

# ORAL PRESENTATIONS

## USMENA IZLAGANJA





## EPIDEMIOLOGY OF THYROID CANCER

### EPIDEMIOLOGIJA RAKA ŠTITNJAČE

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Thyroid cancers are the most common malignant endocrine tumors. Among United States females, thyroid cancer accounts for about 3% of all cancers and is the eighth most common malignancy. Among thyroid carcinomas, the most frequent types are differentiated forms (follicular and papillary). Anaplastic and medullary types are rare. The incidence of thyroid cancer is low in relation to other diseases of thyroid gland. Nodular goiter is 50 to 60 times more often. If all nodular changes are taken into account, the difference is even greater. On the other hand, differentiated thyroid cancers are among few curable cancers. Some oncologists call them “beauty imperfection”.

Thyroid cancer rates are three times higher in women than in men, during the period between puberty and menopause, suggesting that the etiology of thyroid cancer may be related to female sex hormones and reproductive function. This pattern is consistently observed across geographic location and ethnicity. The incidence in women peaks within female reproductive period, whereas in men it increases steadily with age.

The incidence rates of thyroid cancer vary considerably across the world between 2 and 14 cases *per* 100,000. The level of medical care and surveillance practices are thought to contribute to international variation, because thyroid malignancies can remain indolent for many years. The highest incidence rates are found mostly on the islands such as Hawaii, Iceland, in some regions of Sicily and Cyprus. The incidence rates vary between different ethnic groups. Especially interesting are differences between different ethnic groups such as Arab and Jewish populations in Israel, or Southeast Asian and Caucasian population in Hawaii and San Francisco Bay area. High incidence rates were also observed in some

Rak štitnjače je najučestaliji maligni endokrini tumor. Među ženama u SAD rak štitnjače čini oko 3% svih malignoma i osmi je najučestaliji malignitet. Među karcinomima štitnjače najčešći tipovi su diferencirani oblici (folikularni i papilarni). Anaplastični i medularni tipovi su rijetki. Incidencija raka štitnjače je niska u odnosu na druge bolesti štitnjače. Nodularna se guša pojavljuje 50-60 puta češće. Ako se sve nodularne promjene uzmu u obzir, razlika je čak i veća. S druge strane, diferencirani rak štitnjače spada u red od nekoliko izlječivih malignoma. Neki onkolozi ih nazivaju ‘kozmetičkim manjkavostima’.

Stope incidencije raka štitnjače su tri puta više u žena nego u muškaraca, i to u vremenu između puberteta i menopauze, ukazujući na to da bi etiologija raka štitnjače mogla biti povezana sa ženskim spolnim hormonima i reprodukcijom funkcijom. Ovaj obrazac se učestalo zapaža u različitim geografskim lokacijama i etničkim pripadnostima. Incidencija za žene postiže vrhunac u reprodukcijom razdoblju, dok za muškarce stalno raste s godinama.

Stope incidencije raka štitnjače variraju znatno u svijetu između 2 i 14 slučajeva na 100.000. Razina medicinske skrbi i praćenje doprinose međunarodnim razlikama, jer maligniteti štitnjače mogu godinama ostati indolentni. Najviše stope incidencije nađene su uglavnom na Havajskom otočju, Islandu, u nekim regijama Sicilije i Cipra.

Stope incidencije variraju između različitih etničkih skupina. Naročito su zanimljive razlike između različitih etničkih skupina, npr. Arapa i židovske populacije u Izraelu, te jugoistočno azijske i bjelačke populacije na Havajima i u području zaljeva San Francisco. Visoke stope incidencije su također zapažene u nekim epidemio-



epidemiological studies of Jewish communities in the United States. These data may indicate a role of genetic but also of socioeconomic and dietary factors.

Medullary thyroid carcinoma has a well-established familial occurrence and is associated with other endocrine disorders (MEN). For thyroid, cancers of follicular origin, until recently, were thought to arise sporadically without an inherited genetic predisposition. In last years, ever more data are collected on familial non-medullary thyroid cancer (FNTPC), defined by the presence of thyroid cancers of follicular cell origin within two or more first-degree relatives. An autosomal dominant inheritance pattern with reduced penetrance appears likely in most pedigrees. The gene(s) responsible for the majority of FNTPC cases have not yet been characterized. Clinical and genetic studies of FNTPC have yielded conflicting results concerning the aggressiveness of these tumors.

The content of iodine in food has no influence on the overall incidence of thyroid carcinoma, whereas the distribution of types seems to be related to the intake of iodine. In areas with appropriate iodine intake, a higher rate of less aggressive papillary histologic types than of follicular or anaplastic thyroid carcinomas was recorded.

Numerous reports are available on the sensitivity of thyroid gland to radiation-induced oncogenesis. External irradiation of the neck for benign diseases, mainly in children, elevates the risk of thyroid cancer. Special attention was focused on events when great number of people were exposed to radiation, such atomic bomb explosions, atomic bomb testing, and accidents at nuclear plants, especially in Chernobyl. According to these articles, there appears to be a dose-response relation for the risk of developing cancer after exposure to radioactive iodine. On the other hand, radioactive iodine, especially iodine-131, has been used in the diagnosis and treatment of thyroid diseases for more than 50 years. Regardless of the wide use of radioactive iodine, there is no evidence that the risk of thyroid cancer will increase with the treatment of hyperthyroidism with iodine-131 and with the use of diagnostic levels of iodine-131.

Several investigations suggest an increase in cancer incidence in different countries not affected by excess of radiation. The Thyroid Cancer Committee in France reports on an increase of thyroid cancer incidence to 8.1% and 6.2% *per year* in women and men, respectively, mainly due to papillary type with an epidemic of microcarci-

loškim studijama o židovskim zajednicama u SAD. Ovi podaci mogu ukazivati na ulogu genetičkih, ali isto tako socioekonomskih i prehrambenih čimbenika.

Za medularni karcinom štitnjače je dobro poznato obiteljsko pojavljivanje u sklopu s drugim endokrinim poremećajima (MEN). Za rak štitnjače folikularnog podrijetla sve donedavno se mislilo da nastaje sporadično bez nasljedne genetske predispozicije. U novije vrijeme sve je više podataka o obiteljskom ne-medularnom raku štitnjače (ONMRŠ), definiranom prisutnošću raka štitnjače podrijetlom od folikularnih stanica u dvoje ili više rođaka u prvom koljenu. Autosomno dominantni oblik nasljeđivanja s reduciranom stopom kliničke pojavnosti pojavljuje se u najviše slučajeva. Još nije utvrđena uloga gena za većinu ONMRŠ. Kliničke i genetičke studije ONMRŠ su donijele proturječne rezultate o agresivnosti ovih tumora.

Sadržaj joda u hrani nema utjecaja na ukupnu incidenciju karcinoma štitnjače, dok je naprotiv distribucija tipova vjerojatno povezana s unosom joda. U područjima s dostatnim unosom joda zabilježena je veća stopa manje agresivnih papilarnih histoloških tipova od folikularnih i anaplastičnih karcinoma štitnjače.

Dostupni su mnogobrojni dokazi o osjetljivosti štitnjače na zračenjem izazvani razvoj raka. Vanjsko zračenje vrata zbog dobroćudnih bolesti, osobito u djece, povisuje rizik za rak štitnjače. Osobita se pozornost posvećuje događajima kada je velik broj ljudi izložen radijaciji, kao u eksploziji atomskih bomba, atomskim pokusima i nesrećama u nuklearnim pogonima, poglavito u Černobilu. Prema tim člancima, čini se kako postoji odnos doze i odgovora za rizik razvoja raka nakon izlaganja radioaktivnom jodu.

S druge strane, radioaktivni jod, a osobito <sup>131</sup>I, se rabi u dijagnostici i liječenju bolesti štitnjače više od 50 godina. Bez obzira na široku upotrebu radioaktivnog joda, nema dokaza da će se rizik za rak štitnjače povećati s liječenjem hipertireoze pomoću <sup>131</sup>I-joda te primjenom dijagnostičkih doza <sup>131</sup>I-joda.

Nekoliko istraživača ukazuje na porast incidencije raka u različitim zemljama uzrokovan porastom radijacije. Odbor za rak štitnjače u Francuskoj izvještava o porastu incidencije raka štitnjače od 8,1% i 6,2% na godinu u žena i muškaraca, pretežito zbog papilarnog tipa s epidemijom mikrokarcinoma. Oni navode kako epidemiološki podaci ukazuju na vezu između takvog porasta i promijenjenog pristupa u liječenju čvorova štitnjače.

Utvrđeni su i mnogi drugi rizični čimbenici. Bolestnici s prethodnom anamnezom guše ili čvorova imaju



nomas. They state that epidemiologic data favor links between such an increase and the changing approach to thyroid nodule management.

Many other risk factors have been established. Patients with a previous history of goiter or nodules have an increased risk of thyroid cancer. Women who reported the onset of menarche before age 12 or after age 14 were at about 50% increased risk of papillary thyroid cancer; however, this effect differed among age- and ethnic-specific subgroups. The influence of pregnancy on the risk of thyroid cancer is not clearly defined. The risk was reduced in women who had ever used oral contraceptives.

The prevalence of thyroid microcarcinomas found at autopsies is 100-1000 times higher than in clinical cancer. This statement, together with the fact that thyroid cancer may stay *in situ* for years, opens questions about the effects of screening progress on the detection of a large pool of microcarcinomas that increases incidence measurements of thyroid cancers and induces public health concerns.

povećan rizik za rak štitnjače. Žene s ranim početkom menarhe prije 12. godine ili nakon 14. godine imaju oko 50% povećan rizik za papilarni rak štitnjače; međutim, ovaj učinak se razlikuje između dobrih i etničkih podskupina. Utjecaj trudnoće na rizik za rak štitnjače nije jasno utvrđen. Rizik je smanjen u žena koje su u nekom razdoblju uzimale oralne kontraceptive.

Prevalencija mikrokarcinoma štitnjače nađena na autopsijama je 100-1000 puta viša nego kod kliničkog raka. Ova tvrdnja zajedno s činjenicom da rak štitnjače godinama ostaje *in situ* otvara pitanja o učinku napretka probira u otkrivanju velikog *poola* mikrokarcinoma, što povećava incidenciju raka štitnjače i izaziva javnozdravstvenu zabrinutost.

## MOLECULAR GENETICS OF THYROID CANCER MOLEKULARNA GENETIKA TUMORA ŠTITNJAČE

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Cancers develop and progress *via* activation of oncogenes and loss of tumor suppressor genes. The development and progression of thyroid tumors is signaled by phenotype-specific mutations of genes involved in growth control<sup>1</sup>. A sequence of genetic events characterized by deletion and expression of several oncogenes may lead progressively to tumorigenesis. The expression of certain oncogenes is believed to be related to thyroid carcinogenesis and tumor progression. Several oncogenes (*ras*, *ret*, *trk*) and tumor suppressor genes (*p53*, *Rb*, *p16/CDKN2*, *p21<sup>waf1</sup>*) have been associated with different thyroid tumors. *Ras* oncogene activation is an early event and appears to be involved in the genesis of follicular adenoma and carcinoma<sup>2</sup>. Three other genetic

Razvoj tumora općenito vezan je uz aktivaciju onkogeni i gubitak funkcije tumor-supresorskih gena. Razvoj i napredovanje tumora štitnjače vezano je uza specifične mutacije gena koji su uključeni u kontrolu rasta<sup>1</sup>. Slijed genetskih događaja koji uključuje delecije i ekspresiju nekoliko onkogeni može postupno dovesti do nastanka tumora. Vjeruje se da postoji visoka korelacija karcinogeneze tumora štitnjače i njegove progresije s ekspresijom određenih onkogeni. Tako se zna da je nekoliko onkogeni (*ras*, *ret*, *trk*), kao i nekoliko tumor-supresorskih gena (*p53*, *Rb*, *p16/CDKN2*, *p21<sup>waf1</sup>*) povezano s pojavom različitih tumora štitnjače. Aktivacija onkogeni *ras* predstavlja rani događaj i čini se kako je uključena u nastanak folikularnog adenoma i karcinoma<sup>2</sup>. Tri



and/or epigenetic alterations play a role in PTC pathogenesis: activating mutation of *ras* genes, *c-met* overexpression and down regulation of E-cadherin in papillary carcinoma. Recently, another major player in papillary carcinoma etiopathogenesis has been reported: the BRAF gene. Papillary carcinoma is one of the human cancers displaying the highest prevalence of BRAF mutations, which occur almost always in the same hot spot (V600E). The finding of a high prevalence of BRAF mutations, together with the involvement of *ras* mutations and *ret*/PTC rearrangements in the majority of papillary carcinomas, points to the crucial role played by alterations at the *ret/ras/BRAF/MAPK* signal transduction pathway in the pathogenesis of papillary carcinoma<sup>3</sup>.

In our recently published study we found that the majority of malignant thyroid cancers displayed aberrant expression of *FHIT* gene concomitant with *p53* gene inactivation<sup>4</sup>. This is followed by a low rate of apoptosis, which may be important in the development and/or progression of thyroid cancer. We found a higher incidence of *p53* mutation and aberrant processing of *FHIT* mRNA in malignant tumors (papillary, follicular, medullary and anaplastic carcinomas) and in those tumors with distant metastasis. The growth of *p53*/*FHIT* follicular carcinoma of human origin was much faster in nude mice than *p53*<sup>+</sup>/*FHIT*<sup>+</sup> follicular carcinoma, and mice had shorter survival rate. Human *FHIT* gene is a highly conserved gene whose loss of function may be important in the development and/or progression of various types of cancer. Concomitant aberration of *FHIT* gene and *p53* could be responsible for the development of highly malignant types of thyroid cancer and may be considered as a prognostic marker for these tumors<sup>4</sup>.

Despite these intriguing molecular genetic data, molecular events associated with undifferentiated thyroid cancer are not well known. This might change in the near future thanks to new powerful methods in life sciences. Medicine is entering a new era of global approaches in scientific techniques. These approaches, named *-omics* represent a global, systematic and comprehensive way for identifying and describing the processes and pathways involved in normal as well as abnormal states. *Omic*s are global methodologies to characterization of all, or most members belonging to a certain family of molecules, in one single analysis. It is characterized by high-throughput or large-scale experimental methodologies combined with statistical and computational analyses of the results. The fundamental strategy of *omic*s approach is aimed to expand the scope of

ostale genetske i/ili epigenetske promjene imaju ulogu u patogenezi PTC, a to su aktivirajuća mutacija gena *ras*, prekomjerna ekspresija gena *c-met* te smanjena ekspresija E-cadherina u papilarnom karcinomu<sup>2</sup>. Nedavno je pronađen gen *BRAF* kao drugi važan sudionik u etiopatogenezi papilarnog karcinoma. Papilarni karcinom je jedan od ljudskih tumora koji imaju najveću učestalost mutacija u genu *BRAF*, a koje se gotovo uvijek javljaju na istoj ključnoj poziciji (V600E). Otkriće visoke učestalosti mutacija u genu *BRAF*, kao i uloga mutacija u genima *ras* i *ret*/PTC kod većine papilarnih karcinoma upućuju na odlučujuću ulogu koju imaju promjene u signalnom putu *ret/ras/BRAF/MAPK* u patogenezi papilarnog karcinoma<sup>3</sup>.

U našem nedavno objavljenom istraživanju pronašli smo kako je većina malignih tumora štitnjače pokazivala neodgovarajuću ekspresiju gena *FHIT* zajedno s inaktivacijom gena *p53*<sup>4</sup>. To je bilo popraćeno niskom stopom apoptoze, što bi moglo biti važno u razvoju i/ili progresiji tumora štitnjače. Pronašli smo veću pojavnost mutacije *p53* i nepravilnog procesiranja transkripata gena *FHIT* kod malignih tumora (papilarni, folikularni, medularni i anaplastični karcinomi), kao i kod tumora s udaljenim metastazama. Rast folikularnog karcinoma ljudskog podrijetla statusa *p53*<sup>-</sup>/*FHIT*<sup>-</sup> bio je puno brži u "golih miševa" no što je bio rast folikularnog karcinoma *p53*<sup>+</sup>/*FHIT*<sup>+</sup>, a miševi su imali kraće vrijeme preživljenja. Ljudski gen *FHIT* je evolucijski iznimno dobro očuvan gen čiji bi gubitak funkcije mogao biti važan u razvoju i progresiji različitih tipova tumora. Prateći nepravilnosti gena *FHIT* čini se da bi i gen *p53* mogao biti odgovoran za razvoj izrazito malignih tipova tumora štitnjače te bi se mogao razmatrati kao prognostički biljeg za te tumore<sup>4</sup>.

