poglavju o otroških levkemijah.

Tabela 1: *Število bolnikov z akutno mieloično levkemijo po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of acute myeloid leukaemia patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	112	24,1	54,5	21,4	87	26,4	46,0	27,6
1996–2000	126	14,3	66,7	19,0	118	21,2	51,7	27,1
2001–2005	143	18,2	55,2	26,6	150	14,7	48,7	36,7

ACUTE MYELOID LEUKEMIA

ICD 10: C92.0, C92.4, C92.5, C93.0, C94.0, C94.2, C94.4, C94.5, C95.0

EPIDEMIOLOGY

In the period 1991–2005, a total of 813 persons were diagnosed with acute myeloid leukemia (AML), of these 417 males and 396 females. As evident from Figure 1, the time trend in incidence and mortality rates is increasing. Thus crude incidence rate has been increasing by 4.0% and crude mortality rate by 2.3% annually on average. AML being prevailingly a disease of the elderly (Table 1), the upward trend of both age-standardized rates is slower, the age-standardized incidence increasing by 2.4% and the mortality by 0.3% annually on average.

The survival analysis included 736 cases; 28 cases (3.4%) diagnosed only after death, were not considered in the analysis; 49 patients under 20 years of age at diagnosis are presented in the chapter on childhood leukemias.

All cases under analysis were microscopically confirmed. The cases of unclassified AML (85%) were most frequent, while 7% of patients had AML with typical cytogenetic translocations and 8% undifferentiated acute leukemia.

Approximately half of all patients of both genders will develop the disease at an age between 50–74 years. In earlier periods, the proportions of patients that were older or younger from the appointed age group were approximately the same; in the last period, however, the proportion of patients aged 75 years and older has increased while the proportion of patients younger than 50 years at diagnosis has decreased (Table 1).

In the years 2001–2005, 41% of patients with AML did not receive specific treatment. The proportion of untreated patients has remained comparable throughout the period under analysis. In the period 2001–2005, 96% of patients with specific treatment received cytostatics while the remaining ones were irradiated.

In the last period, 78% of patients started their treatment in the UMC Ljubljana, 14% in the UMC Maribor, 3% in GH Celje, while one or two patients respectively were treated also in general hospitals of Novo mesto, Izola, Murska Sobota and Nova Gorica.

The relative survival of patients with AML has been gradually increasing: in 15 years, the 5-year relative survival increased by 5% (Figure 2), in males slightly more than in females (Table 2). The relevance of age at diagnosis is shown in Figure 3: the 5-year relative survival of patients diagnosed before 50 years of age is 47%, patients diagnosed at an age between 50–74 years had 9% 5-year relative survival in the last period, while those aged 75 years and older do not survive five years from diagnosis.

The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 15% (Figure 2); patients surviving the first year may expect to survive five years in 42%.

According to the results of EUROCARE-4 study of patients diagnosed in 2000–2002, the survival of Slovenian patients with AML is statistically significantly below the European average (Figure 4).

CLINICAL COMMENTARY

Uroš Mlakar

The incidence of acute myeloid leukemia is increasing with age. Besides cytogenetic subtype, patient age is the most relevant prognostic factor. Therefore adult patients up to 60 years of age (younger patients) are generally dealt with separately from those who are older. Different studies show that in the last 30 years the survival of younger patients has increased considerably.

Vsi v analizo vključeni primeri so bili mikroskopsko potrjeni. Najpogostejši so bili primeri nekategoriziranih AML (85 %), 7 % bolnikov je imelo AML z značilnimi citogenetskimi translokacijami, 8 % pa nediferencirano akutno levkemijo.

Približno polovica vseh bolnikov obeh spolov zboli v starosti 50–74 let. V zgodnejših obdobjih so bili deleži starejših in mlajših od te starostne skupine približno enaki, v zadnjem obdobju pa se je povečal delež bolnikov, starih 75 let in več, in zmanjšal delež bolnikov, ki so bili ob diagnozi mlajši od 50 let (Tabela 1).

V letih 2001–2005 ni bilo specifično zdravljenih 41 % bolnikov z AML. Delež nezdravljenih bolnikov ostaja vse obdobje analize podoben. Med specifično zdravljenimi se je v letih 2001–2005 96 % bolnikov zdravilo le s citostatiki, ostali pa so bili obsevani.

V zadnjem obdobju je 78 % bolnikov zdravljenje začelo v UKC Ljubljana, 14 % v UKC Maribor, 3 % v SB Celje, po en ali dva bolnika pa še v splošnih bolnišnicah v Novem mestu, Izoli, Murski Soboti in v Novi Gorici.

Relativno preživetje bolnikov z AML se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 5 % (Slika 2), pri moških nekoliko več kot pri ženskah (Tabela 2). Kako pomembna je starost ob diagnozi, kaže Slika 3: petletno relativno preživetje bolnikov, zbolelih pred 50. letom starosti, je 47 %, bolniki, zboleli med 50. in 74. letom, so imeli v zadnjem obdobju petletno relativno preživetje 9 %, medtem ko bolniki, stari 75 let in več, pet let po diagnozi ne preživijo.

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 15 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 42-odstotno petletno relativno preživetje.

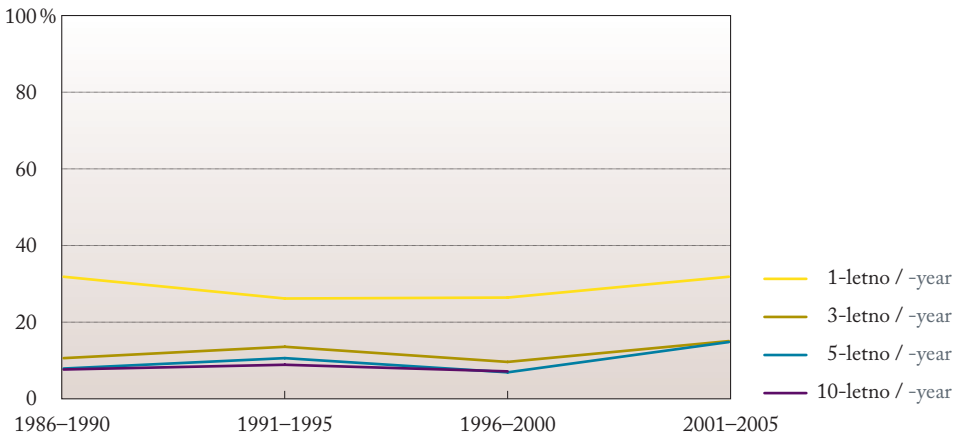
Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z AML statistično značilno manjše od evropskega povprečja (Slika 4).

Tabela 2: *Opazovano in relativno preživetje bolnikov z akutno mieloično levkemijo po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 2: *Observed and relative survival of acute myeloic leukaemia patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	24,1 (17,4–33,5)	10,7 (6,3–18,3)	7,1 (3,7–13,9)	26,4 (18,6–37,5)	13,8 (8,2–23,3)	10,3 (5,6–19,2)
1996–2000	23,8 (17,4–32,5)	8,7 (5,0–15,4)	6,3 (3,2–12,4)	27,1 (20,2–36,5)	8,5 (4,7–15,3)	5,1 (2,3–11,1)
2001–2005	28,0 (21,5–36,4)	11,7 (7,5–18,5)	11,7 (7,5–18,5)	32,7 (26,0–41,1)	14,6 (9,9–21,5)	12,0 (7,7–18,8)

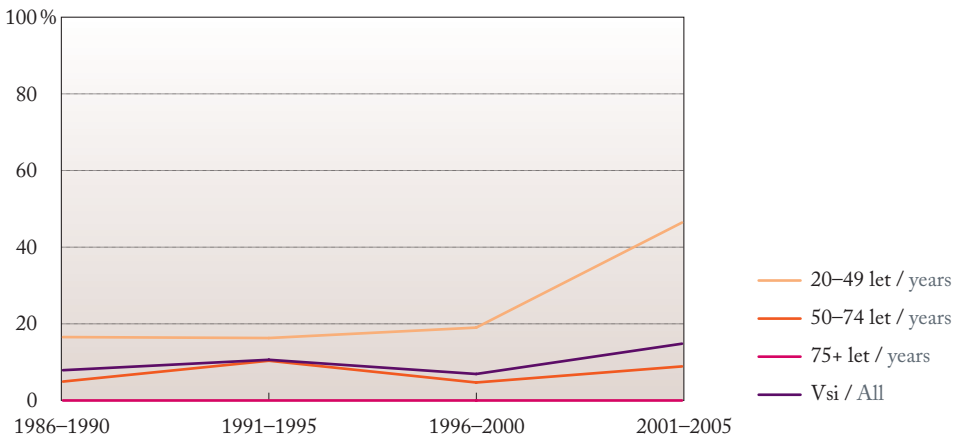
	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	25,2 (15,4–35,0)	12,3 (3,6–21,0)	9,0 (0,5–17,6)	27,3 (15,9–38,8)	15,3 (4,7–25,9)	12,3 (1,8–22,9)
1996–2000	24,8 (15,7–33,9)	10,0 (2,4–17,5)	7,9 (0,4–15,5)	28,0 (18,3–37,6)	9,3 (1,8–16,9)	6,0 (0,0–13,0)
2001–2005	29,4 (20,6–38,2)	13,7 (5,9–21,6)	15,3 (6,6–24,1)	33,9 (25,2–42,7)	16,4 (8,6–24,2)	14,7 (6,4–23,0)



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z akutno mieloično levkemijo po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of acute myeloic leukaemia patients by period of diagnosis.*

This is a result of more intensive chemotherapy, hematopoietic stem-cell transplantation and better supportive therapy. This trend is also observed in Slovenian patients (Figure 3). The results of analysis carried out in patients treated in the years 2003–2007 at the Department of Hematology of the UMC Ljubljana show that the treatment success in younger patients in Slovenia is comparable with the results of large-scale prospective studies (70% of complete remissions, 53% 4-year survival). The prognosis of older patients (> 60 years of age) is poor, since the majority are not suitable for intensive chemotherapy and because they more frequently present with prognostically unfavorable cytogenetic subtypes of AML. Unfortunately, neither was any progress noted in the last decades in the subgroup of elderly patients who are suitable for intensive chemotherapy. The patients who received intensive treatment at the Department of Hematology of the UMC Ljubljana had 12% 3-year survival. Neither was there any statistically significant difference in the survival of elderly patients receiving either intensive or non-intensive therapy.



Slika 3: *Petletno relativno preživetje bolnikov z akutno mieloično levkemijo po starosti in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of acute myeloic leukaemia patients by age and period of diagnosis.*

KLINIČNI KOMENTAR

Uroš Mlakar

Incidenca akutne mieloične levkemije se s starostjo veča. Poleg citogenetične podvrsti bolezni je prav starost bolnika najpomembnejši napovedni dejavnik. Zato se običajno ločeno obravnavajo odrasli bolniki, stari do 60 let (mlajši bolniki), od tistih, ki so starejši. Različne raziskave kažejo, da se je preživetje mlajših bolnikov v zadnjih 30 letih znatno povečalo. Vzrok je bolj intenzivna kemoterapija, presaditev krvotvornih matičnih celic in boljše podporno zdravljenje. Ta trend se kaže tudi pri slovenskih bolnikih (Slika 3). Izsledki analize bolnikov, ki so se v letih 2003–2007 zdravili na Kliničnem oddelku za hematologijo UKC Ljubljana, kažejo, da je uspešnost zdravljenja mlajših bolnikov pri nas primerljiva z izsledki velikih prospektivnih raziskav (70 % popolnih remisij, 4-letno preživetje 53 %). Napoved izida starejših bolnikov (nad 60 let) je slaba, ker jih večina ni primerna za intenzivno kemoterapijo in ker so pri njih pogostejše napovedno neugodne citogenetične podvrste AML. Na žalost tudi pri podskupini starejših bolnikov, ki so primerni za intenzivno kemoterapijo, v zadnjih desetletjih ni prišlo do napredka. Pri bolnikih, ki smo jih na Kliničnem oddelku za hematologijo UKC Ljubljana zdravili na intenziven način, je bilo triletno preživetje 12 %. Prav tako nismo ugotovili statistično pomembne razlike v preživetju starejših bolnikov, ki so se zdravili na intenziven in neintenziven način. Napredek v zdravljenju starejših bolnikov z AML lahko pričakujemo, ko bodo odkrili nova, manj toksična zdravila, in ko bodo izdelana bolj objektivna merila za izbor bolnikov, ki so primerni za intenzivno zdravljenje.

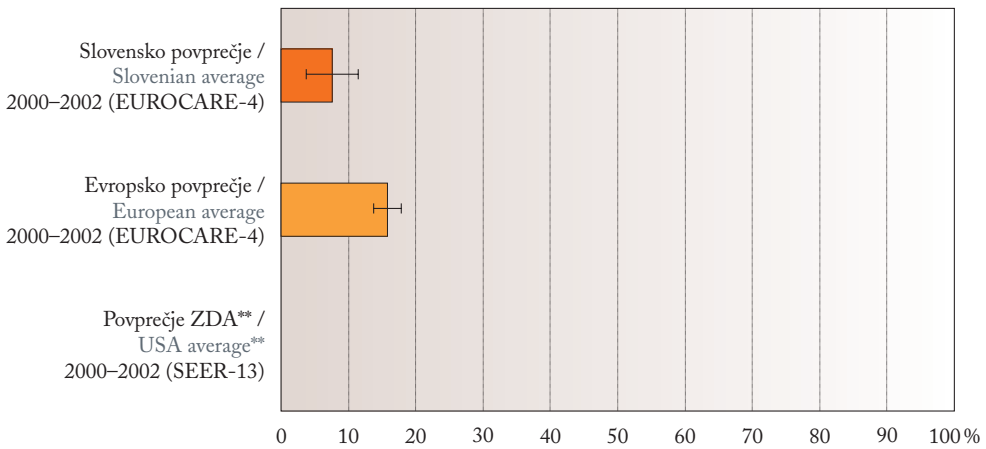
VIRI

Literature

Burnett AK. Acute myeloid leukemia: treatment of adults under 60 years. Reviews in clinical and experimental hematology 2002; 6: 26–45.

Dombret H, Raffaux E, Degos L. Management of elderly patients with acute myeloid leukemia. Hematology 2007; 1: 193–9.

Mlakar U. Zdravljenje akutne mieloične levkemije odraslih – 5-letne izkušnje v UKC Ljubljana. Zdrav Vestn 2008; 77: I-31–5



Slika 4: *Petletno relativno preživetje bolnikov z akutno mieloično levkemijo* (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 4: *5-year relative survival of acute myeloic leukaemia patients* (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

* Nabor MKB10 kod v študiji EUROCARE-4 je nekoliko drugačen kot smo ga uporabili pri ostalih analizah predstavljenih v tem poglavju: v študiji EURCARE-4 so iz analize izvzete akutna promielocitna levkemija (MKB10: C924), akutna mielomonocitna levkemija (MKB10: C925), akutna eritremija in eritrolevkemija (MKB10: C940), akutna panmieloza (MKB10: C945) in akutna levkemija z neopredeljeno vrsto celic (MKB10: C950).
** podatki niso dosegljivi

* The ICD10 code selection in EUROCARE-4 study is slightly different in comparison to the selection applied in other analysis in this chapter: in EUROCARE-4 study the acute promyelocytic leukaemia (MKB10: C924), acute myelomonocytic leukaemia (MKB10: C925), acute erythraemia in erythroleukaemia (MKB10: C940), acute panmyelosis (MKB10: C945) in acute leukaemia of unspecified cell type (MKB10: C950) are excluded.
** data not available

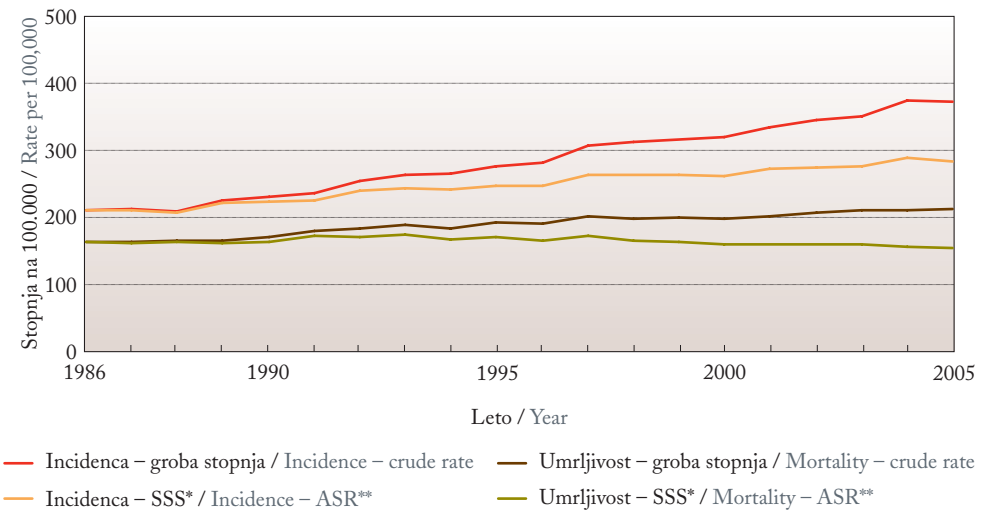
Advances in the treatment of elderly patients with AML may be expected by discovery of new, less toxic medications and drawing up of more objective criteria for the selection of patients suitable for intensive therapy.