Unatoč ovim intrigantnim podacima iz područja molekularne genetike, molekularni događaji vezani uz nediferencirane tumore štitnjače još nisu dobro poznati. To bi se moglo promijeniti u skorjoj budućnosti zahvaljujući novim moćnim metodama. Medicina ulazi u novo doba globalnih znanstvenih pristupa i tehnika. Ti pristupi, objedinjeni u pojmu *-omics*, predstavljaju globalan, sustavan i sveobuhvatan način identifikacije i opisivanja procesa i putova uključenih u normalna i bolesna stanja. *Omic*s su globalne metodologije za karakterizaciju svih ili većine članova određene obitelji molekula u jednoj jedinoj analizi. Njihova je značajka visok protok velikog broja podataka ili eksperimentalne metodologije na velikom broju uzoraka koji se statistički i kompjutorski analiziraju. Temeljna strategija pristupa *-omics* je širenje istraživanja s područja proučavanja pojedinih entiteta

biological investigation from studying single entities (genes/proteins) to studying all possible parameters collectively in a coordinated and systematic fashion. In general, these studies have emphasized the potential of technology for biomarker discovery as well as for addressing the issue of cancer heterogeneity, new classification, early diagnosis and new therapeutic targets. Two important *omics* approaches, transcriptomics and proteomics, have become powerful tools for deciphering the complex signaling pathways in tumor biology. Cancer proteomics has already identified proteins of potential clinical interest. There are two major foci for the use of *omics* in oncology. The first is to discover new molecular markers for the profiling of tumors and the second is to decipher pathways that lead to cancer cell development. Such data are beginning to provide a knowledge basis for the identification of possible therapies for the disease and subsequent development of innovative strategies. Unquestionably, cancer is the disease that has received most attention and the generated data address mainly aspects of clinical oncology. However, functional genomic methods are new and highly dependent on bioinformatics and statistics, which require additional improvement, since the meaning and importance of the results derived from such large-scale experiments are not widely appreciated. The goal of my presentation is to discuss the possible applications of these technologies in thyroid cancer, since they already have great impact on the management of cancer: in the discovery of new drug targets, development of new molecular tools for diagnosis and prognosis as well as in improving treatments by taking into account the molecular characteristics of a given tumor. Practical consequences for treatment derived from better understanding of the molecular basis of cancer cell growth are now emerging, as evidenced by the development of therapeutic strategies. One of the most exciting challenges today is to move cancer *omics* from the “bench side” to the “bedside”.

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## THYROID CANCER RISK FACTORS

### ČIMBENICI RIZIKA RAKA ŠTITNJAČE

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As in cancer in general, the etiology of thyroid cancer remains unknown in the majority of cases. It is necessary to distinguish factors that act as initiators of malignant change and those that act as promoters of thyroid cancer growth. Ionizing radiation is the single proven etiologic factor in the pathogenesis of thyroid cancer. Although radiation can damage cells in several ways, it is generally accepted that it primarily causes carcinoma by its effects on DNA. However, other factors such as thyrotropin (TSH) secretion are necessary for further promotion of thyroid cancer growth. The relationship between radiation and thyroid cancer was first recognized by Duffy and Fitzgerald in 1950. They found that a large number of patients with thyroid carcinomas had a history of radiation therapy in childhood. Radiation therapy was frequently applied for the treatment of benign and malignant diseases such as thymus enlargement, enlarged tonsils and adenoids, cervical lymphadenopathy due to tuberculosis or Hodgkin's disease, skin changes such as angioma, keloid, acne vulgaris, etc. Epidemiologic investigations demonstrated a high prevalence of benign and malignant thyroid tumors in irradiated children. Ron et al. conducted a comprehensive study of the relationship between radiation exposure and thyroid carcinoma combining data from seven studies, and demonstrated a strong positive association between radiation dose and thyroid carcinoma in more than 500 patients. The risk of thyroid carcinoma development increased linearly with the dose. The threshold dose was 0.1 Gy, while at doses below 0.1 Gy the results were equivocal. Some other observations with important clinical implications were noticed: 1) there was a strong inverse relationship between age at exposure and risk of thyroid carcinoma development; 2) there was little evidence for radiation effect in persons exposed after age 15; 3) women tended to be more sensitive to the effect of radiation than men, although the difference was not

Kao i kod raka uopće, etiologija karcinoma štitnjače u većini slučajeva je nepoznata. Potrebno je razlikovati čimbenike-pokretače nastanka karcinoma štitnjače od čimbenika koji potiču njegov daljnji rast. Jedini sigurno dokazani čimbenik nastanka diferenciranih karcinoma štitnjače je ionizirajuće zračenje bilo kojeg uzroka. Premda zračenje može oštetiti stanice na nekoliko načina, glavni pokretač razvoja karcinoma štitnjače je oštećenje DNK. Međutim, za poticaj rasta karcinoma štitnjače vjerojatno su odgovorni i drugi čimbenici poput lučenja tireotropina (TSH). Povezanost između zračenja i karcinoma štitnjače prvi su opisali Duffy i Fitzgerald 1950. godine. Primijetili su da je velik broj bolesnika s karcinomom štitnjače u ranoj mladosti bio ozračen vanjskim snopom u području glave i vrata. U prošlosti se je vanjsko zračenje područja glave i vrata često primjenjivalo u djece kao terapija nekih dobroćudnih i zloćudnih bolesti poput povećanog timusa, tonzila i adenoida, cervikalne limfadenopatije zbog tuberkuloze ili Hodgkinove bolesti, kožnih promjena poput angioma, keloida, akna i drugih stanja. Epidemiološka istraživanja su pokazala visoku prevalenciju benignih i malignih tumora štitnjače u zračenju djece. Ron i suradnici su proveli opsežnu analizu utjecaja zračenja u dječjoj dobi na razvoj karcinoma štitnjače usporedbom podataka sedam zasebnih istraživanja i u više od 500 oboljelih od karcinoma štitnjače pokazali statistički značajnu korelaciju između doze zračenja primljene u djetinjstvu i razvoja karcinoma štitnjače. Rizik nastanka karcinoma štitnjače rastao je linearno s primljenom dozom zračenja. Granica doze bila je 0,1 Gy, a kod doza nižih od 0,1 Gy rezultati su varirali. Također je uočeno nekoliko dodatnih zapažanja koja imaju osobito kliničko značenje: 1. Postoji obrnuta korelacija između dobi izlaganja ionizirajućem zračenju i rizika razvoja karcinoma štitnjače; 2. U osoba starijih od 15 godina učinak zračenja je bio neznan; 3. Žene su osjetljivije na učinak ionizirajućeg zračenja u odnosu na muškarce, premda ta razlika nije bila statistički značajna;



statistically significant; and 4) the risk of thyroid carcinoma development remained elevated for several decades of the initial exposure.

The relationship between internal radiation and thyroid carcinoma is well known, mostly from the consequences of Chernobyl accident. Animal experiments demonstrated carcinogenic potential of iodine-131 ( $^{131}\text{I}$ ), but it was unclear whether the same effect of  $^{131}\text{I}$  existed in humans. Some inhabitants that had been exposed to nuclear test explosions on Marshall Islands in 1954, subsequently developed thyroid carcinomas. The radiation exposure came from  $^{131}\text{I}$ , short-living isotopes of iodine, and external gamma radiation. Chernobyl nuclear power plant accident that occurred in 1986 led to the release of vast amounts of  $^{131}\text{I}$  in the atmosphere (23 to 46 MCi of  $^{131}\text{I}$ ). Soon after the Chernobyl accident, the incidence of childhood papillary thyroid cancer significantly increased in the neighboring areas of Ukraine, Belarus and western part of Russia. Radioactive isotopes of iodine, mostly  $^{131}\text{I}$  in contaminated food, caused a significant radiation dose to thyroid glands. The risk of developing thyroid carcinoma upon exposure to  $^{131}\text{I}$  has been found to increase with decreasing age at exposure. Jacob et al. found a linear dose-response correlation for thyroid carcinoma development, similar to that reported for external radiation. However, there are several distinctive features. The latency period was shorter after the Chernobyl accident than for those exposed to external radiation. Thyroid cancer was more frequent and more aggressive in Belarus children younger than two years at the time of exposure, and almost 62% of these children had thyroid carcinoma invading surrounding tissues in comparison to 40% in older children. Thyroid cancer was more frequent in women than in men (60%:40%). The higher incidence of thyroid cancer in children under 2 years of age is probably due to faster thyroid cell division in these children and therefore the probability of mutations was higher in this age group. Furthermore, due to smaller thyroid in infants, the same dose as in older child will have a higher risk of thyroid cancer development. Most of the patients had a unique histologic pattern of papillary carcinoma with a large solid component (solid subtype), and very aggressive clinical behavior with infiltration of surrounding tissues and lymph node involvement. Thyroid carcinomas due to the radiation exposure were well-differentiated papillary or papillary-follicular carcinomas while anaplastic thyroid carcinomas were very rare. RET/PTC oncogene rearrangements are specific for radiation induced papillary thyroid carcinomas with a frequency of 60% to 70%. RET gene

4. Rizik za razvoj karcinoma štitnjače ostao je povišen nekoliko desetljeća nakon izlaganja zračenju.

Utjecaj unutarnjeg ozračivanja na razvoj karcinoma štitnjače dobro je proučen, a najviše je istražen utjecaj Černobila na razvoj karcinoma štitnjače. Prije toga radili su se pokusi na životinjama i postojala je suglasnost o tome da jod-131 može potaknuti razvoj raka štitnjače, ali nije bilo dokaza na ljudima. Prilikom nuklearnog pokusa na Maršalskim otocima 1954. godine nekoliko osoba koje su se tamo zatekle oboljelo je od karcinoma štitnjače. Uzrok se pripisao djelovanju joda-131 i njegovih kratkoživućih izotopa te vanjskom gama zračenju. Oštećenje reaktora nuklearne elektrane u Černobilu 1986. godine uzrokovalo je oslobađanje velikih količina joda-131 u atmosferu (23 do 46 MCi joda-131). Ubrzo nakon černobilske nesreće incidencija papilarnih karcinoma štitnjače višestruko je porasla u djece u okolnim područjima Ukrajine, Bjelorusije i zapadnog dijela Rusije. Radioaktivni izotopi joda, osobito joda-131, uneseni kontaminiranom hranom, bili su glavni uzrok značajne doze radioaktivnosti na štitnjače. Rizik za razvoj karcinoma štitnjače nakon izlaganja jodu-131 bio je veći što je dob u vrijeme izlaganja bila manja. Jacob i suradnici ustanovili su linearnu povezanost primljene doze radijacije i razvoja karcinoma štitnjače u djece, sličnu kao i za vanjsko zračenje. Međutim, postoje razlike. Vrijeme latencije je kraće u bolesnika nakon černobilskog incidenta u odnosu na karcinome štitnjače izazvane vanjskim zračenjem. Među djecom koja su živjela u Bjelorusiji karcinom je bio mnogo češći i agresivniji u djece mlađe od dvije godine u doba incidenta, a u čak 62% te djece došlo je do širenja karcinoma izvan štitnjače u odnosu na 40% u starije djece. Karcinom štitnjače je bio češći kod ženskog spola u odnosu na muški (60%:40%). Veća učestalost karcinoma u djece mlađe od dvije godine tumači se bržom diobom tirocita u odnosu na stariju djecu, a brža dioba stanica ima veću vjerojatnost mutacija. Budući da je štitnjača u dojenčeta manja u odnosu na starije dijete, ista doza zračenja imati će jači učinak. Većina bolesnika imala je jedinstven histološki nalaz papilarnog karcinoma štitnjače s velikom solidnom komponentom (solidni podtip). Ovakav oblik je vrlo agresivan s infiltracijom okolnih tkiva i zahvaćanjem limfnih čvorova. Svi karcinomi štitnjače nastali kao posljedica izlaganju ionizirajućem zračenju bili su dobro diferencirani papilarni ili papilarno-folikularni karcinomi, dok su anaplastični karcinomi štitnjače izrazito rijetki. Promjene RET protoonkogeni patognomonične su za radijacijski inducirani papilarni karcinom štitnjače i mogu se naći u oko 60% do 70% ovih karcinoma. RET gen kodira transmembranski receptor tirozin kinaze i uključen je u regulaciju rasta,

encodes a transmembrane tyrosine kinase receptor and is involved in the regulation of growth, survival, differentiation and proliferation of cells that originate from neural crest. The Ret protein is not normally present in thyroid follicular cells. RET/PTC oncogenes are mutant forms of the tyrosine kinase receptors RET. RET/PTC1 rearrangements are found in sporadic papillary thyroid cancers in adults, while RET/PTC3 rearrangements are found in radiation induced papillary thyroid cancers in children. BRAF (gene encoding B-type Raf kinase) mutations are present in 45% of sporadic papillary thyroid cancers in adults and in less than 10% of papillary thyroid cancer in children. None of the papillary thyroid cancers with solid component had BRAF mutation. Iodine deficiency in Belarus was a significant additional risk factor for thyroid cancer development in children exposed to ionizing radiation from the damaged reactor. Comparison of Chernobyl with Hiroshima and Nagasaki yielded significant differences. The first cases of thyroid cancer as a consequence of Chernobyl accident appeared after 3 to 4 years, while the first cases of thyroid cancer in Japan appeared 9-10 years after nuclear bomb explosions. Considering morphological characteristics of thyroid carcinomas, the solid subtype of papillary thyroid carcinoma was a frequent finding after Chernobyl accident, while classic papillary thyroid carcinoma was present in Japan. These morphological differences can be explained by the significant difference in iodine intake at the time of exposure to ionizing radiation. However, other etiologic factors may also exist. Severe iodine deficiency was present in most parts of the former Soviet Union, while iodine excess is present in Japan. Potassium iodide (KI), if taken promptly, effectively reduces the dose to the thyroid.

It is generally considered that Chernobyl accident did not increase the incidence of thyroid cancer in other European countries or in other parts of the world. The use of  $^{131}\text{I}$  for diagnostic and therapeutic purposes and the risk of thyroid carcinoma development were studied. These studies demonstrated the use of  $^{131}\text{I}$  for medical purposes to be generally safe. However, some investigations demonstrated a higher frequency of thyroid nodules, thyroid carcinoma and higher mortality from thyroid cancer in comparison to control group. Causal relationship is not clear; it may be because of the underlying thyroid condition or increased surveillance in these patients. Case control studies demonstrated that the second important risk factor for thyroid cancer development is goiter, especially thyroid nodules/adenomas.

preživljenja, diferencijaciju i migraciju stanica koje potječu iz neuralnog grebena. Ret protein se normalno ne nalazi u folikularnim stanicama štitnjače. RET/PTC onkogen je mutirani oblik RET receptora za tirozin kinazu. Kod sporadičnih papilarnih karcinoma štitnjače u odraslih utvrđene su promjene u RET/PTC1, dok su kod radijacijom induciranog papilarnog karcinoma štitnjače u djece utvrđene promjene u RET/PTC3. Mutacije u BRAF (gen za B-tip Raf kinazu) koji je novi molekularni biljeg, javljaju se u oko 45% sporadičnih karcinoma u odraslih osoba, a kod karcinoma u djece ili djece koja su bila izložena radioaktivnom zračenju navedena mutacija je prisutna u manje od 10% bolesnika. Naime, niti jedan tumor sa solidnom komponentom (solidni podtip) nije imao tu mutaciju. Nedostatan unos joda u najizloženijim područjima Bjelorusije bio je važan dodatni čimbenik rizika za razvoj karcinoma štitnjače u djece izložene radioaktivnom zračenju iz oštećenog reaktora. Usporedbom Černobila s posljedicama atomskih bomba bačenih u Japanu za vrijeme drugog svjetskog rata uočene su značajne razlike. Prvi oboljeli od raka štitnjače kao posljedica černobilskog incidenta pojavili su se nakon samo 3-4 godine, za razliku od Japana gdje su se prvi slučajevi javili nakon 9-10 godina od eksplozija atomskih bomba. Prema morfološkom izgledu tumora, u Černobilu je prevladavao solidan podtip papilarnog karcinoma, dok je u Japanu bio klasičan papilarni karcinom. Ove morfološke razlike u obliku papilarnog karcinoma štitnjače tumače se značajnom razlikom u unosu joda u organizam u trenutku izlaganja radioaktivnom zračenju, iako se ne isključuju i drugi uzroci. U zemljama bivšeg Sovjetskog Saveza bilo je mnogo krajeva s teškim nedostatkom joda, za razliku od Japana gdje je unos joda povećan. U prevenciji razvoja karcinoma štitnjače nakon izlaganju jodu-131 primjenjuje se kalij-jodid. Smatra se da černobilski nuklearni incident nije uzrokovao porast incidencije karcinoma štitnjače u ostalim zemljama Europe i svijeta. Istraživanja utjecaja dijagnostičke i terapijske primjene joda-131 u liječenju hipertireoze na razvoj karcinoma štitnjače uglavnom su pokazala da je primjena radioaktivnog joda sigurna. Ipak, u pojedinim istraživanjima nakon primjene joda-131 utvrđena je povećana incidencija čvorova štitnjače, karcinoma štitnjače i veća smrtnost od karcinoma štitnjače u odnosu na kontrolnu skupinu. Uzročno-posljednični odnos povećanog rizika nakon primjene joda-131 nije jasan, ali u obzir treba uzeti i postojeću bolest štitnjače, kao i češće praćenje ovih bolesnika. Analiza kontroliranih istraživanja pokazala je da je drugi važan rizični čimbenik za razvoj karcinoma štitnjače guša, a osobito benigni čvorovi štitnjače/adenomi.



## IODINE INTAKE AND THYROID CANCER

### UNOS JODA I RAK ŠTITNJAČE

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The role of iodine in the pathogenesis of thyroid cancer is both complex and controversial. Animal experiments in the 1960s showed an increased development of thyroid carcinoma after prolonged iodine deficiency. Induced carcinomas were both of papillary and follicular types. Iodine deficient Fisher rats developed chromosomal abnormalities of thyroid cells. The proposed mechanism of tumor development in experimental animals appeared at that time straightforward, a simple example of failure of feedback control. Prolonged iodine deficiency induced compensatory excess secretion of thyrotropin (TSH) with goiter formation, development of follicular hyperplasia, thyroid nodules and adenomas. The next proposed step was malignant change. A similar mechanism was proposed in human thyroid cancer development. Prolonged secretion of TSH was a common denominator of carcinoma development, with endemic goiter as a risk factor, and the best preventive measure iodination of table salt. In the past, there was a clinical impression of strong correlation between endemic goiter and thyroid carcinoma. In 1928, the pathologist Wegelin noted from autopsy findings that thyroid carcinoma was 10 times more frequent in Bern (Switzerland) than in Berlin (Germany). At that time, Bern was an area of endemic goiter and iodine deficiency. A coincidental fall in the prevalence of both goiter and thyroid carcinoma was reported in Switzerland after the introduction of iodine prophylaxis. Furthermore, recent investigations showed that goiter, especially thyroid adenoma, is an important risk factor in thyroid cancer development. Many epidemiological studies compared the incidence and risk of thyroid cancer development between iodine deficient and iodine sufficient areas. In 1987, Belfiore *et al.* compared two areas in Sicily with different iodine intake and demonstrated a statistically higher incidence of thyroid carcinoma in an area with iodine deficiency. The same author demonstrated that the incidence of thyroid carcinoma in patients with non-functional thyroid nodules living in an area of iodine

Uloga joda u patogenezi raka štitnjače je složena i predmet je mnogih oprečnih stavova. Istraživanja na životinjama provedena 60-tih godina prošloga stoljeća pokazala su razvoj guše i raka štitnjače u uvjetima nedostatnog unosa joda. Inducirani karcinomi štitnjače bili su papilarnog i folikularnog tipa. Kod Fisher štakora na dijeti s nedostatnim unosom joda utvrđeni su kromosomski poremećaji stanica štitnjače. Pretpostavljeni mehanizam nastanka tumora štitnjače kod eksperimentalnih životinja činio se vrlo jednostavan kao primjer poremećaja negativne povratne sprege. Nedostatan unos joda uzrokovao je kompenzatorno povećano lučenje TSH uz nastanak guše, potom razvoj folikularne hiperplazije, čvorova i adenoma. Slijedeći pretpostavljeni korak bila je maligna promjena. Pretpostavljeno je da sličan mehanizam nastanka tumora štitnjače postoji i u čovjeka. Produljeno lučenje TSH pretpostavljeno je kao glavni pokretač razvoja karcinoma štitnjače, endemska guša kao rizični čimbenik, a najbolja preventivna mjera jodiranje soli. U prošlosti je postojao klinički dojam snažne povezanosti endemske gušavosti i karcinoma štitnjače. Godine 1928. patolog Wegelin je primijetio iz nalaza autopsije da je karcinom štitnjače 10 puta češći u Bernu u Švicarskoj nego u Berlinu u Njemačkoj. Bern je tada bio područje s nedostatnim unosom joda uz visoku učestalost endemske gušavosti. U Švicarskoj je nakon uvođenja jodne profilakse zabilježen koincidentni pad prevalencije guše i karcinoma štitnjače. Novija istraživanja također su pokazala da je važan rizični čimbenik za razvoj karcinoma štitnjače guša, a osobito benigni čvorovi štitnjače/adenomi. U epidemiološkim istraživanjima uspoređivala se incidencija i rizik za nastanak karcinoma štitnjače u područjima s manjkom joda i dostatnim unosom joda. Belfiore i sur. su 1987. godine usporedili dva područja na Siciliji s različitim unosom joda, a utvrđena je statistički veća učestalost karcinoma štitnjače u području s nedostatnim unosom joda u odnosu na kontrolno područje. Isti autor i sur. pokazali su da je učestalost karcinoma štitnjače u bolesnika s nefunkcionalnim čvorom u području s ne-



deficiency was twice as high as compared to an area with sufficient iodine intake. In countries like Austria and Australia, a significant increase in the incidence of thyroid cancer was recorded after the introduction of iodine prophylaxis and subsequent iodine sufficiency. However, a similar increase in the incidence of thyroid cancer was reported in countries with unchanged iodine intake like USA, France, Scotland and Switzerland. In Tasmania, after a decrease in iodine intake, there was a rise in the incidence of thyroid cancer. It was previously believed that the increased incidence of thyroid cancer in Iceland and Hawaii was a consequence of excess iodine intake. However, nowadays it is considered that it may rather be due to the high natural radiation of the volcanic soil on these islands. All presented data lead to insufficient and controversial conclusions. Therefore, it is generally considered that the incidence of thyroid cancer is not influenced by iodine intake in a population. In many countries, the introduction of iodine prophylaxis coincided with improvements in thyroid cancer diagnostics. Therefore the increase in the incidence of thyroid cancer was partially due to improved diagnostics. However, there is a relatively clear causal relationship between iodine intake and histopathologic type of thyroid carcinoma. Follicular and anaplastic thyroid carcinomas are more frequent in areas with iodine deficiency, whereas papillary thyroid carcinoma is more frequent in areas of iodine sufficiency. In many countries, the introduction of iodine prophylaxis caused a decrease in the number of anaplastic and follicular thyroid carcinoma while the number of papillary thyroid carcinoma increased, resulting in a rise of papillary to follicular cancer ratio. Some of these countries are Austria, Argentina, Australia and Sweden. The effect of the increase in iodine intake on thyroid cancer histopathology is called “papillarization”. With the introduction of iodine prophylaxis, the increase in papillary thyroid carcinoma is not only relative, but absolute in number. Concomitantly with “papillarization” a shift to less advanced tumor stages and a decrease in tumor size were recorded, which together with a decrease in the number of anaplastic and follicular thyroid carcinoma resulted in better prognosis of thyroid carcinoma patients.

In the past, Croatia was an area with a very high prevalence of goiter and presence of cretinism. At the beginning of the 1950s, the prevalence of goiter in the inland parts of Croatia was 50%-90%, with the presence of cretinism. In 1953, the first regulation on universal salt iodination for both human and animal consumption was

dostatnim unosom joda dvostruko veća u odnosu na područje s dostatnim unosom joda. U zemljama poput Austrije i Australije je nakon uvođenja jodne profilakse i postizanja dostatnog unosa joda zabilježen značajan porast incidencije raka štitnjače. Međutim, sličan porast uslijedio je i u zemljama s nepromijenjenim unosom joda poput SAD, Francuske, Škotske i Švicarske. U Tasmaniji je nakon pada unosa joda došlo do porasta incidencije raka štitnjače. Prethodno se smatralo da je visoka incidencija raka štitnjače na Islandu i Havajima posljedica povećanog unosa joda, no danas se smatra da je ona posljedica prirodne radijacije vulkanskih stijena koje su u geološkom sastavu tih otočja. Sve navedeno upućuje na nejasne i suprotne zaključke pa se danas općenito smatra da unos joda ne utječe na pojavnost raka štitnjače. U mnogim zemljama su usporedno s uvođenjem jodne profilakse uvedene nove dijagnostičke metode u otkrivanju raka štitnjače pa je porast incidencije raka štitnjače dijelom posljedica poboljšane dijagnostike. Postoji relativno jasna uzročna veza između unosa joda i patohistološkog tipa tumora. Folikularni i anaplastični karcinom štitnjače javlja se češće u područjima s nedostatnim unosom joda, dok je papilarni karcinom češći u područjima s dostatnim unosom joda. U mnogim zemljama uvođenje jodne profilakse dovelo je do smanjenja broja anaplastičnih i folikularnih karcinoma štitnjače, dok se broj papilarnih karcinoma povećao, rezultirajući povećanjem kvocijenta papilarni-folikularni karcinomi. Primjeri takvih zemalja su Austrija, Argentina, Australija i Švedska. Taj učinak povećanja unosa joda na patohistološka obilježja karcinoma štitnjače naziva se “papilarizacija”. Uvođenjem jodne profilakse ne raste samo relativni udio papilarnih karcinoma, nego raste njihov apsolutni broj. Istodobno s pojavom “papilarizacije” uočen je pomak ka manje uznapredovalim stadijima tumora, smanjenje veličine tumora, što je uza smanjenje anaplastičnog i folikularnog karcinoma štitnjače sveukupno rezultiralo u poboljšanoj prognozi bolesnika. Hrvatska je u prošlosti bila područje s izrazito visokom učestalošću gušavosti uz pojavu kretenizma. Početkom 50-tih godina prošloga stoljeća učestalost guše u kontinentalnim dijelovima zemlje iznosila je 50%-90% uz pojavu kretenizma. Godine 1953. u bivšoj Jugoslaviji uvedena je zakonska odredba o obvezatnom jodiranju sveukupne soli za ljudsku i životinjsku upotrebu s 10 mg kalij jodida (KI) po kilogramu soli. Bio je to jedan od prvih zakona o univerzalnoj jodnoj profilaksi u Europi. Deset godina kasnije zabilježeno je gotovo trostruko smanjenje prevalencije gušavosti u Hrvatskoj uz nestanak kreteni-



introduced in former Yugoslavia with 10 mg of potassium iodide (KI) *per* kg of salt. At that time it was one of the first laws on universal salt iodination in Europe. A three-fold reduction of goiter prevalence together with disappearance of cretinism was recorded ten years later. At the beginning of the 1990s, epidemiological investigations still demonstrated persistence of mild to moderate iodine deficiency in Croatia, with the prevalence of goiter in school children of 8%-35%. In 1996, the new regulation on obligatory salt iodination was introduced in Croatia with 25 mg of KI *per* kg of salt. In 2002, epidemiological investigations demonstrated sufficient iodine intake and eradication of goiter in school children in Croatia. The incidence of thyroid cancer in Croatia has increased more than two-fold in both women and men in the iodine sufficiency period as compared to the period before the implementation of the new act on obligatory salt iodination. However, mortality from thyroid cancer in the iodine sufficiency period was slightly lower in females, and without significant change in males. An increase was recorded in the number of papillary thyroid cancer patients and in the papillary to follicular cancer ratio, with a decrease in size of the newly diagnosed differentiated thyroid carcinoma.

zma. Epidemiološka istraživanja provedena početkom 1990-tih pokazala su postojanje blagog do umjerenog nedostatka joda u Hrvatskoj uz učestalost gušavosti od 8%-35% u školske djece. Zbog toga je 1996. godine u Hrvatskoj uveden novi pravilnik kojim je povećana količina KI u soli na 25 mg/kg. Epidemiološka istraživanja provedena 2002. godine pokazala su dostatan unos joda i potpunu iskorijenjenost gušavosti u školske djece u Hrvatskoj. Incidencija raka štitnjače u Hrvatskoj porasla je više od dva puta u žena i muškaraca u razdoblju s dostatnim unosom joda u odnosu na razdoblje prije uvođenja novog zakona, dok se smrtnost od raka štitnjače smanjila u žena, a ostala je na niskoj razini u muškaraca. Utvrđen je porast papilarnih karcinoma štitnjače uz porast omjera papilarni-folikularni karcinom i smanjenje veličine novootkrivenog diferenciranog karcinoma štitnjače.

## IMPACT OF SONOGRAPHICALLY DISCOVERED INCIDENTALOMAS AND THYROID MICROCARCINOMAS. DO WE OVERDIAGNOSE?

### POSljedICE ULTRAZVUČNOG NALAZA INCIDENTALOMA I MIKROKARCINOMA ŠTITNJAČE. PRETJERUJEMO LI S DIJAGNOSTIKOM?

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In Denmark, with a population of around 5 million, approximately 120 cases of thyroid malignancy are diagnosed annually. This number has been unchanged for the past decades. Around 1500 patients with nodular thyroid disease are offered surgery and approximately the same number are treated with radioiodine annually.

U Danskoj koja ima oko 5 milijuna stanovnika na godinu se otkrije otprilike 120 slučajeva raka štitnjače. Ovaj broj se nije mijenjao posljednjih nekoliko desetljeća. Na godinu se kirurški liječi oko 1500 bolesnika s čvorovima u štitnjači te se otprilike isto toliko bolesnika liječi radiojodom. Iz ovoga proizlazi da je ovih 120 bole-





Thus, the 120 cases are selected from a minimum of 3000 cases, suggesting a 4% risk of malignancy. In fact, since at least as many individuals are diagnosed with nodular thyroid disease but left untreated, the actual risk in a given patient may be as low as 1%-2%<sup>1</sup>. Therefore, the main aim of any diagnostic algorithm is to find the few patients who need surgery, give reassurance to the majority who need no therapy, and offer an alternative to surgery to those having symptomatic benign nodular thyroid disease but who do not require/wish surgery<sup>1,2</sup>.

There are algorithms for the management of patients with a diagnosis of nodular thyroid disease and increasing evidence suggest that in a given patient the likelihood of malignancy is at large independent of whether there is one or several nodules<sup>1,2</sup>. It follows that the risk *per* nodule decreases with the number of nodules, and therefore finding a nodule harboring malignancy in a patient with multinodular goiter resembles that of 'finding the needle in the haystack'. Although there are guidelines for the management of patients with nodular thyroid disease<sup>3-5</sup>, questionnaire surveys indicate that we are far from having reached consensus<sup>1</sup>. The management varies from suggesting surgical therapy (total/near total thyroidectomy) in the majority, as advocated by some<sup>6</sup>, to observation in the vast majority, as advocated by others<sup>1</sup>. Clearly, factors such as local tradition, availability of technology and skilled surgeons, and numerous others play a major role in such decisions.

Management pathways for the incidental thyroid nodule are even less clear-cut and remain controversial<sup>6-8</sup>. As the use of thyroid ultrasound (US) and other neck imaging modalities has increased during the last two decades, nodules too small to be palpated are more often detected and papillary thyroid microcarcinomas (PMCT), defined by the WHO as less than 1.0 cm in size, are identified with greater frequency<sup>7,8</sup>. Categorization of the risk of malignancy, based on clinical examination (history and palpation), biochemical evaluation (TSH and calcitonin), as well as imaging criteria by US (extracapsular growth, lymph node involvement, focality, echogenicity, flow evaluation, elasticity, etc.), can limit but not eliminate the risk of overlooking clinically important thyroid malignancy. This risk is usually considered to be 1% at most<sup>1,2</sup>.

PMCT can broadly be classified into 3 categories, depending on how it is detected: 1) incidental PMCT detected by pathological examination of surgical specimens of the thyroid resected for other disease; 2) latent

snika odabrano iz najmanje 3000 bolesnika, što znači da rizik od maligniteta iznosi 4%. No, ovaj postotak je vjerojatno čak i niži te iznosi oko 1%-2%<sup>1</sup>, jer se barem isto toliko bolesnika s čvorovima u štitnjači uopće ne liječi. Stoga je svrha bilo kojeg dijagnostičkog algoritma odrediti manji broj bolesnika u kojih je potrebna operacija, umiriti većinu onih kojima ne treba nikakva terapija te ponuditi alternativu operaciji u onih koji imaju manifestne dobroćudne čvorove u štitnjači i ne trebaju ili ne žele operaciju<sup>1,2</sup>.

Postoje algoritmi za postupanje s bolesnicima s čvorovima u štitnjači. Sve je više dokaza da je vjerojatnost maligniteta većim dijelom neovisna o tome je li prisutan jedan ili više čvorova u štitnjači<sup>1,2</sup>. Iz ovoga proizlazi da se rizik maligniteta u čvoru smanjuje s brojem čvorova te da pronalaženje čvora sa zloćudnom transformacijom u bolesnika s multinodularnom gušom nalikuje na „iglu u plastu sijena“. Usprkos tome što postoje smjernice za postupanje s bolesnicima s čvorom(vima)<sup>3-5</sup>, provedene ankete pokazuju da smo daleko od konsenzusa<sup>1</sup>. Neki autori preporučuju operaciju (totalna/skoro totalna tireoidektomija) u većini slučajeva, dok drugi preporučuju praćenje u velikoj većini slučajeva. Jasno je da na ovakve odluke snažno utječu razni čimbenici kao tradicija, dostupnost tehnologije i iskusnih operatera i mnogi drugi.

Još je manje jasno kako postupati s incidentalomima te oko toga još uvijek postoje proturječja<sup>6-8</sup>. Kako se posljednja dva desetljeća sve više rabi ultrazvuk štitnjače i druge metode slikovnog prikaza, sve se više otkrivaju nepalpabilni čvorovi u štitnjači kao i papilarni mikrokarcinom štitnjače koji Svjetska zdravstvena organizacija definira kao papilarni karcinom s promjerom manjim od 1 cm<sup>7,8</sup>. Kategorizacija rizika od maligniteta koja se temelji na kliničkom pregledu (povijest bolesti i palpacija), biokemijskim pretragama (TSH i calcitonin), kao i ultrazvučnim značajkama (proboj kapsule, širenje bolesti na limfne čvorove, fokalnost, ehogenost, procjena protoka, elasticitet itd.) može ograničiti, ali ne i u potpunosti ukloniti rizik previda klinički značajnog maligniteta u štitnjači. U većini slučajeva se smatra kako ovaj rizik iznosi najviše 1%<sup>1,2</sup>.