VSE RAKAVE BOLEZNI PRI ODRASLIH (brez kožnega raka)

MKB 10: C00–C96 brez C44

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za katero koli vrsto raka zbolelo 128.406 ljudi, 65.611 moških in 62.795 žensk. Med njimi je imelo 13.654 bolnikov (6401 moški in 7253 žensk) nemelanomskega kožnega raka. Ker je nemelanomski kožni rak zelo pogosta, a praktično popolnoma ozdravljiva bolezen, smo te bolnike izvzeli iz analize časovnega trenda incidence in umrljivosti, pa tudi iz vseh nadaljnjih izračunov preživetja. Kot je razvidno s Slike 1, sta se incidenčni stopnji povečevali hitreje od umrljivostnih stopenj. Groba incidenčna stopnja se je večala povprečno za 3,2 % letno, groba umrljivostna stopnja pa bistveno manj, povprečno za 1,1 % letno. Ker je rak pogostejši med starejšimi (Tabela 1), se starostno standardizirana incidenčna stopnja veča le za povprečno 1,5 % letno, starostno standardizirana umrljivostna stopnja pa se v opazovanem petnajstletnem obdobju manjša povprečno za 0,8 % letno.



* SSS – starostno standardizirana stopnja (standard – slovenska populacija leta 1986)
** ASR – age standardized rate (standard Slovenian population in 1986)

Slika 1: *Groba in starostno standardizirana incidenčna in umrljivostna stopnja vseh rakov (brez kožnega), Slovenija 1986–2005.*

Figure 1: *Crude and age-standardized incidence and mortality rate of all cancer (except skin), Slovenia 1986–2005.*

Tabela 1: *Število odraslih bolnikov z rakom (brez kožnega) po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of adult cancer (except skin) patients by sex and period of diagnosis with their proportions by age.*

	Moški / Males				Ženske / Females			
Obdobje / Period	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)	število / number	20–49 let / years (%)	50–74 let / years (%)	75+ let / years (%)
1991–1995	15.818	13,7	68,7	17,6	14.805	19,3	59,7	21,0
1996–2000	18.506	13,2	68,9	17,9	17.734	19,4	57,9	22,7
2001–2005	21.909	11,6	67,6	20,8	20.328	17,5	55,3	27,2

ALL CANCER SITES IN ADULTS (but skin)

ICD 10: C00–C96 without C44

EPIDEMIOLOGY

In the period 1991–2005, a total of 128,406 persons were diagnosed with any type of cancer, of these 65,611 males and 62,795 females. Among these, 13,654 patients (6401 males and 7253 females) had non-melanoma skin cancer. As non-melanoma skin cancer is a very frequent but practically fully curable disease, these patients were excluded from the incidence and mortality time-trend analysis as well as from all other survival statistics. As evident from Figure 1, the incidence rates have been increasing faster than the mortality rates. The estimated annual percentage increase in crude incidence rate was 3.2% and in crude mortality rate 1.0%. Cancer being more frequent in the elderly (Table 1), the age-standardized incidence rate has been increasing only by 1.5% annually on average while in the observed 15-year period the age standardized mortality rate has been decreasing by 0.8% annually on average.

The survival analysis included 109,100 cases; 13,654 (10.6%) patients with non-melanoma skin cancer and 4585 (3.6%) patients diagnosed only after death were not considered in the analysis; 1067 children and adolescents (0.8%) are presented in a separate chapter.

In all three periods, 92% of cases were microscopically verified. Among these, 14% were defined as malignant tumors, as unspecified carcinomas or as sarcomas. Among others, there were 49% adenocarcinomas, 14% planocellular carcinomas and 4% malignant melanomas. Other histological types were established in less than 3% of patients.

Tabela 2: *Število odraslih bolnikov z rakom (brez kožnega) po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

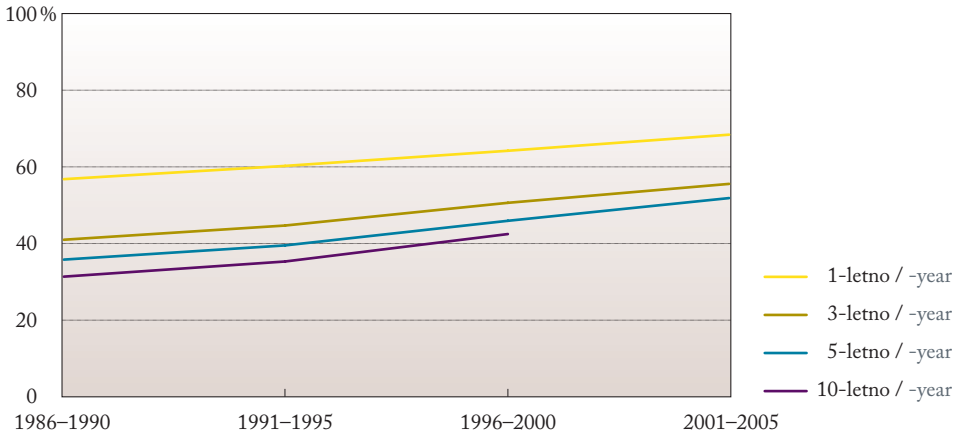
Table 2: *Number of adult cancer (except skin) patients by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Moški / Males					Ženske / Females				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	15.818	30,3	34,4	27,7	7,7	14.805	36,0	33,0	25,2	5,9
1996–2000	18.506	32,3	34,0	27,1	6,6	17.734	38,2	32,8	24,3	4,6
2001–2005	21.909	33,3	33,7	27,6	5,5	20.328	38,3	32,6	25,0	4,1

Tabela 3: *Število odraslih bolnikov z rakom (brez kožnega) po starosti in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

Table 3: *Number of adult cancer (except skin) patients by age and period of diagnosis with their proportions by stage.*

Obdobje / Period	Mlajši od 75 let / Younger than 75 years					Stari 75 let in več / 75 years and older				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	24.732	33,7	35,5	26,1	4,7	5891	30,3	26,3	27,9	15,6
1996–2000	28.913	36,6	34,6	25,0	3,8	7327	29,6	28,7	28,7	13,0
2001–2005	32.144	37,6	33,8	25,4	3,2	10.093	29,8	31,1	29,1	10,0



Slika 2: *Deset-, pet-, tri- in enoletno relativno preživetje odraslih bolnikov z rakom (brez kožnega) po obdobju postavitve diagnoze.*

Figure 2: *10-, 5-, 3- and 1-year relative survival of adult cancer (except skin) patients by period of diagnosis.*

V analizo preživetja je vključenih 109.100 primerov; 13.654 (10,6 %) bolnikov nismo upoštevali, ker so imeli nemelanomskega kožnega raka, 4585 bolnikov (3,6 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti, 1067 otrok in mladostnikov (0,8 %) pa obravnavamo v posebnem poglavju.

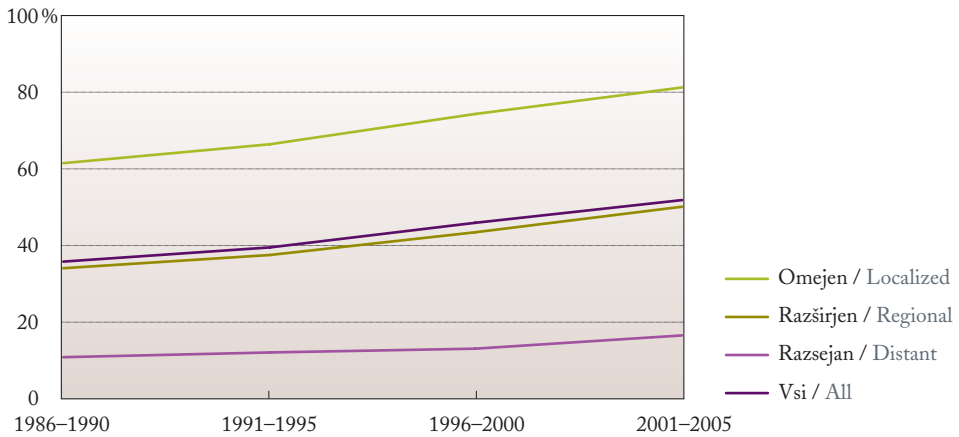
V vseh treh obdobjih je bilo mikroskopsko potrjenih 92 % primerov. Med njimi je bilo 14 % opredeljenih le kot maligni tumor ali pa neopredeljen karcinom oziroma sarkom. Adenokarcinomov je bilo 49 %, ploščatoceličnih karcinomov 14 % in malignih melanomov 4 %. Ostale histološke vrste so bile določene pri manj kot 3 % bolnikov.

Tabela 4: *Opazovano in relativno preživetje odraslih bolnikov z rakom (brez kožnega) po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 4: *Observed and relative survival of adult cancer (except skin) patients by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	50,1 (49,4–50,9)	30,5 (29,8–31,3)	23,6 (23,0–24,3)	66,5 (65,8–67,3)	49,9 (49,1–50,7)	42,3 (41,5–43,1)
1996–2000	54,6 (53,8–55,3)	36,2 (35,5–36,9)	29,1 (28,4–29,8)	69,6 (68,9–70,2)	54,7 (54,0–55,5)	47,6 (46,8–48,3)
2001–2005	60,4 (59,8–61,1)	42,4 (41,7–43,0)	35,0 (34,4–35,7)	72,0 (71,3–72,6)	57,5 (56,8–58,2)	50,7 (49,9–51,4)

	Relativno preživetje / Relative survival (%)					
	Moški / Males			Ženske / Females		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	52,4 (51,6–53,2)	35,0 (34,1–35,8)	29,7 (28,9–30,6)	68,6 (67,8–69,3)	54,7 (53,8–55,6)	49,4 (48,5–50,4)
1996–2000	57,0 (56,2–57,7)	41,3 (40,5–42,1)	36,5 (35,6–37,3)	71,6 (70,9–72,3)	59,7 (58,9–60,5)	55,2 (54,4–56,1)
2001–2005	63,1 (62,4–63,8)	48,5 (47,7–49,2)	44,3 (43,4–45,2)	74,1 (73,4–74,7)	62,9 (62,1–63,6)	59,2 (58,4–60,1)

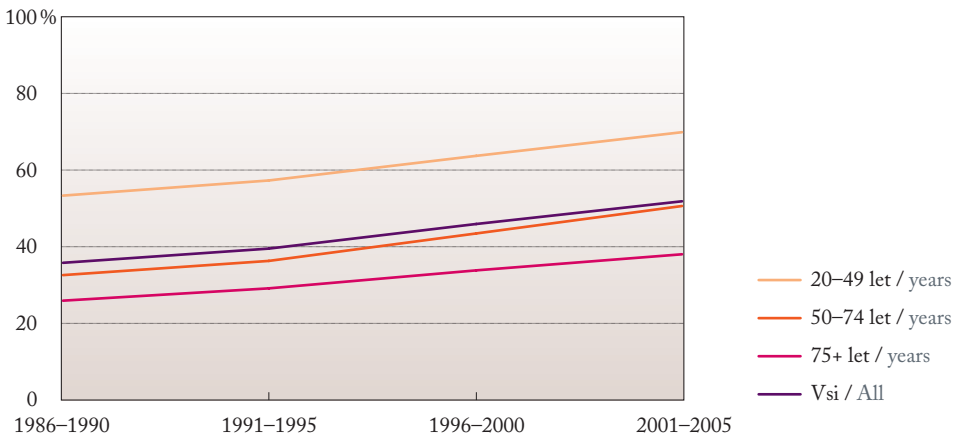


Slika 3: *Petletno relativno preživetje odraslih bolnikov z rakom (brez kožnega) po stadiju in obdobju postavitve diagnoze.*

Figure 3: *5-year relative survival of adult cancer (except skin) patients by stage and period of diagnosis.*

Approximately two thirds of males were aged between 50–74 years at diagnosis, while in the period 2001–2005 slightly over a half of females belonged to this age group. Cancer is relatively rare before the age of 50 years, however, the proportion of patients aged 75 years and older, particularly females, has been increasing (Table 1).

In the observed period there were 5% of patients with undefined stage at diagnosis, their percentage has been slightly decreasing with time. In the period 2001–2005, approximately one third of males had the disease diagnosed in a localized or regional stage, and slightly less in a disseminated stage. The proportion of females with localized disease at diagnosis was by 5% higher than the proportion of those with regional disease; in all three periods, approximately one fourth of females had disseminated disease (Table 2). The higher proportion of localized stage was evident mostly in patients diagnosed before age 75 and not in patients aged 75 or more at the time of diagnosis (Table 3).



Slika 4: *Petletno relativno preživetje odraslih bolnikov z rakom (brez kožnega) po starosti in obdobju postavitve diagnoze.*

Figure 4: *5-year relative survival of adult cancer (except skin) patients by age and period of diagnosis.*

Približno dve tretjini moških sta bili ob diagnozi stari med 50 in 74 let, žensk je bilo v letih 2001–2005 v tej starosti dobra polovica. Pred 50. letom starosti je rak razmeroma redka bolezen, večja pa se delež starih 75 let in več, predvsem pri ženskah (Tabela 1).

V opazovanem obdobju okrog 5 % bolnikov ni imelo določenega stadija ob diagnozi; ta delež se je s časom nekoliko zmanjšal. V letih 2001–2005 je imela med moškimi približno tretjina bolezen odkrito v omejenem ali razširjenem stadiju, nekaj manj pa v razsejanem. Med ženskami je bil delež tistih z omejeno boleznijo ob diagnozi za 5 % večji od deleža tistih z razširjeno boleznijo; v vseh treh obdobjih je imela približno četrtina žensk razsejano bolezen (Tabela 2). Delež bolnikov z omejenim stadijem ob diagnozi se je večal predvsem pri mlajših bolnikih, ne pa pri starih 75 let in več (Tabela 3).

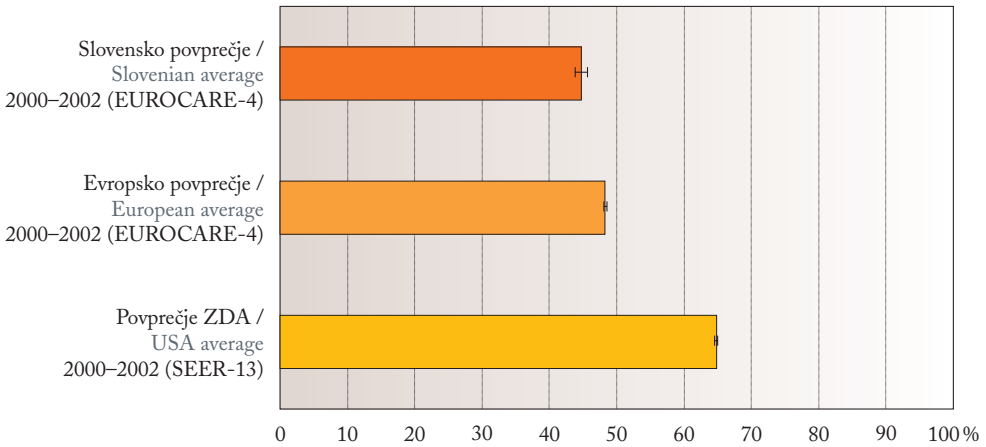
V letih 2001–2005 ni bilo specifično zdravljenih 21 % bolnikov. Delež nezdravljenih bolnikov se je v opazovanem 15-letnem obdobju zmanjšal za 4 %. Med specifično zdravljenimi je bilo v letih 2001–2005 34 % bolnikov samo operiranih, 9 % jih je poleg operacije prejelo še kemoterapijo, po 7 % so jih samo obsevali ali pa so bili zdravljeni s kombinacijo operacije, radio- in kemoterapije, 6 % bolnikov so operirali in obsevali, po 5 % bolnikov pa je prejelo kombinacijo operacije s hormonsko terapijo ali kombinacijo radio- in kemoterapije ali pa samo kemo- ali hormonsko terapijo. Ostale kombinacije zdravljenj so uporabili pri treh ali manj odstotkih bolnikov.

V obdobju 2001–2005 so se bolniki z rakom začeli zdraviti v vseh slovenskih bolnišnicah. Največ se jih je začelo zdraviti na OI Ljubljana (32 %) in v UKC Ljubljana (28 %), 14 % so jih začeli zdraviti v UKC Maribor, 7 % v SB Celje, po 3 % v SB Nova Gorica, SB Slovenj Gradec in SB Novo mesto, po 2 % v SB Murska Sobota in SB Izola, po 1 % pa v SB Jesenice in na Golniku. Manj kot pol odstotka bolnikov se je začelo zdraviti na Ptuju, v Trbovljah in v Brežicah.

Preživetje bolnikov z rakom se postopno povečuje; v 15 letih se je petletno relativno preživetje povečalo za 12 % (Slika 2), za 14 % pri moških in za 10 % pri ženskah (Tabela 4). Kako pomemben je stadij ob diagnozi, kaže Slika 2: v zadnjem obdobju je bilo petletno relativno preživetje bolnikov z omejenim stadijem že več kot 80-odstotno in se je v primerjavi z leti 1991–1995 povečalo za 15 %; za 12 % se je povečalo tudi petletno relativno preživetje bolnikov z razširjeno boleznijo in je v zadnjem obdobju že preseglo 50 %. Petletno relativno preživetje bolnikov, odkritih v razsejanem stadiju, se je v 15 letih povečalo le za 4 % in je še vedno manjše od 20 %. Napovedni dejavnik je tudi starost, saj je bilo petletno relativno preživetje bolnikov, ki so zboleli pred 50. letom, v zadnjem obdobju 70 %, tistih, ki so zboleli med 50. in 74. letom, 50 %, tistih, ki so bili stari 75 let in več, pa le 38 % (Slika 4).

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 52 % (Slika 2); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 74-odstotno petletno relativno preživetje. Petletno relativno preživetje bolnikov, ki so zboleli samo za eno rakavo boleznijo, je bilo 54 %.

Rezultati študije EUROCARE-4 za zbolele v obdobju 2000–2002 kažejo, da je preživetje slovenskih bolnikov z rakom statistično značilno manjše od evropskega povprečja (Slika 5).



Slika 5: *Petletno relativno preživetje odraslih bolnikov z rakom – brez kožnega – (povprečje in 95-odstotni interval zaupanja), zbolelih v letih 2000–2002 v Sloveniji, Evropi in nekaterih območjih v ZDA.*

Figure 5: *5-year relative survival of adult cancer (except skin) patients (average and 95% confidence interval) diagnosed in the period 2000–2002 in Slovenia, Europe and in some regions of the USA.*

In the years 2001–2005, 21% of patients did not receive specific treatment. In the observed 15-year period the proportion of untreated patients has decreased by 4%. Among those receiving specific treatment in the period 2001–2005, 34% were treated by surgery alone, 9% received chemotherapy in addition to surgery, 7% each were either irradiated only, or treated with a combination of surgery plus radio- and chemotherapy, 6% had surgery and irradiation, 5% each received a combination of surgery plus hormone therapy or a combination of radio- and chemotherapy or either chemo- or hormone therapy alone. Other combinations of treatment were used in three or less than three percent of patients.

In the period 2001–2005, cancer patients started their treatment in all Slovenian hospitals. In the period 2001–2005, the majority of them started their treatment at the IO Ljubljana (32%) and in the UMC Ljubljana (28%), 14% in the UMC Maribor, 7% in GH Celje, 3% each in general hospitals of Nova Gorica, Slovenj Gradec and Novo mesto, 2% each in general hospitals of Murska Sobota and Izola, and 1% each in GH Jesenice and at Golnik. Less than a half percent of patients started their treatment in GH Ptuj, GH Trbovlje and GH Brežice.

The relative survival of cancer patients has been gradually increasing: in 15 years, the 5-year relative survival increased by 12% (Figure 2), in males by 14% and in females by 10% (Table 4). The relevance of stage at diagnosis is shown in Figure 2: compared to the period 1991–1995, in the last period the 5-year relative survival of patients with localized stage was already above 80%, thus having increased by 15%, while the 5-year relative survival of patients with regional disease has increased by 12%, already exceeding 50% in the last period. However, in 15 years, the relative survival of patients diagnosed in a disseminated stage has increased only by 4% and is still lower than 20%. Age is a prognostic factor as well, since in the last period the 5-year relative survival of patients aged less than 50 years at diagnosis was 70%, while the rate in those aged between 50–74 years was 50%, and in those aged 75and older it was only 38% (Figure 4).

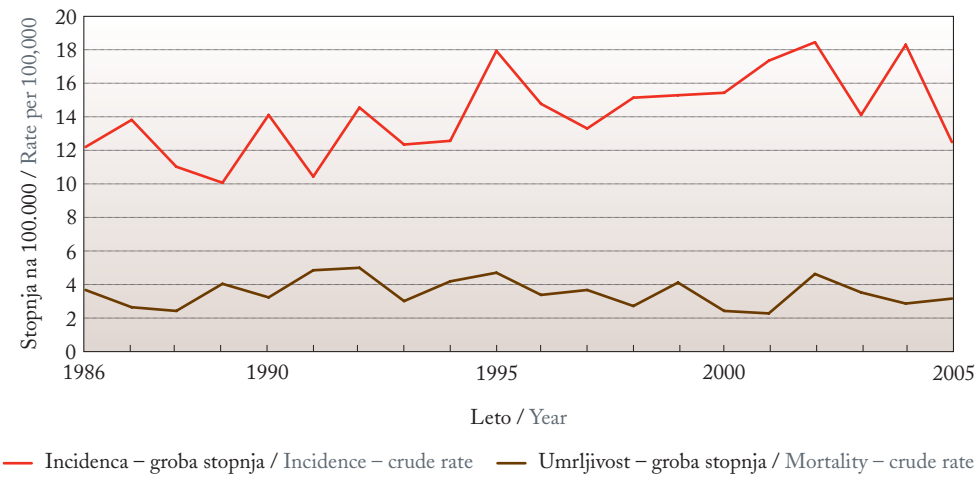
The 5-year relative survival of all patients diagnosed in the period 2001–2005 was 52% (Figure 2); patients surviving the first year may expect to survive five years in 74%. The 5-year relative survival of patients diagnosed with one type of cancer only was 54%.

According to the results of EUROCARE-4 study of patients diagnosed in 2000–2002, the survival of cancer patients in Slovenia is statistically significantly below the European average (Figure 5).

RAK PRI OTROCIH IN MLADOSTNIKIH

EPIDEMIOLOGIJA

V obdobju 1991–2005 je za rakom zbolelo 1067 otrok in mladostnikov, 600 dečkov in 467 deklic. Med njimi je bilo 243 primerov levkemij, 154 primerov tumorjev centralnega živčnega sistema (CŽS), 115 primerov Hodgkinovih limfomov (HL) in 95 primerov ne-Hodgkinovih limfomov (NHL). Kot je razvidno s Slike 1, se groba incidenčna stopnja raka pri otrocih in mladostnikih ves čas opazovanja veča, povprečno za 1,8 % letno, medtem ko se groba umrljivostna stopnja zmanjšuje, povprečno za 2,7 % letno. Časovne trende incidenčnih stopenj posameznih vrst raka je težko ocenjevati, saj je število primerov majhno; trendi najpogostejših vrst so prikazani na Sliki 2. Najbolj se veča incidenca levkemij (1,6-odstotni povprečni letni porast) in NHL (1,2-odstotni povprečni letni porast).



Slika 1: *Groba incidenčna in umrljivostna stopnja raka pri mlajših od 20 let, Slovenija 1986–2005.*

Figure 1: *Crude incidence and mortality rate of cancer in patients younger then 20 years, Slovenia 1986–2005.*

V analizo preživetja je vključenih 1057 primerov; 10 bolnikov (0,9 %) nismo upoštevali, ker jim je bila diagnoza postavljena po smrti. Med njimi je bilo 6 primerov raka krvotvornih in limfatičnih organov ter 4 primeri raka CŽS.

Med vsemi v analizo vključenimi primeri pet bolnikov ni imelo mikroskopsko potrjene bolezni.

Tabela 1: *Število bolnikov z rakom pri mlajših od 20 let po spolu in obdobju postavitve diagnoze ter njihovi deleži po starosti.*

Table 1: *Number of cancer in patients younger then 20 years by sex and period of diagnosis with their proportions by age.*

	Dečki / Boys			Deklice / Girls		
Obdobje / Period	število / number	0–14 let / years (%)	15–19 let / years (%)	število / number	0–14 let / years (%)	15–19 let / years (%)
1991–1995	200	62,5	37,5	161	70,2	29,8
1996–2000	204	58,8	41,2	148	66,2	33,8
2001–2005	189	61,4	38,6	155	58,7	41,3

CANCER IN CHILDREN AND ADOLESCENTS

EPIDEMIOLOGY

In the period 1991–2005, a total of 1067 children and adolescents were diagnosed with cancer, of these 600 boys and 467 girls. Among these, there were 243 cases of leukemias, 154 tumors of the central nervous system (CNS), 115 cases of Hodgkin's lymphoma (HL) and 95 cases of non-Hodgkin lymphoma (NHL). As evident from Figure 1, the crude incidence rate of cancer in children and adolescents has been increasing throughout the observation period, by 1.8% annually on average, while the crude mortality rate has been decreasing, by 2.7% annually on average. The time trends in the incidence rates of individual cancer types are difficult to evaluate since the number of cases is small; the trends for the most frequent types are shown in Figure 2. The highest increase has been noted in leukemias (1.6% average annual increase) and in NHL (1.2% average annual increase).

The survival analysis included 1057 cases; 10 patients (0.9%) diagnosed only after death, were not considered in the analysis. Among these, there were 6 cases of hematopoietic and lymphatic cancers and 4 cases of CNS cancers.

Out of all cases included in the analysis, five patients did not have microscopically confirmed disease.

Tabela 2: *Število bolnikov z rakom pri mlajših od 20 let po spolu in obdobju postavitve diagnoze ter njihovi deleži po stadiju.*

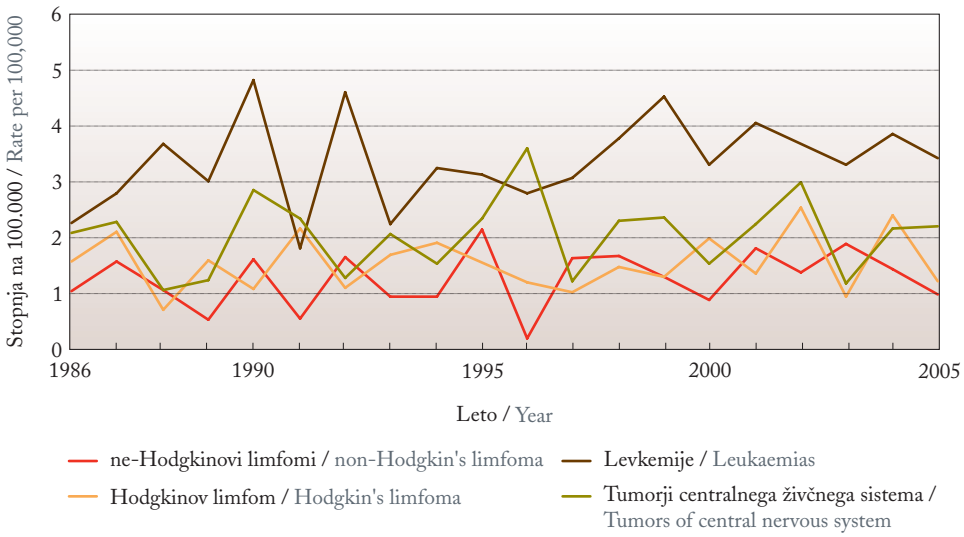
Table 2: *Number of cancer patients younger then 20 years by sex and period of diagnosis with their proportions by stage.*

Obdobje / Period	Dečki / Boys					Deklice / Girls				
	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)	število / number	omejen / localized (%)	razširjen / regional (%)	razsejan / distant (%)	neznan / unknown (%)
1991–1995	200	34,5	25,5	39,5	0,5	161	37,3	19,9	41,6	1,2
1996–2000	204	43,1	18,6	36,8	1,5	148	34,5	25,7	39,2	0,7
2001–2005	189	37,6	26,5	35,4	0,5	155	36,1	23,9	39,4	0,6

Tabela 3: *Število bolnikov z najpogostejšimi raki pri mlajših od 20 let po spolu, stadiju in starosti.*

Table 3: *Number of most common cancers in patients younger then 20 years by sex, stage and age.*

		Levkemije / Leukaemias	Tumorji centralnega živčnega sistema / Tumors of central nervous system	Hodgkinov limfom / Hodgkin limfoma	neHodgkinovi limfomi / nonHodgkin limfoma
Spol/Sex	dečki / boys	41	29	20	22
	deklice / girls	37	17	16	10
Stadij/Stage	omejen / localized (%)	–	32	3	6
	razširjen / regional (%)	–	2	16	5
	razsejan / distant (%)	–	2	8	20
	neznan / unknown (%)	–	0	0	1
Starost/Age	0–14 let / years	56	37	15	22
	15–19 let / years	22	9	17	10



Slika 2: *Groba incidenčna stopnja najpogostejših rakov pri mlajših od 20 let, Slovenija 1986–2005.*

Figure 2: *Crude incidence rate of most common cancers in patients younger then 20 years, Slovenia 1986–2005.*

V obdobju 2001–2005 je bilo med bolniki, mlajšimi od 20 let, približno 60 % otrok, mlajših od 15 let, in 40 % mladostnikov, starih od 15 do 19 let. Razmerje med otroki in mladostniki je pri dečkih ves čas opazovanja približno enako, manjša pa se delež bolnic, mlajših od 15 let, na račun večanja deleža zbolelih mladostnic (Tabela 1).

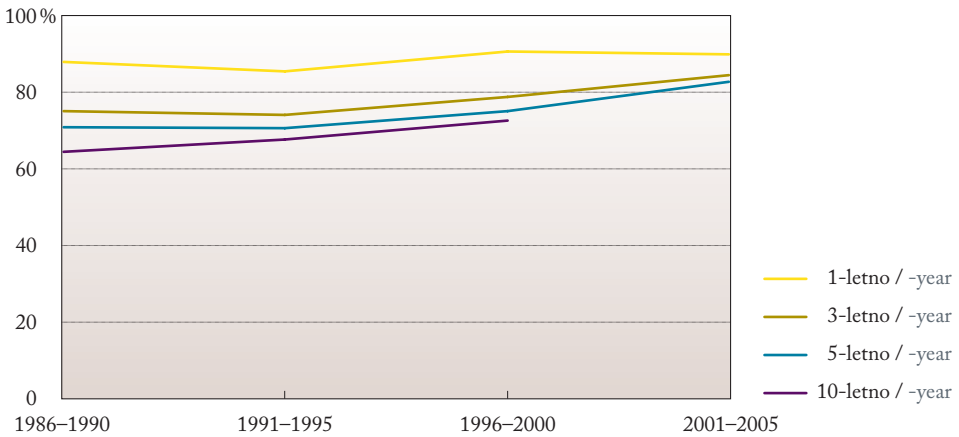
V vseh treh obdobjih je imelo približno enak delež bolnikov (dobra tretjina) ob diagnozi bolezen v omejeni ali pa že v razsejani obliki. Razširjeno bolezen je imela približno četrtina bolnikov, le redkim otrokom in mladostnikom pa stadij bolezni ob diagnozi ni določen. Deleži posameznih stadijev se z leti niso bistveno spreminjali (Tabela 2). Število otrok in mladostnikov z najpogostejšimi vrstami raka po starosti in stadijih, zbolelih v obdobju 2001–2005, prikazuje Tabela 3.