Papilarni mikrokarcinom štitnjače se može klasificirati u tri kategorije, ovisno o načinu otkrivanja: 1) incidentalni papilarni mikrokarcinom koji se otkrije patohistološkim pregledom štitnjače operirane zbog druge patologije; 2) latentni mikrokarcinom štitnjače koji se otkrije slučajno pri autopsiji; 3) okultni papilarni mikrokarcinom koji se otkrije kao izvor (polazište)



PMCT, which are incidentally detected in autopsy specimens of the thyroid; and 3) occult PMCT which are detected as the origin of lymph nodal metastasis and/or distant metastases. In autopsy specimens latent carcinoma is detected in 5.6% to 35.6%<sup>7</sup>, increasing with decreasing size of cut-off. This is the same as that detected incidentally by US<sup>7</sup>. However, the fact that the prevalence of PMCT is about 1000 times higher (around 3.5%) than that of clinically apparent papillary carcinoma (2-12/100,000 women)<sup>7</sup> suggests that PMCT, incidentally detected by e.g., US, rarely become clinically apparent. Therefore, the fact that the increasing incidence of thyroid carcinoma, seen in some countries, is not paired with increasing mortality, suggests that it is due to PMCT, and is rarely harmful for the patient. On the other hand, multifocality and lymph node metastases have been observed at autopsy in 46% and 14%, respectively, of latent papillary carcinomas between 0.5 and 10 mm in diameter. Figures are very similar in studies of surgical specimens of PMCT<sup>7</sup>. The latter findings suggest that all patients with PMCT, and indeed most with nodular thyroid disease, should undergo surgery.

Is it possible to reconcile this apparent contradiction? Much depends on the interpretation and consequences of the natural history of PMCT. Whether multifocality and regional node metastasis predict disease development is questioned. At present there is a consensus regarding incidentally detected PMCT at surgery for benign thyroid diseases. Such patients should be monitored without surgery. At the time of diagnosis, the prognosis of the individual patient, however, remains impossible to predict. The choice is between surgery and follow up. In case of certain unfavorable features (e.g., tumors adjacent to the recurrent laryngeal nerve at the dorsal surface of the lobe, FNA suggesting high grade malignancy, presence of node metastases or distant metastases, enlargement of tumor size or node metastases during follow up or multifocality), surgery is recommended<sup>7-9</sup>. Conservative follow up in 'low risk patients' suggests that few nodules increase in size (6%) and even fewer (1%-2%) develop lymph node metastases during long-term follow up<sup>7</sup>.

In my view, the answer to the question posed in the title is 'yes'. Therefore, early detection and aggressive treatment, with the accompanying risks of side effects and loss of quality of life, should be balanced against the risks of overlooking or postponing the diagnosis of (mainly) papillary thyroid cancer if observation is pre-

metastaza u limfnim čvorovima ili udaljenim metastazama. Pri autopsiji se latentni karcinom otkrije u 5,6% do 35,6% slučajeva, uz porast pojavnosti s rastom broja patohistoloških rezova, što vrijedi i za slučajni nalaz pri ultrazvuku<sup>7</sup>. Međutim, činjenica da je papilarni mikrokarcinom oko 1000 puta češća pojava (oko 3,5%) nego manifestni papilarni karcinom (2-12/100.000 žena)<sup>7</sup> ukazuje na to da papilarni mikrokarcinom, slučajno otkriven pri ultrazvuku, rijetko postaje manifestan. Iz ovoga proizlazi da porast incidencije raka štitnjače u nekim zemljama ne rezultira porastom mortaliteta te da se može pripisati papilarnom mikrokarcinomu koji rijetko ugrožava bolesnika. Međutim, multifokalnost i metastaze u limfnim čvorovima su pronađene u 46% odnosno 14% slučajeva pri autopsiji latentnog papilarnog karcinoma promjera od 0,5 do 10 mm. Podaci iz studija patohistoloških uzoraka papilarnog karcinoma su jako slični<sup>7</sup>. Ti podaci govore u prilog tome da bi se svi bolesnici s papilarnim mikrokarcinomom i većina s nodularnom strumom ipak trebali operacijski liječiti.

Je li moguće pronaći izlaz iz ove proturječnosti? Mnogo toga ovisi o interpretaciji i posljedicama prirodnog tijeka papilarnog mikrokarcinoma. Nije sigurno može li se iz prisutnosti multifokalnosti i metastaza u limfnim čvorovima predvidjeti daljnji razvoj bolesti. U ovom trenutku postoji konsenzus o tome da se bolesnici s incidentalno pronađenim mikropapilarnim karcinomom pri operaciji štitnjače zbog benigne bolesti samo prate te da se ne operiraju. Međutim, nije moguće odrediti prognozu u individualnog bolesnika u vrijeme postavljanja dijagnoze. Može se birati između operacije i praćenja. Operacija se preporuča u slučaju kad su prisutne nepovoljne značajke tumora (npr. lokacija tumora uz povratni laringealni živac na dorsalnoj površini režnja štitnjače, citološka punkcija koja govori u prilog visokog stupnja maligniteta, rast tumora, multifokalnost ili metastaze u lokalne limfne čvorova za vrijeme praćenja)<sup>7-9</sup>. Podaci dobiveni za vrijeme konzervativnog praćenja „niskorizičnih“ bolesnika ukazuju na to da se samo manji broj čvorova (6%) povećava te da se u još manjem broju čvorova (1%-2%) razvijaju metastaze<sup>7</sup>.

Po mojem mišljenju, odgovor na pitanje iz naslova je „da“. Stoga bi trebalo postići ravnotežu između ranog otkrivanja raka i agresivnog načina liječenja, koji je popraćen mogućim komplikacijama i smanjenjem kvalitete života, te rizika od previda ili predugog odgađanja dijagnoze (uglavnom) papilarnog karcinoma štitnjače u slučaju da se u bolesnika provodi samo praćenje. U većine bolesnika s incidentalomom se takva odluka ne može

ferred. At present such a choice cannot be based on evidence in the vast majority of patients with thyroid incidentaloma. The cost – economically and psychosocially – of observation, including regular imaging and rebiopsy, may well outweigh the risk of total/near total thyroidectomy, but is non-clarified.

Finally, it should be remembered that, independent of any consensus or of how meticulously data are obtained, results and conclusions from one study may not necessarily apply to another population due to, e.g., differences in referral pattern, patient selection, methodology of investigations, patient preference and local tradition, as well as epidemiology due to differences in the etiology based on variation in the genetic background and environmental factors, such as iodine intake.

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## WHO CLASSIFICATION OF DIFFERENTIATED THYROID CARCINOMA – RECOMMENDATIONS AND CRITERIA FOR HISTOPATHOLOGICAL DIAGNOSIS

### SZO KLASIFIKACIJA DIFERENCIIRANIH KARCINOMA ŠTITNJAČE – SMJERNICE I KRITERIJI PATOHISTOLOŠKE DIJAGNOSTIKE

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The expected aim of any histological classification of tumors is to define entities that can have not only diagnostic but also prognostic, therapeutic and biological relevance. Nevertheless, it is usually a compromise, sometimes producing controversies, between “lumpers” and “splitters”, and can differ in the emphasis that they lay on features of diagnostic importance, histogenesis, or epidemiological usefulness. It is unreasonable to expect that the classification of thyroid tumors is an exception.

The first World Health Organization (WHO) Histological Classification of Thyroid Tumors was elaborated by the International Committee of Thyroid Pathologists working between 1964 and 1972, and was published in 1974. Due to changes in our understanding of several areas of thyroid pathology since that time, a revised classification was announced in 1988. The major differences in this revision were removal of the subtypes of undifferentiated (anaplastic) carcinoma, including small cell carcinoma; deletion of squamous cell carcinoma as a major tumor type; revision of the nonepithelial and miscellaneous tumors; and addition of malignant lymphoma as a major separate entity. Also, one of the most significant changes was that the term papillary microcarcinoma replaced the previously used term occult papillary carcinoma.

The third WHO Histological Classification of Thyroid Tumors was published in 2004, giving us a recent frame and some new directions and recommendations for both clinicians and pathologists. The previously used frame with 7 major categories (1) epithelial tumors, 2) nonepithelial tumors, 3) malignant lymphomas, 4) miscellaneous tumors, 5) secondary tumors, 6) unclassified

Očekivani cilj bilo koje histološke klasifikacije tumora je definiranje entiteta koji nemaju samo dijagnostičku, nego i prognostičku, terapijsku i biološku primjenjivost. Usprkos tome rezultat je često kompromis, ponekad s proturječnostima nastalim zbog sažimanja, ili opsežnog dijeljenja. Razlike su često posljedica i naglasaka koji može biti dan više na dijagnostičku važnost, histogenezu ili epidemiološku iskoristivost te je nerazumno očekivati da je klasifikacija tumora štitne žlijezde iznimka.

Prva histološka klasifikacija tumora štitnjače Svjetske zdravstvene organizacije (SZO) rezultat je djelovanja Međunarodnog odbora endokrinih patologa između 1964. i 1972. godine, a objavljena je 1974. godine. S obzirom na promjene i napredak u razumijevanju patologije štitnjače revidirana klasifikacija je objavljena 1988. godine. Glavne razlike sastojale su se u izbacivanju podtipova nediferenciranog (anaplastičnog) karcinoma, uključujući karcinom malih stanica, izostavljanju karcinoma pločastih stanica kao jednog od glavnih tumorskih tipova, revizije neepitelijalnih i rijetkih tumora te uvrštavanju limfoma kao zasebne odvojene glavne kategorije. Također je jedna od najznačajnijih promjena bila i uvođenje pojma papilarnog mikrokarinoma koji je zamijenio pojam okultnog papilarnog karcinoma.

Treća histološka klasifikacija tumora štitnjače SZO objavljena je 2004. godine, dajući najnoviji okvir, smjernice i preporuke kako za kliničare tako i za patologe. Prethodno primijenjen okvir od 7 glavnih kategorija (1. epitelijalni tumori, 2. neepitelijalni tumori, 3. maligni limfomi, 4. rijetki tumori, 5. sekundarni tumori, 6. neklasificirani tumori, 7. tumorima slične lezije) napušten je i zamijenjen okvirom sastavljenim od 3 glavne kate-

tumors, and 7) tumor-like lesions) is now abandoned and replaced with a frame composed of 3 major categories (1) thyroid carcinomas, 2) thyroid adenoma and related tumors, and 3) other thyroid tumors). The separation of malignant tumors of differentiated follicular cells based on morphology and clinical features into papillary or follicular carcinomas, regarding tumors with minor papillary component as papillary, has been continued and is strongly supported by molecular studies showing the involvement of distinct genes in these groups, with minor overlapping. The most important variants of papillary carcinoma are the follicular variant, the diffuse sclerosing variant, the tall cell variant and the columnar cell variant. The obligatory presence of the nuclei with features of the conventional papillary carcinoma is required for the diagnosis of the oncocyctic variant of papillary carcinoma.

As in previous editions of WHO classification, the follicular carcinomas have been defined as invasive neoplasms of follicular cells that lack the typical nuclear features of papillary thyroid carcinoma (PTC) and have been divided into two major categories. According to the degree of invasiveness, minimally invasive follicular carcinomas have limited capsular and/or vascular invasion. Widely invasive follicular carcinomas show prominent infiltration of adjacent thyroid tissue and/or blood vessels. Capsular invasion is defined by tumor penetration through the tumor capsule unassociated with the site of the previous fine needle aspiration biopsy. Vascular invasion is defined by the presence of intravascular tumor cells, either covered by the endothelium or associated with thrombus, affecting vessels within or beyond the tumor capsule. Although inclusion of the oncocyctic tumors into follicular tumors is not widely accepted, these tumors are categorized as a variant of follicular carcinoma defined as malignant neoplasms of follicular cell origin composed exclusively or predominantly (>75%) of oncocyctic cells.

The TNM system is endorsed by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC). The recent TNM revision defines T1 tumors as primary tumors of 2 cm or less instead of previously defined T1 tumors as primary tumors of 1 cm or less in greatest dimension, so that it is no longer equal with the pathological definition of microcarcinoma. Also, T3 tumors are defined as a tumors >4 cm in greatest dimension or any tumor with minimal extrathyroid extension, while in older classification they are defined as tumors >4 cm, without any extrathyroid extension.

gorije (1. karcinomi štitnjače, 2. adenom i s njim povezani tumori štitnjače, 3. drugi tumori štitnjače). Podjela zloćudnih tumora podrijetlom od diferenciranih folikularnih stanica, zasnovana na morfoloiji i kliničkim značajkama, na papilarne i folikularne karcinome, svrstavajući tumore s minornom papilarnom komponentom u papilarne karcinome, nastavljena je i dalje, dobivši značajnu potporu u molekularnim istraživanjima koja su dokazala ulogu različitih gena u ovim skupinama s minimalnim međusobnim preklapanjem. Najznačajniji podtipovi papilarnog karcinoma su folikularni podtip, difuzno sklerozirajući podtip, podtip visokih stanica te podtip cilindričnih stanica. Obvezatna prisutnost klasičnih nuklearnih kriterija konvencionalnog papilarnog karcinoma potrebna je za dijagnozu onkocitnog podtipa papilarnog karcinoma.

Kao i u prethodnim izdanjima SZO klasifikacije, folikularni karcinomi su definirani kao invazivne neoplazme podrijetlom od folikularnih stanica s izostankom tipičnih nuklearnih obilježja papilarnog karcinoma štitne žlijezde (PTC), a podijeljeni su u dvije glavne kategorije. S obzirom na stupanj invazivnosti minimalno invazivni folikularni karcinomi pokazuju ograničenu kapsularnu i/ili krvožilnu invaziju. Opsežno invazivni folikularni karcinomi pokazuju prominentnu infiltraciju okolnog tkiva štitnjače i/ili krvnih žila. Kapsularna je invazija definirana prodorom tumora kroz čitavu debljinu kapsule, a nije povezana s prethodnim mjestom citološke punkcije. Vaskularna je invazija definirana nalazom tumorskih stanica koje su pokrivene endotelom ili povezane s trombom, u krvnim žilama smještenim u kapsuli ili izvan nje. Iako uljučivanje onkocitnih tumora u skupinu folikularnih nije široko prihvaćeno, ovi tumori su kategorizirani kao varijanta folikularnog karcinoma definirana kao zloćudna neoplazma podrijetlom od folikularnih stanica, građena u potpunosti ili pretežito (>75%) od onkocitnih stanica.

TNM sustav je odobrila Međunarodna unija za borbu protiv karcinoma (UICC) i Američka združena komisija za karcinome (AJCC). Novi, revidirani TNM sustav definira T1 tumore kao primarne tumore najvećeg promjera do 2 cm, za razliku od prethodne definicije gdje su T1 tumori bili definirani kao primarni tumori promjera do 1cm. Na taj način sadašnja T1 kategorija nije više istovrsna s patolojskom definicijom mikrokarcinoma štitne žlijezde. Isto tako T3 tumori su definirani kao tumori >4 cm u najvećem promjeru ili tumori bilo koje veličine s minimalnom ekstratiroidnom proširenošću, dok su u starom TNM sustavu T3 tumori bili definirani kao tumori >4 cm bez ekstratiroidne proširenosti.



The variety of tumor types derived from the follicular cell, mainly classified into papillary, follicular and possibly oncocytic types, provide major opportunity for genotype-phenotype correlations. Pathways that are involved in tumorigenesis seem to be distinct. Molecular genetic studies suggest that different subpathways are involved even in individual tumor types and that they could correlate with variations in morphology. Recent advances in genotype-phenotype correlation could be essential for understanding of endocrine carcinogenesis and may lead to better methods of diagnosis, avoiding unnecessary aggressive treatment for tumors that are likely to follow a benign course, and inadequate therapy for others anticipated to display aggressive behavior.

Raznolikost histoloških tipova tumora s osnovnom podjelom na papilarni, folikularni i mogući onkocitni tip osigurava glavne mogućnosti za genotipsko-fenotipsku korelaciju. Slijed događaja uključenih u tumorogenezu čini se nedvojbenim. Molekularno genetičke studije smatraju da su različiti putevi uključeni čak u varijante istog tumorskog tipa i da mogu korelirati s varijacijama u morfologiji.

Novija istraživanja u genotipsko-fenotipskoj korelaciji mogu biti osnova za razumijevanje karcinogeneze u endokrinim žlijezdama, što može voditi ka boljoj dijagnostici čime bi se mogla izbjeći nepotrebna agresivna terapija kod tumora s očekivanim dobroćudnim tijekom, kao i neodgovarajuća terapija tumora s očekivanim agresivnim ponašanjem.