Tabela 4: *Opazovano in relativno preživetje bolnikov z rakom pri mlajših od 20 let po spolu in obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja (IZ).*

Table 4: *Observed and relative survival of cancer patients younger then 20 years by sex and period of diagnosis with 95% confidence interval (CI).*

	Opazovano preživetje / Observed survival (%)					
	Dečki / Boys			Deklice / Girls		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	83,5 (78,5–88,8)	72,0 (66.0–78,5)	69,0 (62,9–75,7)	87,6 (82,6–92,8)	76,4 (70,1–83,2)	72,1 (65,4–79,3)
1996–2000	89,7 (85,6–94.0)	75,0 (69,3–81,2)	71,6 (65,6–78,0)	91,9 (87,6–96,4)	83,8 (78,1–89,9)	79,7 (73,5–86,5)
2001–2005	87,8 (83,3–92,6)	80,4 (75.0–86,3)	79,6 (74,0–85,7)	92,3 (88,1–96,6)	89,0 (84,2–94,1)	86,2 (80,7–92,1)

	Relativno preživetje / Relative survival (%)					
	Dečki / Boys			Deklice / Girls		
Obdobje / Period	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)	1-letno / -year (IZ/CI)	3-letno / -year (IZ/CI)	5-letno / -year (IZ/CI)
1991–1995	83,6 (78,3–88,9)	72,2 (65,7–78,7)	69,3 (62,5–76.0)	87,6 (82,4–92,9)	76,5 (69,6–83,3)	72,2 (64,9–79,4)
1996–2000	89,8 (85,5–94,0)	75,1 (68,9–81,3)	71,8 (65,3–78,3)	91,9 (87,4–96,4)	83,8 (77,7–90,0)	79,8 (73,1–86,6)
2001–2005	87,9 (83,1–92,7)	80,6 (74,7–86,4)	79,9 (73,8–85,9)	92,3 (88,0–96,6)	89,1 (84,0–94,1)	86,3 (80,4–92,2)

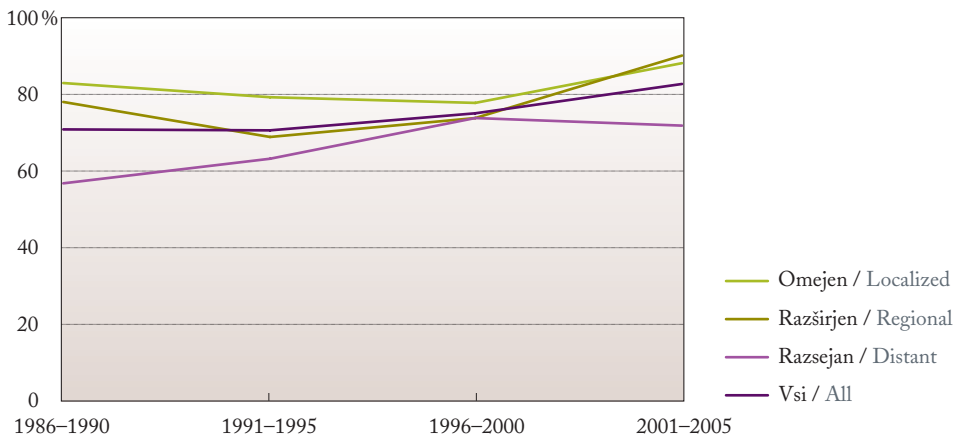


Slika 3: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov z rakom pri mlajših od 20 let po obdobju postavitve diagnoze.*

Figure 3: *10-, 5-, 3- and 1-year relative survival of cancer patients younger then 20 years by period of diagnosis.*

In the period 2001–2005, approximately 60% of patients younger than 20 years were children under 15 years of age and 40% adolescents aged 15–19 years. In boys, the ratio between children and adolescents has been approximately the same throughout the observation period, while in girls the proportion of patients under 15 years of age has been decreasing on the account of a higher proportion of adolescent patients (Table 1).

In all three periods, approximately the same proportion of patients (over one third) presented with localized or disseminated disease at diagnosis. Regional disease was found in approximately one fourth of patients; there were only few children and adolescents without stage determined at diagnosis. The proportions of individual stages did not change significantly with time (Table 2). The number of children and adolescents with the most frequent cancers diagnosed in the period 2001–2005 by age and stage are presented in Table 3.



Slika 4: *Petletno relativno preživetje bolnikov z rakom pri mlajših od 20 let po stadiju in obdobju postavitve diagnoze.*

Figure 4: *5-year relative survival of cancer patients younger then 20 years by stage and period of diagnosis.*

V obdobju 2001–2005 ni bilo specifično zdravljenih 3,5 % otrok in mladostnikov. Delež nezdravljenih bolnikov se v vsem obdobju analize ni bistveno spreminjal. Vsi zdravljeni bolniki z rakom krvotvornih in limfatičnih organov so prejeli citostatike. Približno 80 % teh bolnikov je kot dopolnilno zdravljenje prejelo še kortikosteroide, dodatno obsevanih pa je bilo 18 % bolnikov z levkemijami, 78 % bolnikov s HL in 20 % bolnikov z NHL. Med bolniki s tumorji CŽS jih je bilo 93 % operiranih, polovica med njimi je prejela tudi kemoterapijo, operaciji pa je bila v 38 % dodana še radioterapija.

V obdobju 2001–2005 se je slaba polovica bolnikov začela zdraviti na Pediatrični kliniki v Ljubljani, 27 % v UKC Ljubljana, 13 % na OI Ljubljana in 4 % v UKC Maribor. Posamezni bolniki so se pričeli zdraviti še v splošnih bolnišnicah v Celju, Izoli, Murski Soboti, Novi Gorici, Novem mestu in na Jesenicah. Skoraj vsi, ki so pričeli z zdravljenjem v UKC Ljubljana, so imeli tumor CŽS in so bili tam operirani, na OI Ljubljana pa so večinoma z zdravljenjem pričeli bolniki s HL.

Relativno preživetje otrok in mladostnikov z rakom se veča; v 15 letih se je petletno relativno preživetje povečalo za 12 % (Slika 3), pri deklicah nekaj več kot pri dečkih (Tabela 4). Najmanjše preživetje imajo bolniki z razsejano boleznijo (Slika 4); petletno relativno preživetje bolnikov, zbolelih v obdobju 2001–2005 z razsejano boleznijo, je bilo 72 %, medtem ko je bilo preživetje bolnikov z razširjeno boleznijo 90-odstotno.

Preživetje otrok se bistveno ne razlikuje od preživetja mladostnikov (Slika 5). Pri primerjavi preživetja najpogostejših rakov pri otrocih in mladostnikih (Tabela 5) vidimo, da se je petletno relativno preživetje v 15 letih najbolj povečalo pri bolnikih s tumorji CŽS in pri bolnikih s HL – pri njih je v zadnjem obdobju tudi doseglo 100 %. Preživetje je pri levkemijah in HL zelo podobno pri obeh spolih, medtem ko so pri bolnikih z NHL v zadnjem obdobju bolje preživljale deklice, med bolniki s tumorji CŽS pa dečki.

Prikaz preživetja po stadijih pri najpogostejših vrstah raka otrok in mladostnikov je zaradi majhnega števila bolnikov v posameznem stadiju nezanesljiv. Pri primerjavi preživetij otrok s preživetji mladostnikov pa pri najpogostejših anatomskih mestih opažamo boljše preživetje mlajših od 15 let pri levkemijah, tumorjih CŽS in NHL.

Petletno relativno preživetje vseh zbolelih v obdobju 2001–2005 je bilo 83 % (Slika 3); bolniki, ki preživijo prvo leto, pa lahko pričakujejo 92-odstotno petletno relativno preživetje. Podobno se poveča pričakovano preživetje, če bolnik preživi prvo leto tudi pri posameznih vrstah raka; pri levkemijah s 74 % na 86 %, pri tumorjih CŽS s 69 % na 83 % in pri NHL s 75 % na 96 %.

Rezultati študije EUROCARE-4 za zbolele v obdobju 1995–2002 kažejo, da je preživetje slovenskih otrok in mladostnikov z rakom statistično neznačilno manjše od evropskega povprečja (Slika 6).

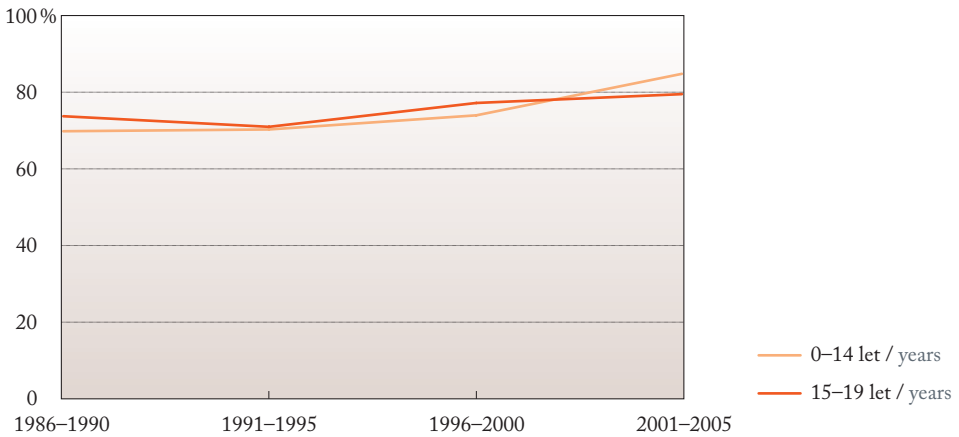
KLINIČNI KOMENTAR

Janez Jazbec

Za Slovenijo velja načelni dogovor, naj se vsi otroci do dopolnjenega 18. leta starosti, pri katerih je postavljen utemeljen sum na raka, diagnostično obdelajo in zdravijo v nacionalnem centru za otroško onkologijo na Pediatrični kliniki v Ljubljani, ki deluje v sklopu UKC Ljubljana in tesno sodeluje z OI Ljubljana. Ker so v sedanjo analizo vključeni mladostniki do 20. leta starosti, je lahko delež bolnikov, ki so specifično zdravljenje začeli v drugih bolnišnicah, posledica obravnave bolnikov med 18. in 20. letom.

Ker so maligne bolezni pri otrocih heterogena skupina, je natančnejša analiza dejavnikov, ki so vzrok opazovanemu izboljšanju preživetja, zelo težka.

Otroci z levkemijami se v Sloveniji zdravijo po shemah zdravljenja, ki izvirajo iz tako imenovane sheme BFM (Berlin-Frankfurt-Münster). V zadnjih letih so vsi bolniki z akutno limfoblastno



Slika 5: *Petletno relativno preživetje bolnikov z rakom pri mlajših od 20 let po starosti in obdobju postavitve diagnoze.*

Figure 5: *5-year relative survival of cancer patients younger then 20 years by age and period of diagnosis.*

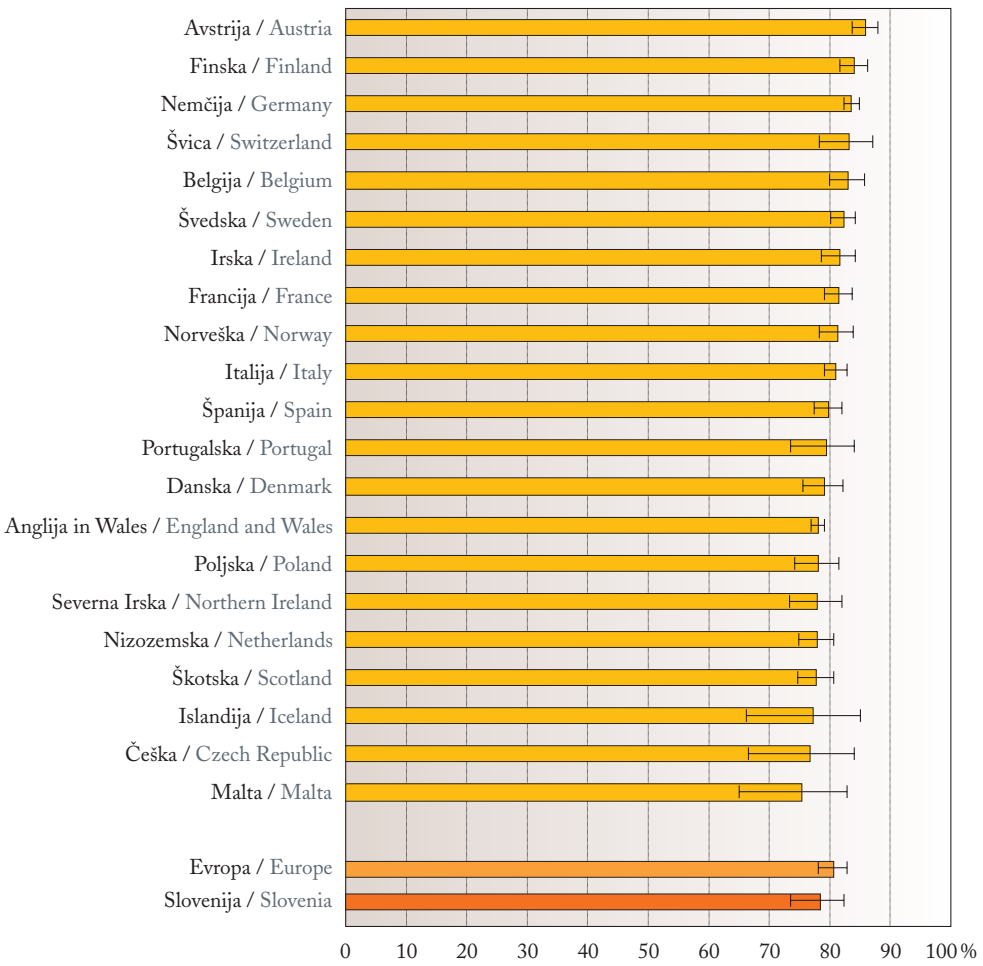
In the period 2001–2005, 3.5% of children and adolescents did not receive specific treatment. The proportion of untreated patients has not changed significantly throughout the period under analysis. All the patients with cancers of hematopoietic and lymphatic organs received cytostatics. Approximately 80% of these patients also received an adjuvant therapy with corticosteroids, while 18% of patients with leukemias, 78% with HL and 20% with NHL were additionally irradiated. Among the patients with CNS tumors, 93% underwent surgery, and half of these also received chemotherapy; in 38% surgery was combined with radiotherapy.

In the period 2001–2005, slightly less than half of the patients started their treatment at the University Children's Hospital in Ljubljana, 27% in the UMC Ljubljana, 13% at the IO Ljubljana and 4% in the UMC Maribor. Individual patients also started their treatment in the GH of Celje, Izola, Murska Sobota, Nova Gorica, Novo mesto and Jesenice. Nearly all those who started their treatment in the UMC Ljubljana had CNS tumors and underwent surgery there, while patients with HL mostly started their treatment at the IO Ljubljana.

The relative survival of children and adolescents with cancer has been increasing: in 15 years, the 5-year relative survival increased by 12% (Figure 3), in girls slightly more than in boys (Table 4). The lowest survival was observed in patients with disseminated disease (Figure 4); the 5-year relative survival of patients with disseminated disease diagnosed in the period 2001–2005 was 72%, while the survival rate of patients with regional disease was 90%. The survival of children does not significantly differ from that of adolescents (Figure 5). When comparing the survival of children and adolescents with the most frequent cancers (Table 5), in 15 years the highest increase in 5-year relative survival is seen in patients with CNS tumors and in patients with HL, in the latter being 100% in the last period. The survival in leukemias and HL is similar in both genders; in the last period, however, better survivors among NHL patients were girls and among patients with CNS tumors boys. The results of survival by stage in the most frequent cancers of children and adolescents are unreliable owing to a small number of patients in individual stages. When comparing the survivals of children with those of adolescents, we note better survivals with leukemias, CNS tumors and NHL in children fewer than 15 years of age.

The 5-year relative survival rate of all patients diagnosed in the period 2001–2005 was 83% (Figure 3); patients surviving the first year may expect to survive five years in 92%. If the patient survives the first year, a similar increase in the expected survival is noted in individual cancer

STAROST / AGE
0–14



Slika 6: *Petletno relativno preživetje bolnikov z rakom (povprečje in 95-odstotni interval zaupanja) starih od 0–14 in od 15–24 let, zbolelih v letih 1995–2002, v Sloveniji in izbranih evropskih državah (EUROCARE-4)*.*

* Vir: Gatta G., Žigon G., Capocaccia R., Coebergh J. W., Desandes E., Kaatsch P., Pastore G., et al. Survival of European children and young adults with cancer diagnosed 1995–2002. Eur J Cancer 2009; 45: 992–1005.

levkemijo vključeni v medcelinsko raziskavo ALL-IC 2002. Po nekaterih ocenah otroških levkemologov je 90-odstotno preživetje verjetno zgornja meja, ki jo je mogoče doseči pri zdravljenju levkemije s trenutnim konceptom zdravljenja. Nakazano zmanjšanje preživetja v zadnjem obdobju je zato treba tolmačiti z zadržkom, saj gre pri njem lahko tudi za naključno nihanje.

Število bolnikov s tumorjem CŽS v otroškem obdobju je sorazmerno stalno. Osnovni način zdravljenja ostaja nevrokirurgija. Delno gre povečanje preživetja verjetno pripisati izboljšanim metodam diagnostike in uvajanju intenzivnejših shem pooperativne kemoterapije, vključno s kemoterapijo z visokimi odmerki s podporo avtolognih matičnih krvotvornih celic.

Delež bolnikov, ki se je zaradi HL zdravil zunaj Pediatrične klinike, je 25 %. Vsi ti bolniki so se zdravili na OI Ljubljana. Večinoma gre za bolnike, starejše od 18 let. Komentar preživetja verjetno ni potreben, saj številke govorijo, da je s sodobnimi načini diagnostike in zdravljenja HL v obdobju otroka in mladostnika ozdravljiva bolezen.

STAROST / AGE 15–24

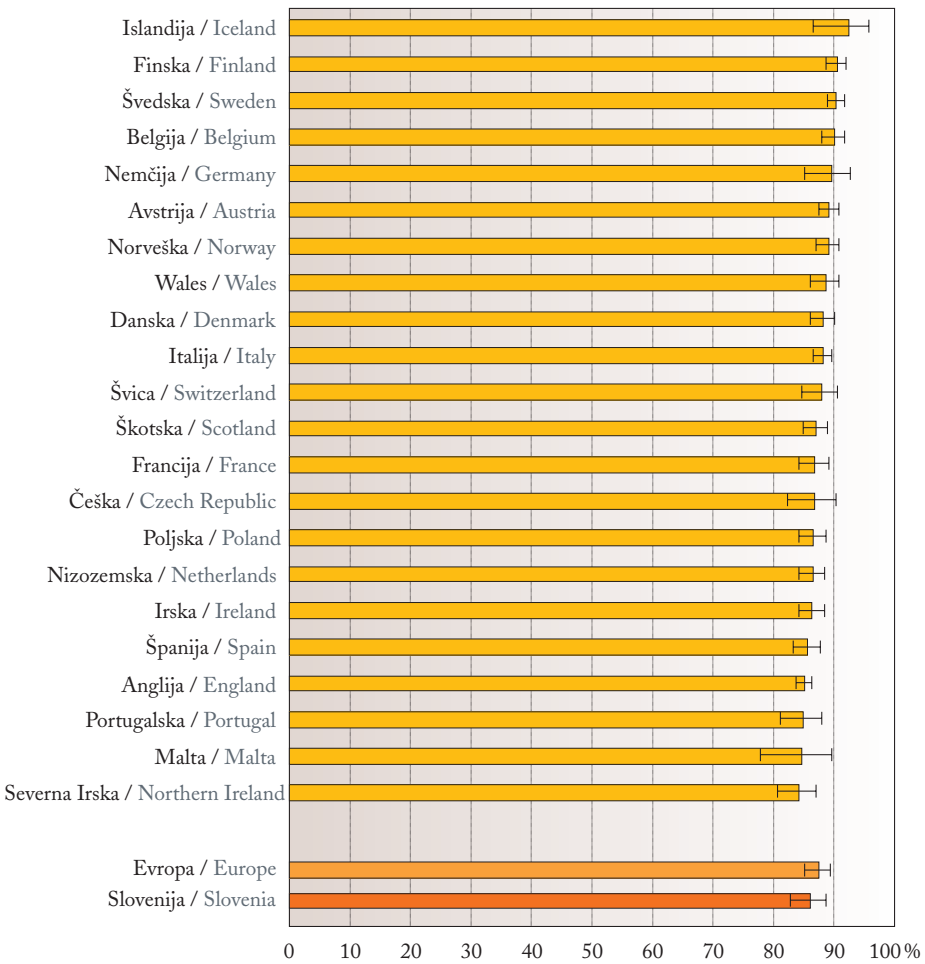


Figure 6: *5-year relative survival of cancer patients (average and 95% confidence interval) aged 0–14 and 15–24, diagnosed in the period 1995–2002 in Slovenia and in European countries (EUROCARE-4)*.*

* Source: Gatta G., Žigon G., Capocaccia R., Coebergh J. W., Desandes E., Kaatsch P., Pastore G., et al. Survival of European children and young adults with cancer diagnosed 1995–2002. Eur J Cancer 2009; 45: 992–1005.

types: in leukemias from 74% to 86%, in CNS tumors from 69% to 83% and in NHL from 75% to 96%.

According to the results of EUROCARE-4 study of patients diagnosed in 2000–2002, the survival of children and adolescents with cancer in Slovenia is below (statistically not significant) the European average (Figure 6).

CLINICAL COMMENTARY

Janez Jazbec

It has been agreed in principle that in Slovenia all children up to their 18 years of age justifiably suspected of having cancer, should undergo a diagnostic workup and treatment at the National Centre for Pediatric Oncology of the University Children's Hospital in Ljubljana functioning within the framework of the UMC Ljubljana and closely cooperating with the IO Ljubljana. As the present analysis includes adolescents up to 20 years of age, the proportion

Tabela 5: *Deset-, pet-, tri- in enoletno relativno preživetje bolnikov, mlajših od 20 let, pri štirih najpogostejših lokacijah raka po obdobju postavitve diagnoze s 95-odstotnim intervalom zaupanja.*

Table 5: *10-, 5-, 3- and 1-year relative survival of cancer patients younger then 20 years by four most common cancer locations and period of diagnosis with 95% confidence interval.*

		Relativno preživetje / Relative survival (%)			
	Obdobje / Period	1-letno / -year	3-letno / -year	5-letno / -year	10-letno / -year
Levkemije / Leukaemias	1991–1995	86,3 (78,4–94,2)	70,1 (59,3–80,9)	62,6 (51,0–74,2)	60,2 (48,4–72,0)
	1996–2000	92,8 (87,1–98,6)	79,6 (70,4–88,8)	77,3 (67,7–86,9)	76,2 (66,4–86,0)
	2001–2005	85,9 (77,8–94,0)	78,3 (68,6–88,0)	74,2 (63,1–85,3)	–
Tumorji centralnega živčnega sistema / Tumors of central nervous system	1991–1995	70,6 (56,9–84,3)	64,8 (50,2–79,4)	59,0 (43,8–74,2)	55,2 (39,6–70,8)
	1996–2000	75,5 (63,0–88,0)	58,6 (43,7–73,5)	54,8 (39,6–70,1)	49,3 (33,7–64,9)
	2001–2005	82,6 (70,9–94,4)	71,8 (57,5–86,1)	68,9 (53,7–84,1)	–
Hodgkinov limfom / Hodgkin's limfoma	1991–1995	95,6 (91,2–100,0)	91,3 (82,6–100,0)	89,2 (79,5–98,9)	87,3 (76,7–97,8)
	1996–2000	100,0	97,1 (94,1–100,0)	91,1 (82,0–100,0)	88,3 (76,4–100,0)
	2001–2005	100,0	100,0	100,0	–
ne-Hodgkinovi limfomi / non-Hodgkin's limfoma	1991–1995	75,8 (59,7–91,9)	72,8 (55,9–89,8)	73,0 (56,0–89,9)	67,1 (48,8–85,4)
	1996–2000	92,6 (85,2–100,0)	81,6 (65,5–97,6)	81,7 (65,6–97,8)	81,9 (65,8–98,0)
	2001–2005	78,2 (62,4–93,9)	75,1 (58,5–91,7)	75,2 (58,5–91,8)	–

V zadnjem petletnem obdobju se je zmanjšalo preživetje moških bolnikov z NHL. Pri dekletih je v isti starostni skupini preživetje v zadnjem obdobju 100 %. Glede na to, da je pristop k diagnostiki in zdravljenju pri obeh spolih enak, bo treba rezultat natančnejše analizirati, saj iz podatkov, ki so trenutno na voljo, razlage za razliko v preživetju med spoloma ni.

VIRI
Literature

Jazbec J, Rajić V, Karas-Kuželički N. Levkemije otroške dobe. Zdrav Vestn 2008; 77 Suppl 1: I-25–30.

Jazbec J, Anžič J, Benedik-Dolničar M, Kitanovski L, Velenšek-Prestor V, Rajić V, Pretnar J. Presaditev krvotvornih matičnih celic pri otrocih v Sloveniji – stanje in perspektive. In: Kržišnik C, Battelino T. Izbrana poglavja iz pediatrije 19: novosti v klinični pediatriji, obnovitvena rehabilitacija, pediatrična alergologija. Ljubljana: Katedra za pediatrijo, 2007; 61–7.

Jazbec J, Ećimović P, Jereb B. Second neoplasms after treatment of childhood cancer in Slovenia. Pediatr Blood Cancer 2004; 42: 574–81.

Velenšek-Prestor V, Jazbec J. Preživetje otrok in mladostnikov s solidnimi tumorji v Sloveniji v obdobju 1990–2000. Slov Pediatr 2002; 9: 94–9.

Mali P, Jazbec J. Preživetje otrok in mladostnikov z nehodgkinovim limfomom v Sloveniji v obdobju 1990–1999. Slov Pediatr 2002; 9: 90–3.

Mali P, Jazbec J. Preživetje otrok in mladostnikov z akutno levkemijo v Sloveniji v obdobju 1990–1999. Slov Pediatr 2002; 9: 86–9.

of patients starting specific treatment in other hospitals could represent the patients treated at an age between 18–20 years.

The fact that malignant diseases in children make a heterogeneous group renders an exact analysis of factors contributing to the observed improvement in survival very difficult.

Children with leukemias in Slovenia are treated according to the schedules derived from the so-called BFM (Berlin-Frankfurt-Münster) schedule. In recent years, all patients with acute lymphoblastic leukemia are included into the intercontinental ALL-IC 2002 study. According to some assessments of pediatric leukemologists, 90% survival is probably the upper limit attainable in leukemia treatment by means of present treatment approach. Therefore, the indicated downward trend in the survival in the last observation period should be interpreted with caution, as it may be a result of random fluctuation.

The number of patients with CNS tumors in childhood is relatively stable. Neurosurgery still remains the basic treatment approach. An increase in the survival could partly be ascribed to the improved diagnostic methods and to the implementation of more intensive postoperative chemotherapeutic schedules, including megatherapy with autologous hematopoietic stem-cell support.

The proportion of patients treated for HL outside the University Children's Hospital amounts to 25%. All these patients, the majority of them being older than 18 years, were treated at the IO Ljubljana. There is probably no need to add any comment on the survival since the rates themselves clearly show that – by means of up-to-date diagnosis and treatment – HL in childhood and adolescence is a curable disease.

In the last 5-year period, the survival of male patients with NHL has decreased. In the same period, the survival of girls in the same age group was 100%. Considering that the same diagnostic and treatment approach is used in both genders, the result calls for a detailed analysis, since on the basis of currently available data the gender-related difference in the survival cannot be explained.

KAJ VSE POVEDO PRIKAZANI REZULTATI

UVOD

Rak je bolezen, s katero se moderna civilizacija vse pogosteje srečuje. Z višjim življenjskim standardom, higienskimi in drugimi javnozdravstvenimi ukrepi se je pričakovana življenjska doba močno podaljšala. Starost je eden glavnih nevarnostnih dejavnikov raka, bolezni, ki je bila v preteklosti redka in v večini primerov smrtna. Z razvojem znanosti in tehnologije imamo danes vrsto orožij, da se z njo spopademo in jo v visokem odstotku obvladamo. Brez merjenja učinka naših intervencij, ki izhajajo iz predkliničnih in kliničnih raziskav na celotni populaciji, pa bi bila borba in uspehi jalovi. V medicini se namreč nemalokrat izkaže, da uspešen eksperiment v laboratoriju ali na izbrani skupini ljudi ne kaže enakega učinka na celotni populaciji bolnikov. Kako uspešni smo pri obvladovanju raka, merimo med drugim tudi s populacijskim preživetjem. S spremljanjem tega kazalca v daljšem časovnem obdobju lahko dokaj zanesljivo ugotovimo, kakšne posledice imajo ukrepi, ki dokazano vplivajo na zgodnje odkrivanje in zdravljenje raka. Izredno pomembno bi bilo, če bi lahko merili tudi kakovost življenja teh bolnikov, vendar so metodologije za to trenutno prezapletene in tudi današnji zajem podatkov tega ne omogoča.

ŠTEVILO IN KAKOVOST PODATKOV, ZBRANIH V REGISTRU RAKA REPUBLIKE SLOVENIJE

Pravzaprav bi moral biti rak preprosto ozdravljiva bolezen, če vemo, da vznikne iz ene same celice. Žal dejstva kažejo ravno obratno. Več kot vemo o biologiji celice, bolj postaja jasno, da je rak bolezen, s katero se bo treba spopasti intenzivno na vseh ravneh (primarna, sekundarna preventiva, zdravljenje, rehabilitacija), da jo bomo uspeli obvladovati, verjetno pa je v celoti ne bomo obvladali nikoli. Ker se v obvladovanje raka vključujejo številni dejavniki, postaja jasno, da so stroški teh naporov visoki; pričakujemo, da se bodo v prihodnje strmo večali. Če ne bomo sprejemali dokazano učinkovitih ukrepov pravočasno in na pravem mestu, raka ne bomo mogli obvladovati kljub vedno večjemu vlaganju v to področje. Za načrtovanje učinkovitih ukrepov na področju raka so zato potrebne analize, kot je ta, ki pa morajo seveda temeljiti na vrsti relevantnih podatkov. Kaj bi bilo potrebno v zajemu naših podatkov v RRS dopolniti ali izboljšati, da bi bile te analize še bolj verodostojne in natančne?

Če razumemo, da je glavni namen zajema podatkov načrtovanje z dokazi podprtih ukrepov in da njihov učinek lahko vrednotimo, potrebujemo danes pri vrednotenju obvladovanja raka naslednje podatke: histološko/citološko diagnozo, zamejitev raka (stadij) in plan ter izvedbo prvega zdravljenja. Za zajem teh podatkov se bo seveda potrebno poslužiti vseh možnosti, ki jih lahko nudi sodobna informacijska tehnologija. Registri raka so dragoceno podatkovno skladišče za številne analize bremena raka v državi, število in kakovost podatkov, ki jih potrebujemo za natančnejše analize preživetja, pa z današnjo tehnologijo zbiranja podatkov, kakovostjo posredovanih podatkov in s številom osebja, ki jih obdeluje, ne sledijo potrebam klinikov. Nujno bo, da v prihodnje skupaj s stroko dorečemo in razširimo nabor podatkov, ki bo omogočil še dodatne, bolj usmerjene analize. Vse te dopolnitve seveda narekujejo posodobitev tehnologije zbiranja in obdelave podatkov RRS, ne nazadnje tudi več osebja; zagotovo pa bo taka investicija stroškovno učinkovita in smiselna.