## TNM CLASSIFICATION AND OTHER THYROID CANCER PROGNOSTIC SYSTEMS

### TNM KLASIFIKACIJA I DRUGI PROGNOŠTIČKI SUSTAVI RAKA ŠTITNJAČE

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#### Introduction

Histopathologic classification of the basic types of thyroid carcinoma (papillary, follicular, medullary and anaplastic) has proved to be the most important prognostic factor, which influences general survival, the length of remission and relapses, and metastasis occurrence<sup>1</sup>. Tumor size, extension, differentiation, presence of metastases and method of carcinoma treatment are important prognostic factors. Age is also a very important prognostic factor. Old age is followed by lower relative survival in all histologic types. The differentiated thyroid carcinoma prognosis is better in patients under age 40 and in cases where carcinoma has not spread outside the thyroid capsule or invaded blood vessels<sup>2</sup>. In cases of follicular and papillary carcinoma, the prognosis is determined by the stage at diagnosis, age at the occurrence

#### Uvod

Patohistološka klasifikacija osnovnih tipova karcinoma štitnjače (papilarni, folikularni, medularni i anaplastični) pokazala se najvažnijim prognostičkim čimbenikom koji utječe na opće preživljenje, duljinu razdoblja remisije, te pojavu recidiva i metastaza<sup>1</sup>. Važni prognostički čimbenici su veličina, proširenost, diferenciranost, pojava metastaza i način liječenja karcinoma. Dob je također vrlo važan prognostički čimbenik. Starija životna dob praćena je nižim relativnim preživljenjem kod svih histoloških tipova. Prognoza diferenciranog karcinoma štitnjače bolja je u bolesnika mlađih od 40 godina i u slučajevima kada se karcinom nije proširio izvan kapsule štitnjače ili invadirao krvne žile<sup>2</sup>. Kod folikularnog i papilarnog karcinoma prognoza je znatno više određena stadijem tumora u vrijeme dijagnoze, dobi obolijevanja i



and tumor differentiation rather than by the follicular or papillary histology<sup>1</sup>. Age over 45, follicular histology, primary tumor larger than 4 cm (T2-3), extrathyroid extension (T4) and distant metastases are independent factors that increase the risk of death in patients with differentiated thyroid carcinoma<sup>3</sup>. Generally, the prognosis is much more favorable for women than for men<sup>4</sup>.

### TNM and other prognostic systems

Different scoring systems have been developed for the prognosis of thyroid carcinoma. Some of them are Tumor–Node–Metastasis (TNM) classification, prognostic system of the European Organization for Research and Treatment of Cancer (EORTC), Age–Metastases–Extent–Size system (AMES), Grade–Age–Metastases–Extent–Size system (GAMES), Age–Grade–Extent–Size system (AGES), Metastases–Age–Completeness of Resection–Invasion–Size system (MACIS), Age–Invasion of blood vessels–Metastases system (AIM), the Ohio State system for papillary or follicular carcinoma (OSU), University of Chicago system for papillary carcinoma, National Thyroid Cancer Treatment clinical system (NTCTCS), Noguchi thyroid clinic staging system, University of Münster staging system, University of Alabama and MD Anderson staging system (UAB&MDA), Cancer Institute of the Hospital of Tokyo staging system (CIH), Ankara Oncology Training and Research Hospital staging system, and others<sup>5</sup>. All of them include histopathologic type of carcinoma as the main component. Most of the staging systems refer only to the papillary and follicular carcinoma (EORTC, AMES, GAMES, OSU) or just to the papillary carcinoma (AGES, MACIS, University of Chicago), and include tumor size (except EORTC), patient age (except for University of Chicago and OSU), sex (EORTC and AMES) and presence of lymph node metastases (University of Chicago, OSU, NTCTCS and TNM, depending on age). Extrathyroid extension and distant metastases are considered in all of the scoring systems and extent of the surgical resection performed only in the MACIS system and TNM system with the application of “R” category<sup>6</sup>. To avoid variation in the schemes of the prognostic systems, the Union International Contre Cancer (UICC) and American Joint Committee on Cancer (AJCC)<sup>7</sup> have accepted the TNM staging system. The differential capability of the existing systems was compared in studies on a larger number of patients, and none of the above mentioned systems showed clear ad-

diferenciranošću tumora nego folikularnom ili papilarnom histologijom<sup>1</sup>. Dob starija od 45 godina, folikularna histologija, primarni tumor veći od 4 cm (T2-3), širenje izvan štitnjače (T4) i udaljene metastaze neovisni su nepovoljni čimbenici koji povećavaju rizik od smrti u bolesnika s diferenciranim karcinomom štitnjače<sup>3</sup>. Općenito, prognoza je značajno povoljnija u žena u odnosu na muškarce<sup>4</sup>.

### TNM i drugi prognostički sustavi

Za prognozu karcinoma štitnjače razvijeni su različiti klinički sustavi procjene (*scoring*): sustav stupnjevanja (*staging*) tumor-čvor-metastaza (*Tumor-Nodus-Metastasis*, TNM), prognostički sustav Europske organizacije za istraživanje i liječenje karcinoma (*European Organization for Research on Treatment of Cancer*, EORTC), sustav dob-metastaze-širenje-veličina (*Age-Metastases-Extent-Size*, AMES), sustav stadij-dob-metastaze-širenje-veličina (*Grade-Age-Metastases-Extent-Size*, GAMES), sustav dob-stadij-širenje-veličina (*Age-Grade-Extent-Size*, AGES), sustav metastaze-dob-potpunost resekcije, invazija-veličina (*Metastases-Age-Completeness of Resection-Invasion-Size*, MACIS), sustav dob-invazija u krvne žile-metastaze (*Age-Invasion to blood vessels-Metastases - AIM*), sustav države Ohio za papilarni ili folikularni karcinom (*The Ohio State system for papillary or follicular carcinoma*, OSU), sustav Sveučilišta u Chicagu za papilarni karcinom (*University of Chicago system for papillary carcinoma*), sustav kliničko-patološkog stupnjevanja Nacionalnog zajedničkog istraživanja liječenja karcinoma štitnjače (*National Thyroid Cancer Treatment*, NTCTCS), Noguchi sustav (*Noguchi thyroid clinic staging system*), sustav Sveučilišta u Münsteru (*University of Münster staging system*), sustav Sveučilišta u Alabami i M D Andersona (*University of Alabama and M D Anderson staging system*, UAB&MDA), sustav Instituta za karcinom bolnice u Tokyu (*Cancer Institute Hospital in Tokyo staging system*, CIH), sustav Bolnice za onkološko istraživanje i usavršavanje u Ankari (*Ankara Oncology Training and Research Hospital staging system*) i drugi<sup>5</sup>, a svi kao glavnu sastavnicu uključuju patohistološki tip karcinoma. Većina sustava procjene odnosi se samo na diferencirani papilarni i folikularni karcinom (EORTC, AMES, GAMES, OSU) ili samo na papilarni karcinom (AGES, MACIS, University of Chicago), te uključuju veličinu tumora (osim EORTC), dob bolesnika (osim University of Chicago i OSU), spol (EORTC i AMES) i prisutnost metastaza u limfnim čvorovima (University of Chicago, OSU, NTCTCS i TNM ovisno o dobi). Ekstratireodno šire-





vantage over the TNM system<sup>8</sup>, which is less complex and easier to use. Therefore, TNM system is widely accepted, recommended for reports, disease outcome prognosis, and comparison of different methods of treatment among groups of patients with similar cases of carcinoma and as a treatment guide for patients with thyroid carcinoma. However, up to this point, with all above mentioned, a minority of studies refer to clinical data based on this classification<sup>9</sup>.

### Differences between the fifth and sixth edition of TNM classification

In the latest, 6<sup>th</sup> edition of the UICC TNM classification, published in 2002<sup>10</sup>, new international standards that describe and categorize the stages of carcinoma and its progression have been set. On classifying differentiated thyroid carcinoma, the 6<sup>th</sup> edition of the TNM system has especially altered the description of primary tumor (T) and the extension to regional lymph nodes (N), and differs from the 5<sup>th</sup> edition published in 1997<sup>10,11</sup>. While the 5<sup>th</sup> edition classifies primary tumors =1 cm in size as T1, and tumors >1=4 cm in size as T2, the 6<sup>th</sup> edition defines tumors =2 cm in diameter as T1, and tumors >2=4 cm in size as T2 tumors<sup>10</sup>. In the 5<sup>th</sup> edition, tumors >4 cm in size without extrathyroid expansion are classified as T3, and all tumors with extrathyroid extension as T4. In the 6<sup>th</sup> edition, tumors >4 cm in diameter or all tumors with minimal extrathyroid extension are defined as T3. T4 is divided into T4a (tumor with expansion outside the thyroid capsule and with invasion of the subcutaneous soft tissue, larynx, trachea, esophagus or recurrent nerve) and T4b (tumor which invades prevertebral fascia and mediastinal blood vessels, or spans to the carotid artery). The N system has also been modified. While the 5<sup>th</sup> edition classifies a metastasis to the unilateral cervical lymph nodes as N1a, the 6<sup>th</sup> edition defines N1a as a metastasis only to group VI lymph nodes (pretracheal, paratracheal and prelaryngeal). In the group of tumor stages, all stages of thyroid carcinoma have been modified. In the beginning, the “occult papillary carcinoma” was defined as a tumor up to 1.5 cm in diameter. Later on, based on the WHO definition and T1 stage from the 5<sup>th</sup> edition of the TNM classification it was replaced by the term “papillary microcarcinoma” of up to 1.0 cm in diameter<sup>4</sup>. According to research in different countries, the incidence of clinically manifested papillary carcinoma is in disproportion with the prevalence of microcarcinoma, which supports the hypothesis that papillary microcarcinoma

nje i udaljene metastaze analiziraju se u svim sustavima procjenjivanja, a opseg učinjene kirurške resekcije samo u sustavu MACIS i sustavu TNM primjenom kategorije “R”<sup>6</sup>. Kako bi se izbjegle razlike u shemama prognostičkih sustava, Međunarodno udruženje za karcinom (*Union International Contre Cancer*, UICC) i Američki udruženi odbor za karcinom (*American Joint Committee on Cancer*, AJCC)<sup>7</sup> prihvatili su sustav stupnjevanja TNM. Studijama na većim skupinama bolesnika uspoređena je razlikovna sposobnost postojećih sustava i niti jedan od navedenih nije pokazao jasnu prednost u odnosu na sustav TNM<sup>8</sup> koji je manje složen i lakši za primjenu. Stoga je sustav TNM široko prihvaćen, preporučen za izvješća, prognozu ishoda bolesti, usporedbu različitih načina liječenja između skupina sličnih slučajeva karcinoma i kao vodič liječenja za bolesnike s karcinomom štitnjače. Međutim, do danas i uz navedeno tek manji broj studija sadržava kliničke podatke temeljene na ovoj klasifikaciji<sup>9</sup>.

### Razlike između 5. i 6. izdanja TNM klasifikacije

U posljednjem 6. izdanju TNM klasifikacije UICC, objavljenom 2002. godine<sup>10</sup>, postavljeni su novi međunarodni standardi koji opisuju i kategoriziraju stadije karcinoma i njegovu progresiju. U klasificiranju diferenciranih karcinoma štitnjače 6. izdanje sustava TNM izmijenilo je naročito opis primarnog tumora (T) i širenje u regionalne limfne čvorove (N), te se razlikuje od 5. izdanja objavljenog 1997. godine<sup>10,11</sup>. Dok 5. izdanje u T1 klasificira primarne tumore veličine ≤1 cm, a u T2 tumore >1?4 cm, 6. izdanje kao T1 definira tumore promjera ≤2 cm, a kao T2 tumore >2=4 cm<sup>10</sup>. U 5. izdanju u T3 klasificira se tumor veličine >4 cm, bez ekstraprednog širenja, a u T4 klasificiraju se svi tumori s ekstraprednim širenjem. U 6. izdanju kao T3 definira se tumor promjera >4 cm ili svi tumori s minimalnim ekstraprednim širenjem. T4 podijeljen je na T4a (tumor sa širenjem izvan kapsule štitnjače i s invazijom subkutanog mekog tkiva, larinksa, traheje, ezofagusa ili nervusa rekurensa) i T4b (tumor koji invadira prijevvertebralnu fasciju, medijastinalne krvne žile ili obuhvaća arteriju karotis). Također je modificiran i sustav N. Dok 5. izdanje klasificira metastaze u unilateralne cervikalne limfne čvorove kao N1a, 6. izdanje definira N1a kao metastaze samo u VI. skupini limfnih čvorova (predtrachealni, paratrachealni i predlaringealni). U skupini stadija tumora modificirani su svi stadiji karcinoma štitnjače. U početku se “okultni” papilarni karcinom definirao kao tumor promjera do 1.5 cm, a kasnije, prema

is a separate clinical entity with a very low rate of morbidity and mortality<sup>4,12</sup>. Therefore, the new TNM system of the UICC for differentiated thyroid carcinoma simplifies and summarizes the categorization of tumors =2 cm in size, including microcarcinomas, which results in an increase in group T1 due to the larger tumor size (up to 2 cm instead of 1 cm in the earlier edition). Thus, the survival without relapse in the new T1 classified differentiated thyroid carcinoma is slightly lower in relation to the older T1 cases<sup>13</sup>. In recent studies, the effects of the 6<sup>th</sup> edition TNM classification usage for differentiated thyroid carcinoma are evaluated in retrospective and survival rates without relapse and they are compared to the earlier, 5<sup>th</sup> edition, so the extension of T1 group to papillary carcinoma of up to 2 cm in size is considered unjustified<sup>14</sup>. The clinical staging system of medullary carcinoma (AJCC) compares survival rate to the size of primary tumor, metastasis to lymph nodes and distant metastasis. The best prognosis is in patients whose carcinoma is detected with provocative screening before the palpable tumor appears<sup>3</sup>. There is no generally accepted staging system for anaplastic (non-differentiated) carcinoma. Therefore, independently of T (or N or M) category, every anaplastic carcinoma is classified as tumor stage IV.

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## PROGNOSTIC FACTORS OF PAPILLARY AND FOLLICULAR THYROID CARCINOMA

### PROGNOSTIČKA OBILJEŽJA PAPILARNOG I FOLIKULARNOG KARCINOMA ŠTITNJAČE

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#### Papillary carcinoma

Papillary carcinoma is the most common type of thyroid malignancy, with a fourfold female predominance. Middle aged people aged 40-50 are most frequently involved. Extrathyroid extension into the soft tissue of the neck is found in about one fourth of cases. Involvement of cervical lymph nodes is very common and may be the first manifestation of the disease. Although rare, hematogenous metastases may involve the lungs and bones, and only rarely the brain.

The overall outcome of patients with papillary carcinoma is good and not significantly different from that of the general population. The following factors are related to prognosis: Age – nearly all deaths occur when tumors manifest at an older age; Sex – females have better prognosis than males; Extrathyroid extension is proved to be a powerful predictor of poor prognosis; Microscopic variants – papillary, especially microcarcinoma, and follicular variants have better prognosis; Size – larger tumors have worse prognosis; Multicentricity – there are still many controversies, some authors state that this factor has no influence on prognosis. The same

#### Papilarni karcinom

Papilarni karcinom je najučestaliji karcinom štitnjače. U žena je četiri puta češći u odnosu na muškarce. Najčešće se javlja u srednjoj životnoj dobi, između 40. i 50. godine. Širenje izvan štitnjače u mekotkivne strukture na vratu nađe se u otprilike jedne četvrtine bolesnika. Zahvaćenost limfnih čvorova na vratu je česta pojava i može biti prvi znak bolesti. Iako rjeđe, moguće su i hematogene metastaze u plućima i kostima, dok su metastaze u mozgu rijetkost.

Preživljenje bolesnika s papilarnim karcinomom je dobro i ne odstupa bitno od sveopće populacije. Slijedeći su čimbenici povezani s prognozom bolesti:

Dob – smrtni ishod bolesti uglavnom se događa u starijoj životnoj dobi;

Spol – žene imaju bolju prognozu u odnosu na muškarce;

Širenje izvan štitnjače je izrazito loš prognostički pokazatelj;

Mikroskopske varijante – papilarni, naročito mikrokarcinom, i folikularni podtip imaju bolju prognozu;

Veličina – veći tumori imaju lošiju prognozu;



problem is present when the role of cervical node metastases is evaluated; Distant metastases – worsen the prognosis; Immunohistochemical characteristics associated with a more aggressive clinical course – up-regulation of cyclin D1, down-regulation of p27, expression of p53, nm23, EMA Leu-M1. A problem of using grade is that the vast majority of institutions do not grade papillary carcinomas; it is of little value, since most of them have been well differentiated. Total surgical resection of the thyroid – it is of special importance when extrathyroid expansion is present. There is a new TNM system endorsed by International Union against Cancer and American Joint Commission on Cancer, with a recent change in the definition of T1.

The principal clinical features that correlate with the prognosis depend on risk group definition, and that was the reason for many schemes proposed by different organizations and institutions, such as EORTC, AMES, AGES and MACIS. All of these are in use, however, in combination with immunohistochemistry data.

### Follicular carcinoma

Follicular carcinoma is less frequent and accounts for 10%-15% of thyroid malignancies. It is more common in women and tends to occur in patients in the fifth decade of life. It rarely occurs in children. It is often larger than papillary carcinoma, “cold” on scintigraphy scan. Tumor is often solid with a fleshy cut surface. The pattern of growth resembles that of an adenoma. Distant metastases are reported in up to 20% of patients at presentation with lung and bone as common sites. Regional lymph node metastases are uncommon.