WHAT CAN BE DERIVED FROM THE PRESENTED RESULTS

INTRODUCTION

Cancer is a disease that modern civilization has to face more and more frequently. A higher standard of life as well as hygienic and other public health measures contributed to a considerable increase in life expectancy. Consequently, the number of cases is increasing, as age is one of the main risk factors for cancer, the disease that used to be quite rare and in most cases fatal in the past. The development in science and technology produced a number of tools, which help us to combat and quite successfully control the disease. However, without evaluating the effects of our interventions, derived from population-based preclinical and clinical research, this fight and its results would be worthless. Namely, in medicine it often turns out that a successful experiment carried out in vitro or in a selected group of people does not yield the same result when applied to the whole population of patients. The success in cancer control is measured among other things by population survival. By following this indicator over a longer period, it is possible to assess quite reliably the results of interventions known to influence early detection and treatment of cancer. It would be very important if we could also measure the quality of patients' life, however the relevant methodologies are presently too complex, and the current data collection does not enable that either.

THE NUMBER AND QUALITY OF DATA COLLECTED BY THE CANCER REGISTRY OF REPUBLIC OF SLOVENIA

Actually, cancer should be an easily curable disease, considering that it originates from a single cell. Unfortunately, the facts show just the opposite, and more that we know about cell biology, more clear it becomes that, in order to control cancer successfully, the disease should be approached intensively at all levels (primary and secondary prevention, treatment and rehabilitation), though a complete control can probably never be attained. Since cancer control includes several factors, obviously, these efforts are associated with high costs, which are expected to increase even more rapidly in the future. If the proven effective measures are not going to be adopted in due time and where necessary, cancer would remain out of control, despite the ever higher investments into this area. Therefore, effective intervention planning in the area of cancer requires analyses such as the present one; however, these must be based on a range of relevant data. What in the CRS's data collection should be upgraded or improved so as to render those analyses even more valid and accurate?

Considering that the main objective of data collection is to plan evidence-based interventions and to facilitate the evaluation of the effect of these interventions, presently the following data are needed for the evaluation of cancer control: histological/cytological diagnosis, cancer staging, treatment planning and primary treatment implementation. In order to collect all these data, it will be necessary to make use of all the facilities offered by current information technology. Cancer registries represent valuable data pools for several analyses of national cancer burden, however, the current technology of data collecting, the quality of the data provided and the number of personnel involved in the data processing are not able to ensure that the scope and quality of data needed for more accurate survival analyses would be consistent with the needs of clinicians. In the future, it will be necessary to define and expand – together with

Pri širjenju števila podatkov, ki se zbirajo in obdelujejo v RRS, bo treba misliti predvsem na naslednje:

Histološka/citološka diagnoza

Že danes, predvsem pa v prihodnje, bo molekularni profil raka odločal o načrtovanju zdravljenja, zato bo potrebno v RRS beležiti histološko/citološko diagnozo na način, da bo mogoče kadar koli preveriti, ali je bilo zdravljenje izvedeno v skladu s smernicami, ki bodo temeljile na genskem podpisu raka. Samo velik delež histološko/citološko potrjenih rakov, za kar gre velika zasluga RRS v preteklosti, bo postal le nujen predpogoj, saj bo moral biti na voljo tudi genski podpis (terapevtske tarče) pri vseh rakavih boleznih, ki se bodo zdravile, da bomo lahko spremljali, ali je bilo predpisano zdravljenje primerno in tudi stroškovno učinkovito.

Stadij

Beleženje stadija raka bo še vedno potrebno, morda še bolj zaradi spremljanja učinkovitosti presejalnih programov, a tudi zaradi ugotavljanja primernosti zdravljenja. Ravno zaradi slednjega in zaradi upoštevanja smernic, ki temeljijo na stadiju TNM, bo treba poleg registrskega uporabiti tudi za vsako anatomsko mesto raka priporočen stadij (TNM ali po kaki drugi klasifikaciji); seveda pa je od poročevalcev RRS odvisno, kako popoln je ta podatek. RRS stadij bolezni po TNM oz. po drugih klasifikacijah beleži že sedaj, vendar prevečkrat v prijavnici ni zapisan. Velikokrat pa je bila nenatančna postavitev stadija tudi povezana z nedostopnostjo diagnostičnih naprav (CT, MRI). Kako je to pomembno, se vidi v slabšem preživetju v primerjavi z zahodnoevropskimi državami, npr. pri uroloških rakih, kjer je bila dostopnost do diagnostičnih možnosti neprimerno boljša.

Načrt in izvedba prvega zdravljenja

Na tem področju bo treba v zajemu podatkov RRS največ dopolniti. Beležiti bo treba odločitev multidisciplinarnega konzilija o predlaganem prvem zdravljenju in nato zabeležiti tudi prejeto zdravljenje (s podatki o operativnem posegu, obsevanju, sistemskem zdravljenju in o tem, kje in kdo je zdravljenje izvedel). Le na ta način bomo lahko zares vrednotili vzroke za ugotovljene rezultate zdravljenja in na njih vplivali, kjer bo to potrebno. Le pravilno načrtovano in izvedeno prvo zdravljenje je lahko učinkovito, s tem pa tudi najbolj stroškovno učinkovito.

KAJ DELAMO DOBRO, KAJ SLABO IN KAJ MORAMO IZBOLJŠATI

Primarna preventiva

Merilo za uspeh primarne preventive je zmanjševanje incidence, kar praviloma spremlja tudi zmanjšanje umrljivosti. Kot je razvidno iz prikazov v posameznih poglavjih in pri vseh rakavih boleznih skupaj, se pri večini incidenca veča, umrljivost pa ostaja enaka (starostno standardizirana se celo zmanjšuje), kar kaže, da smo bolj uspešni pri zdravljenju, ki je seveda neprimerno dražji ukrep z neprimerno več sopojavi kot preprečevanje, npr. z zdravo hrano, s primerno telesno dejavnostjo, z nekajenjem, omejevanjem alkoholnih pijač in izogibanjem karcinogenom v delovnem in bivalnem okolju. Edini rak, kjer se incidenca vztrajno manjša pri obeh spolih, je želodčni rak, pa še tu je trend zmanjševanja v Sloveniji počasnejši kot drugod po svetu. Pri moških sta se incidenca in umrljivost za pljučnim rakom na račun manjšanja deleža kadilcev ustalila, medtem ko se pri ženskah strmo večata. Očitno so ukrepi na področju omejevanja kajenja vplivale predvsem na odrasle moške, zato bo treba najti nove poti, kako vplivati tudi na ženske in mlade.

the competent profession – the range of data that would facilitate additional, more directed analyses. Of course, all these amendments require that the data collecting and processing technologies of the CRS be updated and more personnel employed, but undoubtedly such an investment would prove cost-effective.

When expanding the range of data to be collected and processed by the CRS, particularly the following should be considered:

Histological/cytological diagnosis

Already today, but even more so in the future, treatment planning will depend on the molecular profile of cancer, and therefore in the CRS histological/cytological diagnosis should be registered in such a way that it will be possible to check at any time whether the treatment was carried out in accordance with the guidelines based on cancer gene transcript. A large proportion of histologically/cytologically confirmed cancers – which is definitely the result of the CRS's efforts in the past – will become an ultimate prerequisite only, since gene transcripts (therapeutic targets) will also have to be available in all cancers treated, thus enabling us to assess whether the prescribed treatment was both suitable and cost-effective.

Stage

Stage registration will still be necessary, perhaps even more so, to facilitate the surveillance of the effectiveness of screening programs rather than to assess the adequacy of therapy. For that very reason, as well as for taking account of the guidelines based on the TNM staging system, apart from the registry's also a staging (according to TNM or any other classification) recommended for each cancer site in accordance with the pathologist's definition will have to be used; the completeness of these data, however, depends on the reporters to CRS. So far, stage according to TNM or some other classifications has already been registered by the CRS, however, too often this information is lacking on the notification form. Stage registration will have to be improved particularly in urological cancers, where inaccurate staging was also associated with lacking access to diagnostic facilities (CT, MRI). The importance of this is reflected in a lower survival in comparison with West European countries, where the accessibility of diagnostic facilities is much better.

Primary treatment planning and performance

This segment of CRS's data acquisition requires major upgrading. Registration will have to include the decision by a multidisciplinary team counsel on the proposed primary treatment as well as the therapy received (including information on surgical interventions, irradiation, systemic therapy and specifying where and who performed the treatment). All these data will enable us to actually evaluate the reasons for the obtained treatment results and influence them as necessary. Only a correctly planned and performed primary treatment may be successful and thus also cost-effective.

WHAT ARE WE DOING WELL, WHAT ARE OUR WEAKNESSES AND WHAT SHOULD BE IMPROVED

Primary prevention

In primary prevention, the measure of success is a decreasing incidence, generally also accompanied by a decreasing mortality. As evident from the presentations in individual chapters and for all cancers combined, in the majority of them the incidence rates are increasing while the

Sekundarna preventiva

Merilo za učinkovitost presejalnih programov je zmanjšanje umrljivosti za rakom; pri rakavih boleznih, pri katerih s presejanjem zdravimo predrakave spremembe, pa tudi incidence (npr. pri raku materničnega vratu, debelega črevesa in danke). Tako se pri nas že kažejo učinki presejalnega programa za raka materničnega vratu ZORA. Pri raku dojk se počasi veča delež bolnic z omejenim stadijem (brez prizadetih pazdušnih bezgavk ob diagnozi), verjetno na račun večje skrbi žensk za svoje zdravje in oportunističnega presejanja. Starostno standardizirana umrljivost se manjša, delno na račun zgodnejše diagnoze, predvsem pa na račun boljšega dopolnilnega zdravljenja. Glede na podatek, da je petletno relativno preživetje bolnic z rakom dojk, ki nimajo prizadetih pazdušnih bezgavk ob diagnozi, več kot 95-odstotno (govori o odlično izvedenih postopkih zdravljenja raka dojke v naši državi!), bi s kakovostnim presejalnim programom lahko še zmanjšali umrljivost. Pri raku debelega črevesa in danke pa odkrijemo manj kot 15 % bolnikov z omejenim stadijem, pri njih pa je petletno relativno preživetje več kot 90-odstotno. S kakovostnim presejalnim programom bi z odstranjevanjem predrakastih polipov zmanjšali incidenco, raka pa bi v skoraj treh četrtinah odkrili v omejenem stadiju.

Zdravljenje

Merilo za uspeh terapevtskih ukrepov je preživetje, seveda je pri tem treba upoštevati stadij bolezni in starost bolnikov, saj imajo starejši bolniki vrsto spremljajočih bolezni, pri katerih je potrebno zdravljenje prilagoditi ali pa ga sploh ni možno izvesti. Ravno zato je zelo pomembno, da specifično zdravljenje izvajajo za to usposobljeni strokovnjaki onkologi, ki se pretežni del svojega časa ukvarjajo z bolniki z rakom in obravnavajo zadostno število bolnikov. Takšne so tudi mednarodne zahteve in definicije*. Kako se teh načel držimo v Sloveniji? Kot je razvidno iz posameznih poglavij, se bolniki z rakom zdravijo praktično v vseh slovenskih bolnišnicah. To je tudi pričakovati, saj pomembnejših ukrepov na tem področju, ki bi kaj spremenili, v teh obdobjih praktično ni bilo. Verjetno pa je to področje, kjer bo moralo priti do dodatnih sprememb predvsem pri redkih rakavih boleznih, ki jih morajo zdraviti v enem centru; pogostejše pa v več, vendar v tistih, ki so za to dodatno usposobljeni. Podatek iz pričujoče publikacije, ki to podpira, je razlika v preživetju bolnikov z NHL, zdravljenih na OI Ljubljana, kjer se zdravi 80 % slovenskih bolnikov, v primerjavi z ostalimi 20 %, ki se zdravijo v ostalih bolnišnicah. Ob upoštevanju ostalih dejavnikov (stadij, starost), ki so bili vključeni v multivariatni model, je tveganje smrti kar 2,5-krat manjše pri bolnikih, zdravljenih na OI Ljubljana. Iz dostopnih podatkov seveda ne moremo izluščiti natančnih vzrokov. Ker so NHL še vedno relativno redka bolezen, je nedvomno bolj smotrno, da se ti bolniki zdravijo tam, kjer so zaradi večjih izkušenj možnosti ozdravitve večje.

Na podoben način bo treba napraviti natančnejše analize, ki presegajo obseg te publikacije, tudi za druge rakave bolezni in na ta način ugotoviti centre, ki bodo bolj usmerjeni v zdravljenje določenih bolezni. Ob tem bo treba upoštevati tudi pogostost bolezni in dostopnost posameznih načinov zdravljenja.

Kirurgija ostaja še vedno najpogostejši način zdravljenja raka pri bolnikih vseh starosti, saj so jo kot edini način zdravljenja uporabili v zadnjem obdobju pri 43 % bolnikov, kot sestavni del pa še pri nadaljnjih 33 % bolnikov. Odstotek bolnikov, ki je bil zdravljen z obsevanjem, je bil v obdobju 1991–1995 43 %, v obdobju 2001–2005 se je zmanjšal za več kot četrtino, na 31 %. Potrebno je analizirati, ali gre dejansko za manjši odstotek indikacij za obsevanje pri posameznih

* **Onkolog** je zdravnik ali zdravnica, ki **polni delovni** čas zdravi bolnike z rakom. Je dodatno usposobljen/-a na področju **internistične**, **obsevalne** ali **kirurške onkologije**. Zna uporabljati specifično onkološko zdravljenje in simptomatsko, psihološko, podporno in paliativno zdravljenje, ki ga izvaja dnevno za izboljšanje kakovosti življenja bolnikov z rakom. Je usposobljen/-a in se še naprej izobražuje za uporabo takih postopkov, ki najbolj koristijo bolniku, ob tem, da zna upoštevati psihološke in socialne potrebe bolnikov z rakom in njihovih družin. (http://www.esmo.org/about-esmo/bylaws.htmlc1006)

mortality remains the same (the age-standardized is even decreasing), which shows that our treatment is more successful – albeit these measures being much more expensive and entailing much more adverse effects – than prevention, e. g. by means of healthy nutrition, adequate physical activity, non-smoking, reduced alcohol drinking and avoiding exposure to carcinogens in workplace and living environment. Stomach cancer is the only cancer with a persistent downward trend in the incidence in both genders, but even there the decreasing trend in Slovenia is slower than elsewhere in the world. While the incidence and mortality for lung cancer in males have become stable on the account of a decreasing proportion of smokers among them, the relevant rates in females are undergoing a steep increase. Obviously, smoking restriction measures have exerted a prevailing influence on adult males, and therefore new ways should be sought to influence women and adolescents as well.

Secondary prevention

A measure of the effectiveness of screening programs is a reduced cancer mortality and – in cancers where screening is intended to detect precancerous changes – also a reduced incidence (e. g. in cervical and colorectal cancers). Thus we can already witness the effects of our ZORA screening program for cervical cancer. In breast cancer the proportion of patients with localized stage (without lymph node involvement at diagnosis) is slowly increasing, probably on the account of greater awareness of women regarding their health, and also as a result of opportunistic screening. Age-standardized mortality is decreasing, partly due to earlier detection, but mainly due to better adjuvant therapy. Considering the fact that the five-year relative survival of breast cancer patients without lymph node involvement at diagnosis is over 95% (which speaks for an excellent approach to the treatment of breast cancer in Slovenia!), a quality screening program may further reduce the relevant mortality rates. In colorectal cancer, less than 15% of patients are diagnosed in a localized stage, where the five-year relative survival exceeds 90%. A quality screening program may reduce the incidence as a result of detected and removed premalignant polyps, while in almost three fourths of cases cancer could be detected in a localized stage.