Depending on the degree of invasiveness, follicular carcinoma is divided into the minimally invasive and widely invasive forms. Minimally invasive – the diagnosis of malignancy depends entirely on the demonstration of blood vessels and/or capsular invasion. The blood vessel invasion is almost never evident on gross examination. The vessel should be of venous caliber, located within the capsule. Interruption of the capsule must be full thickness to be qualified as capsular invasion. Widely invasive – it is a high risk counterpart of the minimally invasive subtype. They show widespread infiltration of blood vessels and/or adjacent thyroid tissue. Many of these tumors are poorly differentiated carcinomas at the cytoarchitectural level. There are marked prognostic differences that show invasion of the capsule only and those that show vascular invasion, with or without capsular invasion. Among those with vascular invasion, there

Multicentricnost – još uvijek postoje brojne kontroverze. Pojedini autori drže kako ovaj čimbenik nema utjecaja na prognozu bolesti. Isti se problem javlja kada se procjenjuje utjecaj metastaza u limfne čvorove vrata;

Udaljene metastaze – pogoršavaju prognozu bolesti;

Imunohistokemijske značajke povezane s agresivnijim kliničkim ponašanjem – jača izražajnost ciklina D1, slabija izražajnost p27, izražajnost p53, nm23, EMA, Leu-M1. Problem upotrebe gradusa je u tome što većina institucija ne gradi ovaj karcinom, jer nije od posebnog značenja pošto su gotovo svi dobro diferencirani;

Totalna kirurška ablacija štitnjače – naročito je važna kada postoji širenje izvan štitnjače. U upotrebi je novi TNM sustav što su ga sastavili International Union Against Cancer i American Joint Commission on Cancer, sa zadnjom promjenom za T1 tumor.

Osnovna klinička obilježja koja koreliraju s prognozom ovise o definiranju rizičnih skupina, pa je to bio razlog što su mnoge organizacije i klinike predlagale svoje sheme kao što su EORTC, AMES, AGES, MACIS. Sve su one u uporabi, ali u kombinaciji s rezultatima imunohistokemijskih analiza.

### Folikularni karcinom

Folikularni karcinom se javlja rjeđe i čini 10%-15% karcinoma štitnjače. Češći je u žena i ima tendenciju pojavljivanja u petom desetljeću života. Rijetko se javlja u djece. Uglavnom je veći od papilarnog karcinoma, scintigrafski “hladan”. Tumor je solidan, mesnate površine. Načinom rasta podsjeća na adenom. Udaljene metastaze su prisutne kod otprilike 20% bolesnika već prilikom dijagnosticiranja bolesti, a uobičajena mjesta su pluća i kosti. Metastaze u regionalne limfne čvorove su rijetke. Ovisno o stupnju invazije, folikularni karcinom dijeli se na minimalno i opsežno invazivni. Minimalno invazivni – dijagnoza maligniteta ovisi isključivo o dokazivanju invazije u krvne žile i/ili invaziji čahure. Invazija u krvne žile obično nije makroskopski vidljiva. Žile trebaju biti venskog tipa te smještene u čahuri. Da bi se nešto okvalificiralo kao invazija čahure, ona mora biti u potpunosti probijena. Opsežno invazivni – to je visoko rizična varijanta, suprotna od minimalno invazivnog tipa. Pokazuje obilnu infiltraciju u krvne žile i/ili okolno tkivo štitnjače. Mnogi od ovih tumora su na stanično arhitektonskoj razini slabo diferencirani. Postoji izrazita razlika u prognozi onih koji pokazuju invaziju samo kapsule i onih koji imaju vaskularnu invaziju s invazijom čahure ili bez nje. Među onima s vaskularnom invazijom prognoza je različita i ovisi o broju krvnih žila koje su zahvaćene: s



is a prognostic difference depending on the number of vessels involved: with limited vascular invasion <4 vessels, and with extensive vascular invasion >4 vessels involved.

A genetic abnormality recently detected in the subset of follicular carcinomas is the translocation resulting in the PAX8-PPAR gamma1 fusion. It is suggested that this rearrangement tends to have vascular invasion and solid histology.

Risk group analysis indicated age greater than 45, local extension, tumor greater than 4 cm, oncocyctic tumor type and distant metastases to have a significant role in the prognosis.

ograničenom vaskularnom invazijom <4 krvne žile; s obilnom vaskularnom invazijom >4 krvne žile.

Nedavno su otkrivene genetske abnormalnosti povezane s folikularnim karcinomom i ta translokacija tipično formira PAX8-PPAR gamma1. Sugerira se da karcinomi s ovom preraspodjelom gena imaju vaskularnu invaziju i solidnu histološku sliku.

Analiza rizičnih skupina potvrdila je dob veću od 45 godina, širenje izvan štitnjače, tumor veći od 4 cm, onkocitni podtip i udaljene metastaze kao loše prognostičke čimbenike.

## NOVEL APPROACHES AND STRATEGIES IN THE DIAGNOSIS OF THYROID CANCER

### NOVI PRISTUPI U DIJAGNOSTICI RAKA ŠTITNJAČE

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Clinical palpable thyroid nodules are frequent in adult population, especially in countries affected by moderate or severe iodine deficiency. Neck ultrasound (US) is able to detect subclinical thyroid nodules increasing their frequency up to 50% in those older than 60. Most thyroid nodules are benign lesions. However, a wide variation is observed between clinical and surgical series: about 5% of clinical thyroid nodules are cancer, but in surgical series the incidence may vary between 8% and 20%.

In many European countries, where a state of moderate iodine deficiency is still present, non-selection of clinical thyroid nodules would expose an enormous number of people to surgical treatment annually. Considering that only a small proportion of the great number of such nodules would eventually prove to be a thyroid carcinoma, surgical complications would be compounded by an unacceptably high financial cost. Therefore, thyroid nodules must undergo strict selection based on a rational diagnostic protocol devoted to distinguishing between a benign and a malignant lesion.

Klinički palpabilni čvorovi štitnjače su česti u odrasloj populaciji, a osobito u zemljama s umjerenom ili teškom jednom deficijencijom. Ultrazvukom vrata je moguće otkriti supkliničke čvorove štitnjače, što povećava njihovu učestalost sve do 50% u osoba starijih od 60 godina.

Većina čvorova štitnjače su benigni. Ipak, širok stupanj varijacije je uočen između kliničkih istraživanja i operacijski odstranjenih čvorova: u kliničkim istraživanjima oko 5% čvorova štitnjače su karcinomi, dok je incidencija karcinoma štitnjače kod operacijski odstranjenih čvorova između 8% i 20%.

U mnogim europskim zemljama gdje još uvijek postoji umjerena jodna deficijencija, nepostojanje odabira palpabilnih čvorova za operacijski zahvat dovelo bi do iznimno velikog broja operacija štitnjače svake godine. Uzevši u obzir mali udio karcinoma koji bi se otkrili u tako velikom broju čvorova, komplikacije kirurškog liječenja bi uzrokovale neprihvatljivo visok financijski izdatak. Zbog toga je potreban strog odabir čvorova štitnjače, utemeljen na racionalnim dijagnostičkim smjericama koje omogućuju razlikovanje benignih i malignih lezija.



First of all, in the assessment of thyroid nodules clinical evaluation is very important; as reported by recent consensus, a firm or hard consistency is associated with an increased risk of malignancy. However, this clinical parameter is highly subjective and dependent on the skill of the examiner. After the introduction of US in the clinical management of thyroid illness, several studies have been performed to establish the ability of US to differentiate benign from malignant lesions. Among several US patterns, hypoechogenicity of the nodule, spot microcalcifications and absence of a halo sign have been reported to be useful in predicting thyroid malignancy. However, the predictive value of US increases only at the expense of its sensitivity, and malignancy is predicted with high specificity by thyroid US only in less than 20% of patients. This percentage can be improved when multiple suspicious patterns are simultaneously present in a thyroid nodule.

Very recently US elastography, a newly developed dynamic technique, has been developed. US elastography provides an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. Interestingly, recent studies have shown that US elastography may predict malignancy with a high specificity and sensitivity (96% and 82%, respectively). On the basis of these new data, US elastography seems to have great potential as a new tool for the diagnosis of thyroid cancer, especially in nodules with indeterminate cytology, even though larger prospective studies are needed to confirm preliminary observations. On the other hand, conventional US maintains a pivotal importance to define which nodules are suitable for the US elastographic characterization, excluding nodules in which the presence of calcified shell is revealed.

Fine needle aspiration cytology (FNAC) is one of the most common and accurate methods in the primary diagnosis of benign and malignant thyroid pathology. However, this procedure may have some intrinsic limitations related to inadequate sampling and overlapping cytologic patterns between benign and malignant neoplasms. The differential diagnosis, among hyperplastic adenomatous nodule, follicular adenomas, especially in the follicular variant, and follicular carcinomas is sometimes difficult even for skillful cytologists, and may require histologic confirmation.

Thyroid cancers are known to overexpress a number of genes, such as EGF-receptor, c-erb-2, IGF-1 p53, dipeptidyl aminopeptidase IV, c-Met and CD44E. However, these genes are not adequate for diagnostic pur-

U obradi čvorova štitnjače vrlo važnu ulogu ima klinička procjena; kao što je prikazano u nedavno objavljenim smjernicama, solidna ili tvrda konzistencija je udružena s povećanim rizikom maligniteta. Međutim, ovaj klinički parameter je dosta subjektivan te ovisi o vještini ispitiivača. Nakon uvođenja ultrazvuka u dijagnostičku obradu bolesti štitnjače provedeno je nekoliko studija kako bi se utvrdila osjetljivost i specifičnost ultrazvuka u razlikovanju dobroćudnih od zloćudnih lezija. Među nekoliko ultrazvučnih obilježja, hipoechogenost čvora, točkasti mikrokalcifikati i izostanak znaka "halo" su se pokazali korisnim obilježjima u predviđanju maligniteta štitnjače. Ipak, prediktivna vrijednost ultrazvuka se povećava na račun osjetljivosti, a malignitet je moguće predvidjeti s visokom specifičnošću u manje od 20% bolesnika. Ovaj postotak se može poboljšati kada su višestruka sumnjiva ultrazvučna obilježja istodobno prisutna u čvoru štitnjače.

Nedavno je razvijena nova dinamična tehnika, ultrazvučna elastografija. Ultrazvučna elastografija omogućava procjenu krutosti tkiva mjerenjem stupnja čvrstoće pod primjenom vanjske sile. Novije studije su pokazale kako ultrazvučna elastografija može predvidjeti malignitet s visokom specifičnošću i osjetljivošću (96% i 82%). Na temelju ovih podataka čini se da ultrazvučna elastografija ima velik potencijal kao nova metoda dijagnostike raka štitnjače, poglavito kod čvorova s neodređenom citologijom, iako su šire prospektivne studije potrebne za potvrđivanje preliminarnih opažanja. S druge strane, konvencionalna ultrasonografija ostaje bitna za definiranje čvorova koji su prikladni za primjenu ultrazvučne elastografije isključujući čvorove koji imaju kalcificiranu cijelu površinu čvora.

Citološka punkcija je jedna od najčešćih i najtočnijih metoda u primarnoj dijagnostici dobroćudnih i zloćudnih promjena štitnjače. Međutim, ova metoda može imati neka ograničenja povezana s neprimjerenim uzorkovanjem i djelomičnim preklapanjem citoloških uzoraka između dobroćudnih i zloćudnih neoplazma. Diferencijalna dijagnoza između hiperplastičnog adenomatoznog čvora, folikularnih adenoma, osobito u folikularnoj varijanti, i folikularnih karcinoma katkada predstavlja problem i iskusnim citolozima, te postavljanje dijagnoze može zahtijevati histološku potvrdu.

Za rak štitnjače je poznato da pokazuje pojačanu ekspresiju određenih gena, kao receptora za EGF (engl. *epidermal growth factor*), c-erb-2, IGF-1, p53, dipeptidil aminopeptidaze IV, c-Met i CD44E. Ovi geni nisu pogodni za dijagnostičku primjenu, jer njihova ekspresija nije



poses because their expression is not restricted to cancer cells and not all tumors overexpress these markers. In recent studies, two genes, oncofetal fibronectin (onfFN) and Galectin-3 (Gale-3), have been proposed as possible targets for the preoperative diagnosis of thyroid carcinomas. Recently it has been shown that in a large series of thyroid neoplasms, the expression of onfFN mRNA evaluated by reverse transcription-polymerase chain reaction (RT-PCR) was significantly increased in papillary and anaplastic carcinomas, compared to normal thyroid tissue and follicular adenomas. Gale-3 is localized predominantly in the cytoplasm, but is also detected in the nucleus, on the cell surface and in the extracellular environment. Increased expression of Gale-3 is associated with *in vitro* malignant progression. As for onfFN, Gale-3 is highly expressed in papillary and follicular carcinomas, and at a variable level in medullary carcinomas. Unfortunately, both Gale-3 and onfFN are unable to clear cut between follicular adenomas and carcinomas, which represents the most important challenge for the FNAC. Because Gale-3 and onfFN expression may be easily evaluated by immunohistochemistry, a potential role of these markers for the differential diagnosis between benign and malignant follicular thyroid tumors is still under debate.

Recent studies have shown that activating point mutations in BRAF oncogene are present in approximately 45% of PTCs. BRAF belongs to the RAF family of serine/threonine kinases, which includes two other isoforms, ARAF and CRAF (RAF-1). BRAF is located downstream of RAS and upstream of MAPK kinase in the classic MAPK cascade. The high prevalence combined with the PTC specificity renders BRAF an attractive molecular marker for PTC diagnosis. Furthermore, the specificity (one selective codon) and the nature of the mutation (a single nucleotide change) render PTC-associated BRAF mutations easily detectable from a technical point of view. Larger and prospective studies will be necessary to calculate the diagnostic utility of FNA molecular analysis. Of course, the absence of BRAF mutations will not exclude a malignant condition. Nonetheless, a positive finding, especially in follicular neoplasms, can support decision making on the extent of surgery, indicating the need for performing total thyroidectomy rather than lobectomy.

ograničena na stanice raka, a svi tumori također ne pokazuju pojačanu ekspresiju ovih biljega. U novijim studijama su dva gena, onkofetalni fibronektin (onfFN) i Galektin-3 (Gale-3), predloženi kao mogući biljezi za prijeoperacijsku dijagnostiku karcinoma štitnjače.

Nedavno je pokazano na velikim skupinama neoplazma štitnjače da je ekspresija mRNA za onfFN određena metodom lančane reakcije polimerazom nakon reverzne transkripcije (RT-PCR) značajno povišena kod papilarnih i anaplastičnih karcinoma štitnjače u usporedbi s normalnim tkivom štitnjače i folikularnim adenomima. Galektin-3 je pretežito lokaliziran u citoplazmi, ali se također može naći i u jezgri, na površini stanice i u izvanstaničnom prostoru. Pojačana ekspresija Gale-3 je povezana s malignom progresijom *in vitro*. Kao i onfFN, Gale-3 je jako ekspimiran u papilarnim i folikularnim karcinomima, dok je u medularnih karcinoma zabilježena različita razina ekspresije ovih gena. Nažalost, Gale-3 i onfFN nisu u mogućnosti jasno razlučiti folikularne adenome od karcinoma, što predstavlja najveći izazov za citološku punkciju. Budući da se ekspresija Gale-3 i onfFN može jednostavno odrediti imunokemijskim metodama, potencijalna uloga ovih biljega u diferencijalnoj dijagnozi dobroćudnih i zloćudnih folikularnih tumora štitnjače je još uvijek tema rasprave.

Nedavno objavljene studije su pokazale da su aktivirajuće točkaste mutacije u BRAF onkogenu prisutne u otprilike 45% papilarnih karcinoma štitnjače. BRAF pripada RAF obitelji serin/treoninskih kinaza, kojoj također pripadaju druge dvije izoforme, ARAF i CRAF (RAF-1). BRAF je smješten nizvodno od RAS i uzvodno od MAPK kinaze u klasičnoj MAPK kaskadi. Visoka učestalost u kombinaciji sa specifičnošću za papilarni karcinom štitnjače čini BRAF privlačnim molekularnim biljgom za dijagnozu papilarnog karcinoma štitnjače. Nadalje, mutacije u BRAF genu povezane s papilarnim karcinomom štitnjače se tehnički mogu jednostavno otkriti zbog njihove specifičnosti (jedan selektivni kodon) i naravi mutacije (promjena u jednom nukleotidu). Velike i prospektivne studije će biti nužne za procjenu dijagnostičke korisnosti molekularne dijagnostike u citološkim uzorcima. Naravno, odsutnost BRAF mutacije neće isključiti malignost. Svedeno, pozitivni nalaz, posebno u folikularnim neoplazmama, može pomoći u donošenju odluke o opsegu operacijskog zahvata, ukazujući na potrebu totalne tireoidektomije radije nego lobektomije.

## ULTRASONOGRAPHY IN THYROID CANCER ULTRAZVUČNA DIJAGNOSTIKA RAKA ŠTITNJAČE

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Thyroid nodules are frequently detected. The prevalence in our adult population is about 50%. However, only a small number of nodules can be detected by palpation. When ultrasonography of the thyroid gland is performed, numerous nodules are discovered. Impalpable thyroid nodules are also incidentally detected during ultrasonography evaluation of other neck structures like carotid arteries, parathyroid glands, lymph nodes, etc. These nodules are called incidentalomas. The majority of thyroid nodules are benign, but in 5% additional studies reveal carcinoma. The main diagnostic challenge is to reliably distinguish malignant from benign nodules.

High resolution ultrasonography with transducers of 7 to 13 MHz is the method of choice for evaluating thyroid morphology. This sensitive method can detect cystic lesions as small as 2 mm, and solid nodules of 3 mm. It is not possible to differentiate malignant from benign nodules by ultrasonography. However, there are certain ultrasonographic features suggestive of either benign or malignant nature of the lesion.

*Malignancy is suggested by:*

- Hypoechoogenicity. About 90% of carcinomas are hypoechoogenic. However, most benign nodules appear also hypoechoogenic relative to normal thyroid tissue. Since there are many more benign than malignant nodules, the majority of nodules with hypoechoogenicity are also benign.
- The presence of irregular margin.
- Nodule shape that is taller than wider.
- Microcalcifications - punctate, hyperechoogenic foci which represent calcium deposits. The presence of microcalcifications has low sensitivity but high specificity in detection of malignant nodules.
- High intranodular flow on color and power Doppler.
- Increase in size over time.
- Invasion into surrounding structures, which is characteristic of fast growing nodules.
- Metastases in neck lymph nodes.

Nodularna struma je čest nalaz u našoj populaciji, smatra se da oko 50% odraslih ljudi ima čvorove. Palpacijom se otkrije samo manji broj čvorova, dok se ultrazvučnom pretragom štitnjače registriraju i brojni nepalpabilni čvorovi. Ultrazvučnom dijagnostikom drugih struktura vrata, npr. karotidnih arterija, parotidnih žlijezda, limfnih čvorova kao usputni nalaz registriraju se nepalpabilni čvorovi u štitnjači zvani incidentalomi. Većina čvorova u štitnjači je dobroćudna, dok se u oko 5% daljnjim dijagnostičkim postupcima nađe rak štitnjače. Kod ovako velike učestalosti čvorova u općoj populaciji učinkovito razlikovanje zloćudnih od dobroćudnih čvorova predstavlja svakodnevni klinički problem.

Ultrazvučna pretraga sondama visoke frekvencije od 7-13 MHz je metoda izbora za ispitivanje morfologije štitnjače. Ova osjetljiva metoda omogućuje otkrivanje cističnih tvorba u štitnjači promjera već od 2 mm i solidnih čvorova veličine od 3 mm. Ultrazvukom nije moguće pouzdano otkrivanje zloćudnih čvorova. Postoje, međutim, određene značajke koje mogu upućivati na dobroćudne ili zloćudne promjene.

*Na maligne promjene upućuju:*

- Hipoehogeni izgled čvora. Smatra se da su oko 90% neoplazma hipoehogene. Mnogi dobroćudni čvorovi su, međutim, također hipoehogeni. Kako ima znatno više dobroćudnih od zloćudnih čvorova, većina hipoehogenih čvorova je dobroćudna.
- Neravni rub čvora.
- Oblik čvora (viši nego širi, znači anteroposteriorni promjer veći od tranzverzalnog).
- Mikrokalcifikati. To su sitni punktififormni hiperehogeni odjeci koji predstavljaju depozite kalcija. Utvrđeno je da nalaz mikrokalcifikata ima malu osjetljivost, ali vrlo visoku specifičnost u otkrivanju zloćudnih čvorova.
- Pojačana unutarnja prokrvljenost čvora.
- Rast čvora tijekom ultrazvučnih kontrola.
- Invazija okolnih anatomskih struktura, koja se viđa vrlo rijetko, a znakovita je za zloćudne čvorove koji vrlo brzo rastu.
- Metastatski promijenjeni limfni čvorovi vrata.



When several of these features are present, there is a greater chance that the nodule is malignant. It should be noted, however, that multinodularity does not exclude thyroid carcinoma. The probability of finding thyroid carcinoma is the same in a thyroid with a solitary nodule or multiple nodules. The size of the nodule is not indicative of malignancy. Malignant nodules range from a few mm to several cm in size. When nodules are found, ultrasonography-guided fine needle aspiration cytology (FNAC) should be performed. If the nodule is less than 1 cm and there is no clinical suspicion of thyroid cancer, FNAC is not recommended unless several ultrasonographic characteristics suggestive of malignancy are present. The reason for this is that nodular goiters are very common, up to 50% of adults have one or more nodules, whereas the number of thyroid carcinoma is about 6 to 8 per 100 000 individuals in countries with high incidence. Nevertheless, at autopsy thyroid cancer is detected in 4% to 36% of individuals, which means that most of thyroid carcinomas are indolent throughout one's lifetime.

#### Ultrasonographic characteristics of malignant tumors

##### *Epithelial tumors*

##### Differentiated tumors

– Papillary carcinoma occurs most frequently, and it accounts for about 80% of all thyroid malignancies. On ultrasonography, it is characterized by hypoechogenicity, irregular margin and microcalcifications. Increased nodular flow is visualized by color and power Doppler. However, not all these features are always present. Sometimes, hypoechogenicity is the only characteristic of thyroid carcinoma. When papillary carcinoma is diagnosed, it is necessary to evaluate neck lymph nodes, since this tumor spreads through the lymphatics. Microcalcifications in metastatic lymph nodes are often present. Also, these regional metastases can undergo cystic degeneration, which means that they become partially or completely anechogenic. Sometimes, regional metastases are isoechogetic, with an appearance similar to the thyroid gland.

– *Follicular carcinoma is diagnosed in about 10% of patients. Most frequently, it is a solitary nodule in the thyroid. Usually it is a hypoechogenic nodule, but sometimes it is isoechogetic, similar to the surrounding thyroid tissue. Ultrasonography cannot reliably differentiate follicular adenoma from carcinoma. Most often, FNAC will not rule out carcinoma either, so these*

Vjerojatnost da će čvor u štitnjači biti malignan je veća kada je prisutno više navedenih značajka. Prisutnost više čvorova ne isključuje mogućnost postojanja raka štitnjače, vjerojatnost je ista kod multiplih i solitarnih čvorova. Veličina čvora također ne utječe na mogućnost postojanja tumora, vjerojatnost malignosti jednaka je kod čvorova od nekoliko mm kao i kod čvorova od nekoliko cm. U slučaju nalaza čvorova potrebno je učiniti ciljanu punkciju pod kontrolom ultrazvuka i citološku analizu punktata. Mišljenja smo, međutim, kako ne treba punktirati čvorove manje od 1 cm osim ako ne postoji izrazita sumnja na maligne promjene, što znači da je istodobno prisutno više znakova koji ukazuju na malignost. Smatra se, naime, da oko 50% ljudi ima čvorove u štitnjači, a učestalost raka štitnjače u zemljama s visokom incidencijom je 6 do 8 na 100.000 ljudi. Na autopsiji se, međutim, rak štitnjače nalazi u 4%-36% obduciranih, što znači da su velika većina okultni tumori koji se će ostati indolentni tijekom života.

#### Ultrazvučne značajke raka štitnjače

##### *Epitelijalni tumori*

##### Diferencirani

– Papilarni karcinom je najčešći, nalazi se u oko 80% bolesnika. Ultrazvučno se prikazuje kao hipoehogeni čvor neravnih rubova unutar kojeg se nalaze karakteristični sitni hiperehogeni odjeci koji odgovaraju punktfornim kalcifikatima, a na obojenom i *power* dopleru nalazi se pojačana intranodularna prokrvljenost. Međutim, ne nalaze se uvijek sve ove značajke pa se papilarni karcinom ponekad prikazuje samo kao hipoehogeni čvor. S obzirom na to da su limfni putovi glavni način širenja ovog tumora, potrebno je uvijek pregledati limfne čvorove vrata. Sitni kalcifikati često se nalaze i u metastatski promijenjenim limfnim čvorovima. Također, metastatski promijenjeni limfni čvorovi mogu cistično degenerirati, znači ultrazvučno su u cijelosti ili djelomice anehogeni, što je znakovito gotovo isključivo za metastaze papilarnog karcinoma. Ponekad se lokalne metastaze mogu prikazati i izoehogeno, slično tkivu štitnjače.

– Folikularni karcinom (u oko 10% bolesnika) najčešće se javlja kao solitarni tumor u štitnjači. Većinom je hipoehogeni, ali može biti i izoehogeni u odnosu na okolni parenhim. Nema sigurnih ultrazvučnih značajka koje omogućuju razlikovanje folikularnog adenoma od karcinoma. Ciljanom citopunkcijom također nije moguće razlikovanje ovih promjena, pa je potrebno takve bolesnike uputiti na operacijski zahvat. Kako je najčešći način



*patients should undergo surgery. Since this tumor spreads via blood vessels, regional metastases in lymph nodes are rarely found.*

### Undifferentiated tumor

- Anaplastic carcinoma develops after dedifferentiation of papillary or follicular tumors. Lately, it is detected very rarely. Usually, a nodule with hypoechogenicity and irregular margins is found on ultrasonography, which is not possible to differentiate from the surrounding structures. This tumor is one of the most aggressive human carcinomas. It usually spreads to the muscle, trachea and blood vessels. It shows decreased blood flow on color and power Doppler.

### C cell derived tumors

- Medullary carcinoma is ultrasonographically similar to papillary carcinoma. Lymph node metastases are often found. After total thyroidectomy, microcalcifications are detected in the majority of regional metastatic lymph nodes.

### Nonepithelial tumors and metastases from other primaries

Other nonepithelial tumors (lymphoma, sarcoma, hemangioepithelioma) as well as metastases from other primary tumors are not often detected. Usually, ultrasonography detects a hypoechogenic nodule that cannot be differentiated from other thyroid nodules. FNAC is used for the diagnosis.

### Regional lymph node metastases

When thyroid cancer is detected, ultrasonography should be used preoperatively to evaluate regional lymphadenopathy as well as postoperatively during the follow up of patients. It is necessary to assess the number, shape, size and ultrasonographic appearance of nodes. Normal lymph nodes are small, with an appearance similar to fatty tissue. This is the reason why these nodes are not visible on ultrasonography. Suspect lymph nodes are hypoechogenic without hilum or with asymmetric hilum. These nodes have a more round shape, with a ratio of anteroposterior to transverse diameter greater than 0.5. Sometimes metastatic lymph nodes from papillary carcinoma are isoechogenic, similar to thyroid tissue. Lymph nodes can form conglomerates. They can contain microcalcifications or undergo cystic degeneration. Increased intranodular blood flow can be found using color and power Doppler. Malignant regional lymph

širenja ovog tumora putem krvnih žila, ultrazvučnim pregledom vrata rijetko se registriiraju metastatski promijenjeni limfni čvorovi.

### Nediferencirani tumori

- Anaplastični karcinom štitnjače za koji se smatra da najčešće nastaje dediferencijacijom papilarnog i folikularnog tumora nalazi se posljednjih godina iznimno rijetko. Ultrazvučno se obično prikazuje kao hipoehogeni čvor neravnih rubova, neoštro ograničen od okolnog tkiva. Najčešće se ne širi u limfne čvorove vrata, već zahvaća okolne mišiće, traheju i krvne žile. Na obojenom i *power* dopleru vrlo je oskudno prokrvljen.

### Tumor podrijetlom od C stanica

- Medularni karcinom je ultrazvučno sličan izgledu papilarnog karcinoma. Metastaziranje u limfne čvorove vrata je često. Smatra se da se nakon odstranjenja štitnjače sitni punktiformni kalcifikati nalaze u većini metastatski promijenjenih limfnih čvorova vrata.

### Neepitelijalni tumori i metastaze drugih tumora

- *Neepitelijalni tumori* (limfomi, sarkomi i hemangioendoteliomi) štitnjače kao i metastaze drugih primarnih tumora u štitnjači nalaze se rijetko. Prikazuju se najčešće kao hipoehogeni čvorovi koji se ultrazvučno ne razlikuju od drugih čvorova štitnjače, dijagnoza se postavlja ciljanom citološkom punkcijom.

### Lokalne metastaze raka štitnjače

Da bi se utvrdila proširenost bolesti u bolesnika s dokazanim karcinomom štitnjače prije operacijskog zahvata kao i kasnije tijekom praćenja bolesnika, treba ultrazvučno pregledati cijelu prednju vratnu regiju, kao i supraklavikularne i infraklavikularne regije. Kod pregleda limfnih čvorova treba odrediti njihov broj, oblik, veličinu i ultrazvučni izgled. Normalni limfni čvorovi su mali, ultrazvučno sličnog izgleda kao okolno masno tkivo, pa se ne prikazuju. Limfni čvorovi za koje se sumnja da su metastatski promijenjeni su hipoehogeni, bez hilusa ili s asimetričnim hilusom. Oni su više okruglog oblika, tako da je odnos anteroposteriornog i tranzverzalnog promjera veći od 0,5. Ponekad se metastatski promijenjeni limfni čvorovi kod papilarnog karcinoma prikazuju izoehogeni, slični tkivu štitnjače. Limfni čvorovi mogu tvoriti konglomerate. Mogu sadržavati sitne kalcifikate ili cistično degenerirati. Kod upotrebe obojenog i *power* doplera mogu pokazivati pojačanu prokrvljenost. Ultra-



nodes as small as a few mm can be detected. When suspected lymph nodes are found, ultrasound guided FNAC should be performed. In addition, recent studies have shown that the diagnosis of regional metastases from differentiated thyroid carcinoma is enhanced by the determination of thyroglobulin in fine needle aspirates, particularly from cystic nodes.

zvučno se mogu registrirati metastaski promijenjeni limfni čvorovi veličine već nekoliko mm. Kod sumnje na sekundarizam u limfnim čvorovima potrebno je učiniti ciljanu citološku punkciju pod kontrolom ultrazvuka. Nedavno je u cilju pouzdanije dijagnostike uvedeno i određivanje tumorskog biljega tireoglobulina u punktatu suspektih lokalnih metastaza kod diferenciranih karcinoma, što je osobito korisno kod cistično promijenjenih limfnih čvorova, kada se ciljanom citološkom punkcijom često dobije negativan nalaz.

## RADIONUCLIDE IMAGING OF THYROID CANCER RADIONUKLIDNA DIJAGNOSTIKA RAKA ŠTITNJAČE

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Radionuclide imaging of the thyroid is certainly of great value in patients with nodular thyroid disease. Thyroid scintigraphy with  $^{99m}\text{Tc}$  pertechnetate ( $^{99m}\text{TcO}_4$ ) or iodine radionuclides ( $^{131}\text{I}$  or  $^{123}\text{I}$ ) allows for assessment of thyroid regional function. On the basis of the pattern of radionuclide uptake, nodules may be classified as hyperfunctioning (“hot”) or hypofunctioning (“cold”). Hot nodules almost never represent clinically significant malignant lesions, whereas cold nodules have been reported to carry a malignant risk of about 5% to 15%. Because the majority (77% to 94%) of thyroid lesions are cold and only a small minority of these are malignant, the predictive value of hypofunctioning nodules for the presence of malignant involvement is low. The diagnostic value of scintigraphy is further reduced in lesions smaller than 1 cm, which may not be identified by scintigraphy. It may be questioned whether there is a role for scintigraphy in the diagnosis of thyroid malignancy. Besides the previously mentioned low sensitivity and specificity of scintigraphy, thyroid ultrasound with greater resolution and fine needle aspiration cytology facilitates accurate diagnosis of malignant lesions. But information on the functional characterization of thyroid nodules is useful for planning subsequent diag-

Radionuklidna dijagnostika standardni je dio dijagnostičkog algoritma u bolesnika s nodozno promijenjenom štitnjačom. Scintigrafija štitnjače s tehnejom pertechnetatom ( $^{99m}\text{TcO}_4$ ) ili radioaktivnim jodom ( $^{131}\text{I}$  ili  $^{123}\text{I}$ ) omogućava ispitivanje regionalne funkcije štitnjače. Ovisno o nakupljanju radiofarmaka čvorovi se klasificiraju kao čvorovi s pojačanom funkcijom (“topli”) ili smanjenom funkcijom (“hladni”). Topli čvorovi gotovo nikada nisu zloćudne naravi, dok je rizik maligniteta u hladnim čvorovima 5%-15%. Kako je većina (77%-94%) čvorova hladno, a samo manji dio njih je zloćudan, hipofunktionalnost čvorova ima malu prediktivnu vrijednost za malignost. Dijagnostička vrijednost scintigrafije još je manja kod promjena manjih od 1 cm koje mogu biti nevidljive na scintigramu.

Postavlja se pitanje koja je uloga scintigrafije u dijagnostici raka štitnjače. Naime, osim spomenute niske specifičnosti i osjetljivosti scintigrafije s  $^{99m}\text{Tc}$  pertechnetatom i/ili radiojodom za karcinom štitnjače, ultrazvuk sa značajno boljom rezolucijom od scintigrafije, uz citološku analizu aspirata omogućava relativno jednostavnu i točnu dijagnozu zloćudne promjene. Ipak, poznavanje funkcionalnog statusa čvorova štitnjače je korisno u planiranju dijagnostičkih postupaka, otkrivajući



nostic management, avoiding fine needle biopsy in hyperfunctioning nodules.