Treatment

Although survival is the measure of therapeutic success, stage of disease and patients' age should be taken into account as well, since elderly patients present with a number of concomitant diseases, so their treatment has to be adjusted or is not feasible at all. Therefore it is of particular importance that specific treatment be carried out by adequately qualified experts-oncologists, prevailingly involved in the management of cancer patients and thus having sufficient experience in this area of expertise. This is consistent with the international requirements and definitions too*. And how are these principles respected in Slovenia? As evident from individual chapters of this report, cancer patients are treated in practically all general hospitals of Slovenia. Such situation is not surprising since practically no major interventions to change it in any way have been undertaken in this respect in the past 15 years. Probably this is an area where certain additional changes will have to be made particularly as regards rare cancers, which should be treated in a single center, while more frequent cancers may be treated in several institutions, however these should be additionally qualified to do that. Further evidence that supports this view can be found in the present publication showing the difference between the survival

* **An oncologist** is a physician taking care of cancer patients **full-time**. He/she has training in **Medical Oncology or Radiation Oncology or Surgical Oncology**. He/she is able to use **the respective** therapies and symptomatic, psychological, supportive, palliative, and after care in daily clinical practice to improve the quality-of-life of cancer patients. He/she will be trained and continue to update his/her knowledge in the application of such interventions for optimal benefit, taking into account the psychological and social needs of cancer patients and their families. (http://www.esmo.org/about-esmo/bylaws.htmlc1006)

rakavih boleznih (npr. pri Hodgkinovi bolezni, drugih limfomih in seminomih) ali pa niso prav postavljene indikacije za obsevanje (v obdobju 2001–2005 je bilo obsevanih samo 7 % bolnikov z rakom prostate). Pri zdravljenju s kemoterapijo vidimo ravno obratno; v letih 1991–1995 jo je prejelo 26 % bolnikov kot prvo zdravljenje samo ali v kombinaciji z ostalimi načini, v obdobju 2001–2005 pa 3 % več. Zavedati pa se moramo, da tu ni upoštevano hormonsko in tarčno zdravljenje, ki je v zadnjem času v strmem porastu, tako po indikacijah kot po trajanju (več let, doživljenjsko). Zato bo treba pri racionalnem načrtovanju potreb po posameznih profilih specialistov v prihodnje te trende upoštevati, da bo kakovost zdravljenja primerna in zares učinkovita.

of patients with NHL treated at the IO Ljubljana (80% of NHL patients in Slovenia) and the remaining 20% treated in other hospitals. Taking into account other factors (stage, age) included in the multivariate model, patients treated at the IO Ljubljana have as much as 2.5-fold lower risk of death. The available data do not provide conclusive information on the exact reasons for such results, however. As NHL is a relatively rare disease, it seems definitely more reasonable that the patients are treated there where their chances of cure are, because of more experienced stuff, better.

Similar, more detailed analyses, which exceed the scope of this publication, will also have to be carried out for other cancers in order to identify the centers that would be most competent for treatment of particular diseases. At the same time it will be necessary to take into account the frequency of diseases and the accessibility of individual treatment modalities.

Surgery still remains the most important method of cancer treatment in patients of all ages; thus, in the last period it was used as monotherapy in 43% of patients and as part of combined therapy in another 33%. In the period 1991–1995, the proportion of patients treated by irradiation represented 43%, whereas in the period 2001–2005 this percentage decreased by more than one-fourth, being 31%. It would be necessary to analyze whether the decrease is actually due to a lower percentage of indications for irradiation in individual cancers (e. g. in Hodgkin's disease, other lymphomas and seminomas) or perhaps the indications for irradiation are not established correctly (in the period 2001–2005 irradiation treatment was used in only 7% of patients with prostate cancer!). The opposite situation is observed as regards chemotherapy: in the period 1991–1995, 26% of patients received it in the course of their primary treatment either alone or in combination with other methods, whereas in the period 2001–2005 this percentage increased by 3%. It should be kept in mind, however, that this score does not include the use of hormone and targeted therapy, which has been recently on the steep increase so in terms of indications as well as the duration of treatment (several years or lifelong). Therefore, these trends should be taken into account in order to rationally plan the need for individual profiles of specialists in the future and thus ensure an adequate quality and effectiveness of therapy.

PREGLED NAJPOMEMBNEJŠIH UGOTOVITEV

1. Preživetje odraslih bolnikov z rakom (brez kožnega) se s časom pri večini rakavih bolezni pomembno izboljšuje; v desetih letih (1991–1995 in 2001–2005) se je petletno relativno preživetje vseh bolnikov izboljšalo za 12 % (s 40 % na 52 %), moških za 14 % (s 30 % na 44 %) in žensk za 10 % (z 49 % na 59 %).
2. Pri pogostejših rakavih boleznih, ki v obdobju 2001–2005 posamično predstavljajo 3 % ali več skupnega bremena raka pri odraslih, skupaj pa 61 %, se je preživetje v 10 letih povečalo za 10 % ali več pri vseh rakavih boleznih, razen pri dveh, kjer tudi v Evropi ni večjega napredka (pljuča, maternično telo); najbolj se je preživetje povečalo pri raku prostate (za 26 %), sledijo debelo črevo (16 %), dojka (14 %), kožni melanom (12 %), danka (11 %) in želodec (10 %) (Tabela 1).
3. Po rezultatih raziskave EUROCARE-4 za bolnike, zbolele v letih 2000–2002, pri vseh v točki 2 omenjenih rakavih boleznih preživetje slovenskih bolnikov zaostaja za evropskim povprečjem, največ pri raku prostate, za 16 % (Tabela 1).
4. Skupina redkejših rakavih bolezni, ki v obdobju 2001–2005 posamezno predstavljajo manj kot 3 % skupnega bremena raka pri odraslih, je heterogena. V prvi skupini so rakave bolezni, pri katerih je preživetje slovenskih bolnikov enako ali celo boljše od evropskega povprečja (Tabela 2). Med njimi z najboljšim preživetjem izstopajo bolniki z rakom mod, ščitnice in Hodgkinovo boleznijo, ki se že sedaj zdravijo v zato usmerjenih centrih. V drugi skupini redkejših rakov (Tabela 3) so bolniki, katerih preživetje zaostaja za evropskim povprečjem (urološki in hematološki raki ter večina rakov glave in vratu).
5. Nekatere od rakavih bolezni z najslabšim preživetjem (pljučni rak, rak žrela in požiralnika) so kot opomin narave človeški neumnosti; zdravljenje ni uspešno, z zdravim življenjskim slogom pa bi jih večino lahko preprečili!
6. Ker se prebivalstvo stara, zboli za rakom vse več starejših. V zadnjem obdobju je bila že petina odraslih moških z rakom (brez kožnega) in skoraj tretjina žensk ob diagnozi stara 75 let ali več – Tabela 1, poglavje *Vse rakave bolezni pri odraslih (brez kožnega)*. V primerjavi z mlajšimi je njihovo petletno relativno preživetje statistično značilno manjše, vendar se ravno tako s časom izboljšuje – Slika 4, poglavje *Vse rakave bolezni pri odraslih (brez kožnega)*. Eden od razlogov za slabše preživetje je zanesljivo ta, da se s časom ni večal delež bolnikov z omejenim stadijem, kot se je pri mlajših bolnikih – Tabela 3, poglavje *Vse rakave bolezni pri odraslih (brez kožnega)*. V omejenem stadiju je namreč preživetje tudi pri starejših bolnikih statistično značilno boljše kot pri ostalih stadijih. Drug razlog pa je ta, da imajo starejši bolniki vrsto spremljajočih bolezni in niso vedno sposobni za specifično onkološko zdravljenje oziroma ga ni mogoče izpeljati do konca. Kljub temu pa je ravno specifično in boljše podporno zdravljenje lahko glavni razlog, da se je petletno relativno preživetje bolnikov, starih 75 let in več, v opazovanem obdobju povečalo z 29 % na 38 %.
7. Med bolniki z rakom je manj kot 1 % otrok in mladostnikov; zbolevajo predvsem za levkemijami, tumorji osrednjega živčnega sistema in limfomi in imajo boljše petletno relativno preživetje kot odrasli; tisti, zboleli v letih 2001–2005, 83-odstotno, za 12 % večje od tistih, zbolelih deset let prej. Rezultati raziskave EUROCARE-4 za zbolele v obdobju 1995–2002 kažejo, da je preživetje slovenskih otrok in mladostnikov v evropskem povprečju.

OVERWIEV OF THE MOST IMPORTANT FINDINGS

1. In the majority of cancers (other than cutaneous), the survival of adult patients has gradually undergone a significant improvement; in ten years (1991–1995 and 2001–2005), the 5-year relative survival of all patients increased by 12% (from 40% to 52%), in males by 14% (from 30% to 44%) and in females by 10% (from 49% to 59%).
2. In more frequent cancers, in the period 2001–2005 individually representing 3% or more and altogether 61% of total cancer burden in adults, in ten years, the survival increased by 10% or more in all but two cancers, where no significant improvement has been achieved in other European countries either (lung, corpus uteri); the highest increase in the survival was observed in prostate cancer (by 26%), followed by colon (16%), breast (14%), cutaneous melanoma (12%), rectum (11%) and stomach (10%) (Table 1).
3. According to the results of EUROCARE-4 study of patients diagnosed in the period 2000–2002, the survival of Slovenian patients in all more frequent cancers is lagging behind the European average, most apparently in prostate cancer – by 16% (Table 1).
4. The group of less frequent cancers, in the period 2001–2005 representing individually less than 3% of total cancer burden in adults, is heterogeneous. The first group consists of cancer diseases in which the survival of Slovenian patients is equal or even better than the European average (Table 2). Among these, the best survival is observed in patients with testicular and thyroid cancer and Hodgkin's disease, who are already now treated in adequately specialized centers. The second group consists of rare cancers (Table 3), where the survival of patients lags behind the European average (urological and hematological cancer and most of the head and neck cancers).
5. Certain cancers with the worst prognosis (cancers of the lung, larynx and esophagus) appear as nature's warning to human stupidity; treatment is not successful but a healthy lifestyle could prevent most of them!
6. As population is ageing, the number of cancer cases increases especially among the elderly. In the last period, a fifth of adult males with cancer (but skin) and nearly a third of females were aged 75 years or more at diagnosis – Table 1, chapter *All cancers other than cutaneous in adults*. Their survival is statistically significantly below the survival of younger patients, but is improving with time – Figure 4, chapter *All cancers other than cutaneous in adults*. One of the reasons for lower survival in the elderly may be the fact that the proportion of patients with localized stage of the disease at diagnosis has not increased with time as in younger patients – Table 3, chapter *All cancers other than cutaneous in adults*. The survival of the elderly with localized disease is statistically significantly better than in more advanced stages. The second reason may be the presence of many concomittant diseases in the elderly, which render specific oncological treatment more difficult or impossible to carry out. Nevertheless, better palliative and specific oncological treatment are probably the main reasons for the 9% increase in 5-year relative survival of patients aged 75 years or more (from 29% to 38%) in the period studied.
7. There are less than 1% of children and adolescents among cancer patients; they prevailingly present with leukemias, tumors of the central nervous system and lymphomas and have better 5-year relative survival than adults; in those diagnosed in the period 2001–2005 the 5-year relative survival is 83%, i. e. by 12% better than in patients diagnosed ten years earlier. According to the results of EUROCARE-4 study of patients diagnosed in the period 1995–2002, the survival of Slovenian children and adolescents is comparable with the European average.

Tabela 1: *Primerjava petletnih relativnih preživetij bolnikov z najpogostejšimi vrstami raka.*

Table 1: *Comparison of 5-year relative survivals of patients with most frequent cancer sites.*

Mesto raka / Cancer site	Število novih primerov 2001–2005 / Number of new cases 2001–2005	Delež (%) vseh novih primerov 2001–2005 / % of all new cases 2001–2005	5-letno relat. preživetje zbolelih 1991–1995 / 5-year relative survival of patients diagnosed in 1991–1995	5-letno relat. preživetje zbolelih 2001–2005 / 5-year relative survival of patients diagnosed in 2001–2005	Razlika med preživetjem 2001/5 in 1991/5 / Difference in survival 2001–2005 vs. 1991–2005	Petletno relat. preživetje slovenskih bolnikov 2000–2002 / 5-year relative survival of Slovenian patients 2000–2002 (EUROCARE-4)	Evropsko povprečje 2000–2002 / European average 2000–2002 (EUROCARE-4)	Razlika med slovenskim preživetjem in evropskim povprečjem* / Difference between Slovenian and European average survival*
Prostata / Prostate	3615	8,6	52,4	78,2	25,8	63,3	79,7	−16,4*
Debelo črevo / Colon	3256	7,7	41,6	57,7	16,2	51,5	56,7	−5,2*
Dojka / Breast	5236	12,4	69	83,3	14,3	75,2	82,2	−7,0*
Kožni melanom / Cutaneous melanoma	1526	3,6	69,3	81,4	12	79,2	86,3	−7,1*
Danka / Rectum	2709	6,4	34	45,4	11,4	49,5	57,1	−7,6*
Želodec / Stomach	2278	5,4	18,6	28,3	9,7	23,2	23,4	−0,2
Maternično telo / Corpus uteri	1488	3,5	78,4	82,6	4,2	78,7	78,1	0,6
Pljuča / Lung	5453	12,9	10,2	12,4	2,2	9,9	12	−2,1*

* Razlika je statistično značilna ($p < 0,05$). / The difference is statistically significant ($p < 0.05$).

Tabela 2: *Primerjava petletnih relativnih preživetij bolnikov z redkejšimi vrstami raka, ki so po petletnem relativnem preživetju primerljiva z evropskim povprečjem.*

Table 2: *Comparison of 5-year relative survivals of patients with rare cancer sites; the survival of Slovenian patients is in line with the European average or even higher.*

Mesto raka / Cancer site	Število novih primerov 2001–2005 / Number of new cases 2001–2005	Delež (%) vseh novih primerov 2001–2005 / % of all new cases 2001–2005	5-letno relat. preživetje zbolelih 1991–1995 / 5-year relative survival of patients diagnosed in 1991–1995	5-letno relat. preživetje zbolelih 2001–2005 / 5-year relative survival of patients diagnosed in 2001–2005	Razlika med preživetjem 2001/5 in 1991/5 / Difference in survival 2001–2005 vs. 1991–2005	Petletno relat. preživetje slovenskih bolnikov 2000–2002 / 5-year relative survival of Slovenian patients 2000–2002 (EUROCARE-4)	Evropsko povprečje 2000–2002 / European average 2000–2002 (EUROCARE-4)	Razlika med slovenskim preživetjem in evropskim povprečjem* / Difference between Slovenian and European average survival*
Maternični vrat / Cervix uteri	971	2,3	65	78,6	13,6	65,2	65,2	0
Ne-Hodgkinovi limfomi / Non-Hodgkin lymphoma	1165	2,8	50,1	60,7	10,6	55,3	53,6	1,7
Akutna limfoblastna levkemija / Acute lymphoblastic leukemia	59	0,1	12,4	22,5	10,1	30,1	27,2	2,9
Jajčnik / Ovary	863	2	34,2	44,2	10	36,8	36,5	0,3
Ščitnica / Thyroid	557	1,3	82,1	91,3	9,2	93,3	85,5	7,8
Hodgkinov limfom / Hodgkin's lymphoma	204	0,5	80,8	89,5	8,6	84,2	81,4	2,8
Grlo / Larynx	536	1,3	58,4	62,8	4,4	69	67,3	1,7
Trebušna slinavka / Pancreas	1210	2,9	2,5	5,2	2,8	4,8	4,7	0,1
Mehka tkiva (sarkomi) / Soft tissues (sarcomas)	302	0,7	52,9	55	2,1	64	60,6	3,4
Modo / Testis	448	1,1	95,2	95	-0,2	96	95,8	0,2

* Nobena od razlik ni statistično značilna ($p < 0,05$). / Non of the difference is statistically significant ($p < 0.05$).

Tabela 3: *Primerjava petletnih relativnih preživetij bolnikov z redkejšimi vrstami raka, ki po petletnem relativnem preživetju zaostajajo za evropskim povprečjem.*

Table 3: *Comparison of 5-year relative survivals of patients with rare cancer sites; the survival of Slovenian patients is below the European average.*

Mesto raka / Cancer site	Število novih primerov 2001–2005 / Number of new cases 2001–2005	Delež (%) vseh novih primerov 2001–2005 / % of all new cases 2001–2005	5-letno relat. preživetje zbolelih 1991–1995 / 5-year relative survival of patients diagnosed in 1991–1995	5-letno relat. preživetje zbolelih 2001–2005 / 5-year relative survival of patients diagnosed in 2001–2005	Razlika med preživetjem 2001/5 in 1991/5 / Difference in survival 2001–2005 vs. 1991–2005	Petletno relat. preživetje slovenskih bolnikov 2000–2002 / 5-year relative survival of Slovenian patients 2000–2002 (EUROCARE-4)	Evropsko povprečje 2000–2002 / European average 2000–2002 (EUROCARE-4)	Razlika med slovenskim preživetjem in evropskim povprečjem* / Difference between Slovenian and European average survival*
Ustna votlina / Oral cavity	473	1,1	34,2	48	13,8	29,6	49,8	−20,2*
Ledvica / Kidney	1185	2,8	52,6	60,9	8,3	51,6	55,1	−3,5
Ustno žrelo / Oropharynx	626	1,5	25,8	31	5,2	31,4	44,5	−13,1*
Akutne nelimfoblastne levkemije / Acute lymphoblastic leukemia	293	0,7	10,5	14,9	4,4	7,6	15,8	−8,2*
Plazmocitom / Plasmacytoma	429	1	27,1	31,4	4,3	26,5	35,9	−9,4*
Spodnje žrelo / Hypopharynx	268	0,6	21,1	24,6	3,5	19,4	27,8	−8,4
Sečni mehur / Urinary bladder	1242	2,9	48,2	50,7	2,5	48,7	67,3	−18,6*
Požiralnik / Esophagus	449	1,1	7	9,3	2,3	5,1	10,3	−5,2*
Kronična limfocitna levkemija / Chronic lymphocytic leukemia	351	0,8	60,3	62,4	2,1	64	70,2	−6,2
Žolčnik in žolčni vodi / Gallbladder and bile ducts	639	1,5	7,4	9	1,7	12,9	14,4	−1,5
Možgani / Brain	586	1,4	16,5	17,9	1,3	13,2	17,1	−3,9
Jetra (jetrnocelični karcinom) / Liver (hepatocellular carcinoma)	357	0,8	7,6	5,4	−2,2	4,4	9,4	−5

* Razlika je statistično značilna ($p < 0,05$). / The difference is statistically significant ($p < 0.05$).

STROKOVNI IN AKADEMSKI NAZIVI TER USTANOVE ZAPOSLITVE VSEH SODELUJOČIH

PROFESSIONAL AND ACADEMIC TITLES WITH AFFILIATIONS OF ALL CONTRIBUTORS

Avtorji / Authors

izr. prof. dr. Maja Primic-Žakelj, dr. med., specialistka epidemiologinja,
Epidemiologija in register raka, Onkološki inštitut Ljubljana
Assoc. Prof. Maja Primic-Žakelj, MD, PhD, Specialist in Epidemiology,
Epidemiology and Cancer Registry, Institute of Oncology Ljubljana

doc. dr. Vesna Zadnik, dr. med., specialistka javnega zdravja,
Epidemiologija in register raka, Onkološki inštitut Ljubljana
Assist. Prof. Vesna Zadnik, MD, PhD, Specialist in Public Health,
Epidemiology and Cancer Registry, Institute of Oncology Ljubljana

Tina Žagar, univ. dipl. fiz., mlada raziskovalka,
Epidemiologija in register raka, Onkološki inštitut Ljubljana
Tina Žagar, BSc, Physics, Junior Researcher,
Epidemiology and Cancer Registry, Institute of Oncology Ljubljana

izr. prof. dr. Branko Zakotnik, dr. med., specialist internist,
Sektor internistične onkologije, Onkološki inštitut Ljubljana
Assoc. Prof. Branko Zakotnik, MD, PhD, Specialist in Internal Medicine,
Division of Medical Oncology, Institute of Oncology Ljubljana

Sodelavci / Co-workers

asist. Franc Anderluh, dr. med., specialist radioterapevt in onkolog,
Sektor radioterapije, Onkološki inštitut Ljubljana
Assist. Franc Anderluh, MD, Specialist in Radiotherapyt and Oncology,
Division of Radiotherapy, Institute of Oncology Ljubljana

izr. prof. dr. Nikola Bešić, dr. med., specialist kirurg,
Sektor operativnih strok, Onkološki inštitut Ljubljana
Assoc. Prof. Nikola Bešić, MD, PhD, Specialist in Surgery,
Division of Surgery, Institute of Oncology Ljubljana

prof. dr. Peter Černelč, dr. med., specialist internist, Klinični oddelek za hematologijo,
Interna klinika, Univerzitetni klinični center Ljubljana
Prof. Peter Černelč, MD, PhD, Specialist in Internal Medicine, Department
of Hematology, Division of Internal Medicine, University Medical Centre Ljubljana

prof. dr. Tanja Čufer, dr. med., specialistka internistka, višja svetnica, Klinični oddelek
za pljučne bolezni in alergijo – Bolnišnica Golnik in Medicinska fakulteta Ljubljana
Prof. Tanja Čufer, MD, PhD, Specialist in Internal Medicine, Higher Councillor,
University Clinic of Respiratory and Allergic Diseases Golnik

izr. prof. dr. Andrej Debeljak, dr. med., specialist internist, svetnik,
Klinični oddelek za pljučne bolezni in alergijo – Bolnišnica Golnik
Assoc. Prof. Andrej Debeljak, MD, PhD, Specialist in Internal Medicine,
Councillor, University Clinic of Respiratory and Allergic Diseases Golnik

asist. mag. Ibrahim Edhemović, dr. med., specialist kirurg,
Sektor operativnih strok, Onkološki inštitut Ljubljana
Assist. Ibrahim Edhemović, MD, MSc., Specialist in Surgery,
Division of Surgery, Institute of Oncology Ljubljana

asist. dr. Janez Eržen, dr. med., specialist kirurg,
Klinični oddelek za torakalno kirurgijo, Univerzitetni klinični center Ljubljana
Assist. Janez Eržen, MD, PhD, Specialist in Surgery, Department of Thoracic Surgery,
Division of Surgery, University Medical Centre Ljubljana

doc. dr. Albert Peter Fras, dr. med., specialist ginekolog porodničar in specialist radioterapevt,
Sektor operativnih strok, Onkološki inštitut Ljubljana
Assist. Prof. Albert Peter Fras, MD, PhD, Specialist in Gynecology and Obstetrics,
Specialist in Radiotherapyt, Division of Surgery, Institute of Oncology Ljubljana

prof. dr. Eldar M. Gadžijev, dr. med., specialist kirurg, višji svetnik,
Sektor operativnih strok, Onkološki inštitut Ljubljana
Prof. Eldar M. Gadžijev, MD, PhD, Specialist in Surgery, Higher Councillor,
Division of Surgery, Institute of Oncology Ljubljana

doc. dr. Marko Hočevar, dr. med., specialist kirurg,
Sektor operativnih strok, Onkološki inštitut Ljubljana
Assist. Prof. Marko Hočevar, MD, PhD, Specialist in Surgery,
Division of Surgery, Institute of Oncology Ljubljana

doc. dr. Janez Jazbec, dr. med., specialist pediater, hemato-onkolog,
Klinični oddelek za otroško hematologijo in onkologijo,
Pediatrična klinika Ljubljana, Univerzitetni klinični center Ljubljana
Assist. Prof. Janez Jazbec, MD, PhD, Specialist in Pediatrics and Hemato-Oncology,
Unit of Oncology and Haematology, Division of Pediatrics, University Medical Centre
Ljubljana

doc. dr. Barbara Jezeršek Novaković, dr. med., specialistka internistka,
Sektor internistične onkologije, Onkološki inštitut Ljubljana
Assist. Prof. Barbara Jezeršek Novakovič, MD, PhD, Specialist in Internal Medicine,
Division of Medical Oncology, Institute of Oncology Ljubljana

prim. izr. prof. dr. Andrej Kmetec, dr. med., specialist urolog, svetnik,
Klinični oddelek za urologijo, Kirurška klinika, Univerzitetni klinični center Ljubljana
Assoc. Prof. Andrej Kmetec, MD, PhD, Specialist in Urology, Councillor, Department
of Urology, Division of Surgery, University Medical Centre Ljubljana

prim. Elga Majdič, dr. med., specialistka radioterapevtka in onkologinja,
Sektor radioterapije, Onkološki inštitut Ljubljana
Elga Majdič, MD, Specialist in Radiotherapy and Oncology, Division of Radiotherapy,
Institute of Oncology Ljubljana

doc. dr. Uroš Mlakar, dr. med., specialist internist, Klinični oddelek za hematologijo,
Interna klinika, Univerzitetni klinični center Ljubljana
Assist. Prof. Uroš Mlakar, MD, PhD, Specialist in Internal Medicine, Department
of Hematology, Division of Internal Medicine, University Medical Centre Ljubljana

mag. Mojca Modic, dr. med., specialistka internistka, Klinični oddelek za hematologijo,
Interna klinika, Univerzitetni klinični center Ljubljana
Mojca Modic, MD, MSc, Specialist in Internal Medicine, Department of Hematology,
Division of Internal Medicine, University Medical Centre Ljubljana

asist. dr. Irena Oblak, dr. med., specialistka radioterapevtka in onkologinja,
Sektor radioterapije, Onkološki inštitut Ljubljana
Assist. Irena Oblak, MD, PhD, Specialist in Radiotherapy and Oncology,
Division of Radiotherapy, Institute of Oncology Ljubljana

dr. Janja Ocvirk, dr. med., specialistka internistka,
Sektor internistične onkologije, Onkološki inštitut Ljubljana
Janja Ocvirk, MD, PhD, Specialist in Internal Medicine,
Division of Medical Oncology, Institute of Oncology Ljubljana

izr. prof. dr. Mirko Omejc, dr. med., specialist kirurg, Klinični oddelek za abdominalno kirurgijo, Kirurška klinika, Univerzitetni klinični center Ljubljana
Assoc. Prof. Mirko Omejc, MD, PhD, Specialist in Surgery, Department
of Abdominal Surgery, Division of Surgery, University Medical Centre Ljubljana

prof. dr. Stanislav Repše, dr. med., specialist kirurg, Klinični oddelek za abdominalno kirurgijo, Kirurška klinika, Univerzitetni klinični center Ljubljana
Prof. Stanislav Repše, MD, PhD, Specialist in Surgery, Department of Abdominal Surgery,
Division of Surgery, University Medical Centre Ljubljana

prim. dr. Boris Sedmak, dr. med., specialist urolog, svetnik,
Klinični oddelek za urologijo, Kirurška klinika, Univerzitetni klinični center Ljubljana
Boris Sedmak, MD, PhD, Specialist in Urology, Dept of Urology, Department
of Surgery, University Medical Centre Ljubljana

mag. Uroš Smrdel, dr. med., specialist radioterapevt in onkolog,
Sektor radioterapije, Onkološki inštitut Ljubljana
Uroš Smrdel, MD, MSc, Specialist in Radiotherapy and Oncology,
Division of Radiotherapy, Institute of Oncology Ljubljana

izr. prof. dr. Miha Sok, dr. med., specialist kirurgije, Klinični oddelek za torakalno kirurgijo, Kirurška klinika, Univerzitetni klinični center Ljubljana
Assoc. Prof. Miha Sok, MD, PhD, Specialist in Surgery, Department of Thoracic Surgery,
Division of Surgery, University Medical Centre Ljubljana

izr. prof. dr. Primož Strojan, dr. med., specialist radioterapevt in onkolog,
Sektor radioterapije, Onkološki inštitut Ljubljana
Assoc. Prof. Primož Strojan, MD, PhD, Specialist in Radiotherapy and Oncology,
Division of Radiotherapy, Institute of Oncology Ljubljana

dr. Breda Škrbinc, dr. med., specialistka internistka,
Sektor internistične onkologije, Onkološki inštitut Ljubljana
Breda Škrbinc, MD, PhD, Specialist in Internal Medicine,
Division of Medical Oncology, Institute of Oncology Ljubljana

prof. dr. Lojze Šmid, dr. med., svetnik, specialist otorinolaringolog, Klinika za otorinolaringologijo in cervikofacialno kirurgijo, Univerzitetni klinični center Ljubljana
Prof. Lojze Šmid, MD, PhD, Specialist in Otorhinolaryngology, Councillor, Department
of Otorhinolaryngology and Cervicofacial Surgery, University Medical Centre Ljubljana

izr. prof. dr. Marjetka Uršič-Vrščaj, dr. med., specialistka ginekologinja in porodničarka,
Sektor operativnih strok, Onkološki inštitut Ljubljana
Assoc. Prof. Marjetka Uršič-Vrščaj, MD, PhD, Specialist in Gynecology and Obstetrics,
Division of Surgery, Institute of Oncology Ljubljana

asist. dr. Vaneja Velenik, dr. med., specialistka radioterapevtka in onkologinja,
Sektor radioterapije, Onkološki inštitut Ljubljana

Assist. Vaneja Velenik, MD, PhD, Specialist in Radiotherapy and Oncology,
Division of Radiotherapy, Institute of Oncology Ljubljana

doc. dr. Samo Zver, dr. med., specialist interne medicine,
Klinični oddelek za hematologijo, Interna klinika, Univerzitetni klinični center Ljubljana
Assist. Prof. Samo Zver, MD, PhD, Specialist in Internal Medicine, Department
of Hematology, Division of Internal medicine, University Medical Centre Ljubljana

izr. prof. dr. Matjaž Zwitter, dr. med., specialist radioterapevt in onkolog,
Sektor radioterapije, Onkološki inštitut Ljubljana
Assoc. Prof. Matjaž Zwitter, MD, PhD, Specialist in Radiotherapy and Oncology,
Division of Radiotherapy, Institute of Oncology Ljubljana

doc. dr. Janez Žgajnar, dr. med., specialist kirurgije, strokovni direktor,
Onkološki inštitut Ljubljana
Assist. Prof. Janez Žgajnar, MD, PhD, Specialist in Surgery, Medical Director,
Institute of Oncology Ljubljana

prim. Mirjana Žumer-Pregelj, dr. med., specialistka urologinja,
Klinični oddelek za urologijo, Kirurška klinika, Univerzitetni klinični center Ljubljana
Mirjana Žumer Pregelj, MD, Specialist in Urology, Department of Urology,
Division of Surgery, University Medical Centre Ljubljana

Analiza podatkov EUROCARE-4 in SEER / Analysis of Eurocare-4 and SEER data

Silvia Francisci, Enota za onkološko epidemiologijo, Državni center za epidemiologijo,
nadzor in promocijo zdravja, Vrhovni inštitut za javno zdravje, Rim, Italija
Silvia Francisci, Cancer Epidemiology Unit, National Center for Epidemiology,
Surveillance and Health Promotion, Istituto Superiore di Sanita, Rome, Italy

Recenzenta / Reviewers

Prof. dr. Vera Pompe Kirn, dr. med., specialistka socialne medicine, višja svetnica,
Register raka Republike Slovenije, Onkološki inštitut Ljubljana
Prof. Vera Pompe Kirn, MD, DSc, Specialist in Social Medicine, Higher Councillor,
Cancer Registry of Republic of Slovenia, Institute of Oncology Ljubljana

izr. prof. dr. Matjaž Zwitter, dr. med., specialist radioterapevt in onkolog,
Sektor radioterapije, Onkološki inštitut Ljubljana
Assoc. Prof. Matjaž Zwitter, MD, PhD, Specialist in Radiotherapy and Oncology,
Division of Radiotherapy, Institute of Oncology Ljubljana

Lektor za slovenščino / Reader for Slovenian language

Jože Faganel, prof. slov. in franc, višji strokovni sodelavec specialist ZRC SAZU
Jože Faganel, BA, Specialist on Terminology, ZRC SAZU

Prevod / Translation

Olga Shrestha, univ. dipl. ang. prev.
Olga Shrestha, BA, English Translation

Oblikovanje / Design

Monika Fink-Serša, univ. dipl. inž. arh., Nava d. o. o.
Monika Fink-Serša, BSc, Architecture, Nava d. o. o.

70 let
years

ONKOLOŠKI INŠTITUT LJUBLJANA

INSTITUTE OF ONCOLOGY LJUBLJANA

ISBN 978-961-6071-53-6

register raka republike slovenije cancer registry of republic of slovenia ljubljana 2009