Due to the low specificity of scintigraphy with  $^{99m}\text{TcO}_4$  and/or iodine radionuclides in the assessment of malignancy in thyroid nodules, different radiopharmaceuticals with the affinity of accumulation in malignant lesions like  $^{201}\text{Tl}$  chloride,  $^{99m}\text{Tc}$  sestamibi and  $^{99m}\text{Tc}$  tetrofosmin are used.  $^{201}\text{Tl}$  has been studied in differentiating diagnosis of benign and malignant cold thyroid nodules and has yielded equivocal results (sensitivity 57%-100% and specificity 26%-86%). It appears that a delayed imaging or quantitative analysis (retention index) is more valuable for malignant detection than an early image. Few studies suggest that  $^{201}\text{Tl}$  scan is a useful tool for detecting malignancy in cold thyroid nodules classified as non-diagnostic or suspected lesions by fine needle aspiration cytology. Similar results were obtained with the use of  $^{99m}\text{Tc}$  labeled cationic complexes (sestamibi and tetrofosmin). Sestamibi shows high uptake in cells with high mitochondrial activity like Hürthle cells, but cannot differentiate adenoma from carcinoma.

Over the last years, an increasing amount of papers have been published that stress the importance of  $^{18}\text{F}$ FDG positron emission tomography (PET) scanning in patients with thyroid carcinoma. Because most tumors have an increased metabolism and also an increased number of glucose transporter proteins, they can be imaged with  $^{18}\text{F}$ FDG that remains trapped in tumor cells. Visibly elevated accumulation of  $^{18}\text{F}$ FDG has been established in patients with Hürthle cell and anaplastic carcinomas, while in patients with differentiated thyroid carcinoma the accumulation is moderately elevated. The reported sensitivity and specificity of  $^{18}\text{F}$ FDG scintigraphy using different SUV thresholds for differentiation between benign and malignant nodules were 60%-100% and 63%-91%, respectively.  $^{18}\text{F}$ FDG PET has a relatively high negative predictive value for malignancies (83%), and can be able to differentiate follicular adenoma from carcinoma. Thus, in case of indeterminate cytology, FDG-PET seems to be the method of choice to decide on the way of treatment (thyroid surgery or further follow up) and to reduce the number of unnecessary surgery (39% in one reported study). A new development in the clinical decision making in patients with thyroid cancer is combined CT-PET camera imaging, high resolution imaging which combines functional with anatomical information.

Radionuclide imaging is more important in the follow up of patients who have been operated on for thy-

funkcionalne čvorove koje nije potrebno citološki procjenjivati.

Zbog male specifičnosti i osjetljivosti scintigrafije s  $^{99m}\text{Tc}$  pertehnetatom i/ili radiojodom u procjeni malignosti čvorova štitnjače upotrebljavaju se različiti radiofarmaci s afinitetom za nakupljanje u zloćudnim promjenama, kao  $^{201}\text{Tl}$ -klorid,  $^{99m}\text{Tc}$  sestamibi i  $^{99m}\text{Tc}$  tetrofosmin.  $^{201}\text{Tl}$  rabi se za razlikovanje dobroćudnih i zloćudnih čvorova štitnjače s dvojbjenim rezultatima (osjetljivost 57%-100%, specifičnost 26%-86%). Izgleda da su kasni scintigrami i kvantitativna analiza (retencijski indeks) vrijedniji za otkrivanje maligniteta od ranih snimaka. Nekoliko studija ukazuje na korist od primjene  $^{201}\text{Tl}$  za otkrivanje maligniteta u hladnim čvorovima štitnjače koji su citološki bili nedijagnostički ili sumnjivi na malignitet. Slični rezultati dobiveni su i uporabom  $^{99m}\text{Tc}$  obilježenih kationskih kompleksa (sestamibi i tetrofosmin). Sestamibi se pojačano nakuplja u stanicama s velikom mitohondrijskom aktivnošću kao što su Hürthleove stanice, ali ne može sa sigurnošću razlikovati adenom od karcinoma.

Posljednjih godina objavljeno je mnoštvo članaka koji naglašavaju važnost  $^{18}\text{F}$ FDG pozitronske emisijske scintigrafije u bolesnika s karcinomom štitnjače. Pojačan metabolizam u mnogim tumorima uz povećan broj transportnih proteina za glukozu omogućava snimanje pomoću  $^{18}\text{F}$ FDG koji ostaje vezan u tumorskim stanicama. Značajno povišena akumulacija  $^{18}\text{F}$ FDG utvrđena je u bolesnika s karcinomom Hürthleovih stanica i anaplastičnim karcinomom, dok je u bolesnika s diferenciranim karcinomom štitnjače nakupljanje umjereno. Semikvantitativna analiza primjenom standardiziranih vrijednosti preuzimanja (*standardized uptake values*, SUV) poboljšava razlikovanje dobroćudne i zloćudne promjene. U objavljenim radovima uz uporabu različitih pragova SUV za razlikovanje dobroćudnih i zloćudnih čvorova štitnjače osjetljivost i specifičnost iznosile su 60%-100%, odnosno 63%-91%.  $^{18}\text{F}$ FDG PET ima veliku negativnu prediktivnu vrijednost za malignitet (83%), što omogućava razlikovanje folikularnog adenoma od karcinoma. Stoga u bolesnika s nedefiniranim citološkim nalazom može biti metoda izbora kod donošenja odluke o daljnjem postupku (operacija ili dalje praćenje) smanjujući broj nepotrebnih operacija (39% u objavljenoj studiji). Novu dimenziju u kliničkom odlučivanju kod bolesnika s rakom štitnjače donosi CT-PET, pretraga visoke rezolucije koja kombinira funkcionalnu s anatomskom informacijom.

Radionuklidna dijagnostika je značajnija u praćenju bolesnika operiranih od raka štitnjače. U ovih bolesnika

roid cancer. In these patients, after surgery and ablative therapy with  $^{131}\text{I}$ , scintigraphy with different radiopharmaceuticals like radioiodine,  $^{201}\text{Tl}$ ,  $^{99\text{m}}\text{TcMIBI}$ ,  $^{99\text{m}}\text{Tc(V)}$  DMSA is an important part of diagnostic algorithm. Whole body scintigraphy with  $^{131}\text{I}$  or  $^{123}\text{I}$  is a standard procedure to detect well differentiated thyroid cancer metastases. Because of the relatively low sensitivity (45%-75%) of radioiodine whole body scintigraphy for recidivism and metastases, whole body scintigraphy with  $^{201}\text{Tl}$  and  $^{99\text{m}}\text{Tc}$  labeled cations (sestamibi and tetrofosmin) is useful, especially in patients with elevated tumor marker Thyroglobulin (Tg) and negative radioiodine scan.

As with other imaging techniques, the value of  $^{18}\text{F}$ FDG PET is greater in the follow up of thyroid cancer patients, particularly in patients with negative radioiodine scan and elevated Tg. In these patients the reported sensitivity and specificity was 85%-94% and 90%-95%, respectively. Tumor to background contrast and tumor detection is better after TSH stimulation, either by thyroid hormone withdrawal or stimulation with recombinant TSH.

Somatostatin receptor imaging (SRI) with  $^{99\text{m}}\text{Tc}$  and  $^{111}\text{In}$  radiolabeled somatostatin analogue can be used to demonstrate medullary and differentiated thyroid carcinoma. In patients with medullary thyroid carcinoma, the sensitivity of SRI to detect tumor localization is 50%-70%. Somatostatin receptors are present on a variety of neuroendocrine tumors, and these can be visualized. Although papillary, follicular and anaplastic thyroid cancers, and Hürthle cell carcinomas do not belong to the group of classic neuroendocrine tumors, the majority of patients with these cancers show uptake of radiolabeled somatostatin analogues although they do not accumulate radioiodine. In some patients with iodine negative metastases it could open new therapeutic options.

poslije operacije i ablacijske terapije pomoću  $^{131}\text{I}$  scintigrafija s različitim radiofarmacima kao što su radioaktivni jod,  $^{201}\text{Tl}$ ,  $^{99\text{m}}\text{Tc}$  sestamibi,  $^{99\text{m}}\text{Tc(V)}$  DMSA je važan dio dijagnostičkog algoritma. Scintigrafija cijelog tijela s  $^{131}\text{I}$  ili  $^{123}\text{I}$  je standardni postupak otkrivanja presadnica diferenciranog raka štitnjače. Zbog relativno niske osjetljivosti (45%-75%) radiojodne scintigrafije cijelog tijela korisne su scintigrafije cijelog tijela s  $^{201}\text{Tl}$  i  $^{99\text{m}}\text{Tc}$  obilježenim kationima (sestamibi i tetrofosmin), osobito u bolesnika s povišenom razinom tumorskog biljega tireoglobulina i negativnim radiojodnim scintigramom.

I vrijednost  $^{18}\text{F}$ FDG PET je veća u praćenju bolesnika s karcinomom štitnjače, poglavito u onih s negativnim radiojodnim scintigramom i povišenim tireoglobulinom. U ovih bolesnika osjetljivost metode je 85%-94%, a specifičnost 90%-95%. Otkrivanje tumora je bolje nakon stimulacije povišenim TSH, bilo prekidom hormonalne terapije ili stimulacijom rekombinantnim TSH.

Scintigrafija somatostatinskih receptora s obilježenim somatostatinskim analogima  $^{111}\text{In}$ -DTPA oktreatidom može se upotrebljavati za prikaz medularnog i diferenciranog karcinoma štitnjače. U bolesnika s medularnim karcinomom štitnjače osjetljivost somatostatinske scintigrafije iznosi 50%-70%. Somatostatinski receptori prisutni su u različitim neuroendokrinim tumorima, te se mogu scintigrafski prikazati. Iako papilarni, folikularni i anaplastični karcinomi štitnjače, kao i karcinomi Hürthleovih stanica ne pripadaju skupini klasičnih neuroendokrinih tumora, većina bolesnika s ovim tumorima nakuplja obilježeni somatostatinski analog, čak i ako ne nakupljaju radiojod. U nekih bolesnika to može otvoriti nove terapijske mogućnosti.

## CYTOLOGICAL DIAGNOSIS OF THYROID CANCER CITOLOŠKA DIJAGNOSTIKA RAKA ŠTITNJAČE

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Thyroid nodules have always commanded a great deal of attention because they are sometimes visible, are often palpated by the patient, and always raise the question of cancer. A series of diagnostic procedures including ultrasonography, scintigraphy and fine needle aspiration biopsy (FNAB) are employed in preoperative differential diagnosis between benign and malignant thyroid lesions. Because most of thyroid nodules (95%) are benign, their clinical evaluation should be as selective as possible in the recommendation for surgical removal. FNAB has become the most important modality in the evaluation of any thyroid nodule because it is quick, inexpensive, involves minimal risk of complications, and has high diagnostic accuracy. Given the high prevalence of thyroid nodules, thyroid FNAB could easily be the most common type of FNAB specimens in a cytology laboratory. Although this technique can easily identify most thyroid lesions, it is still difficult to discriminate between adenomatoid nodules, follicular adenomas, well-differentiated follicular carcinomas, and follicular variants of papillary carcinomas.

Thyroid FNAB gives indeterminate results for malignancy in 5%-29% of patients, and surgical excision, with its attendant high cost and potential morbidity, is usually required to fully evaluate such patients.

However, most controversial is the management of patients with follicular lesions of the thyroid. An inherent limitation of thyroid FNAB is its inability to separate follicular carcinomas from follicular adenomas. This separation depends on capsular or vascular invasions that are impossible to assess on cytology. Therefore, cytopathologist should rely on other features such as the amount of colloid and architectural arrangement of follicular cells to assess the cancer risk of follicular lesions. The evaluation of these features lacks reproducible criteria and tends to be subjective, arbitrary, and subject to the individual cytopathologist's experience. In addition, the interpretation of thyroid FNAB may also be affected by the aspirator's clinical impression when a

Čvorovi štitnjače oduvijek privlače posebnu pozornost, jer su ponekad vidljivi, često ih bolesnik sam napipa, a uvijek pobuđuju sumnju na tumor. Različite dijagnostičke metode uključujući ultrazvuk, scintigrafiju i citološku punkciju štitnjače rabe se u prijeoperacijskoj diferencijalnoj dijagnostici između dobroćudnih i zloćudnih promjena štitnjače. Kako je velika većina (95%) čvorova štitnjače dobroćudna, njihova klinička procjena treba biti što selektivnija u probiru bolesnika koji se upućuju na kirurški zahvat. Citološka punkcija štitnjače postala je najznačajniji oblik procjene čvorova štitnjače zbog svoje brzine, niskih troškova, malog rizika od komplikacija te visoke dijagnostičke pouzdanosti. S obzirom na velik broj ljudi s čvorovima štitnjače citološka punkcija štitnjače mogla bi lako postati najčešći vid aspiracijske citologije u citološkim laboratorijima. Iako se ovom metodom s lakoćom prepoznaje većina promjena štitnjače, još uvijek postoje poteškoće u razlikovanju između adenomatoidnih čvorova, folikularnih adenoma, dobro diferenciranih folikularnih karcinoma i folikularne varijante papilarnog karcinoma.

Citološka punkcija štitnjače daje neodređene nalaze u pogledu zloćudnosti u 5%-29% bolesnika, pa je za potpunu procjenu čvorova kod tih bolesnika potrebno kirurško odstranjenje uz povećanje zdravstvenih troškova i rizik kirurškog zahvata.

Međutim, najkontroverzniji je postupak kod bolesnika s folikularnim promjenama štitnjače. Naime, zbog naravi same metode citološka punkcija štitnjače ne može razlikovati folikularne karcinome od folikularnih adenoma. Oni se međusobno razlikuju po tumorskoj invaziji čahure ili krvnih žila, što se ne može citološki utvrditi. Stoga se citolog oslanja na druge značajke, kao što su količina koloida ili izgled nakupina folikularnih stanica, kako bi procijenio rizik da je neka folikularna promjena zloćudna. Procjeni ovih značajka nedostaju kriteriji dosljednosti, subjektivni su, podložni slobodnoj procjeni, te ovisе o iskustvu pojedinog citologa. Uz to, interpretacija citomorfološkog nalaza podložna je kliničkom



cytopathologist performs the aspiration. Consequently, reporting FNAB of follicular lesions has become somewhat arbitrary. Although papillary carcinomas have characteristic nuclear features, some of these features are not specific and may occur to a lesser degree in benign thyroid conditions. And again, although most cytopathologists would agree on when to render a diagnosis of papillary carcinoma, reporting of less definitive specimens may be subject to individual experience and clinical impression.

Accordingly, the diagnostic schemes found in the literature on thyroid FNA reporting seem random and confusing. It is obvious that many terms have been used to convey the same idea. At the same time, the same terms have different indications. Reporting scheme on the basis of the possibility of finding carcinoma on resection is proposed.

Consequently, on the basis of data reported in the literature and our own experience we implement the following diagnostic scheme:

The inadequate category is usually consisted of those specimens that contain virtually no or very few follicular cells. FNAB should be repeated.

The benign lesions category includes lesions that could be cytologically diagnosed as benign with confidence and accuracy. More common diagnoses in this category are nodular goiter, Hashimoto thyroiditis and adenomatoid nodule. Lesions in this group can be managed conservatively, and if the nodules continue to enlarge, then repeat FNAB or surgical excision is indicated.

The indeterminate lesions category comprises a large spectrum of lesions with cytological features more or less suggestive of but not diagnostic for malignancy. More common diagnoses in this category are cellular follicular lesion, follicular neoplasm, Hürthle cell neoplasm and suspect papillary carcinoma. Two less worrisome lesions, cellular follicular lesion and suspect follicular neoplasm, with a low (less than 5%) probability of malignancy, should be managed conservatively with follow up monitoring. Follicular and Hürthle cell neoplasms with a higher malignancy risk (10%-30%) as well as suspect papillary carcinomas with the highest probability of malignancy (55%-84%) should be treated surgically.

The malignant neoplasms category includes all specimens in which an unequivocal diagnosis of malignancy can be made. The overwhelming majority in this category are papillary carcinomas (75%-90%), followed by medullary carcinomas (5%-10%) and anaplastic carcinomas (1%-3%). Rarely, cytological diagnoses of low dif-

dojmu ako osoba koja analizira razmaz izvodi i punkciju. Zbog svega toga je izvještaj o citološkoj punkciji folikularnih promjena štitnjače ponešto proizvoljan. Čak i kod papilarnog karcinoma koji ima znakovite promjene na jezgrama te promjene nisu specifične i mogu se javiti u manjem stupnju kod dobroćudnih promjena štitnjače. I ponovno, iako se većina citologa slaže u postavljanju dijagnoze papilarnog karcinoma, izvještavanje o razmazima s nedostatkom svih morfoloških značajka uvjetovano je pojedinačnim iskustvom i kliničkim dojmom.

Posljedica toga su različiti obrasci citoloških izvještaja koji djeluju nedosljedno i zbunjujuće. Upotrebljavaju se različiti nazivi za istu promjenu. Isto tako, isti nazivi upućuju na različit daljnji postupak. Obrasci izvještavanja trebaju biti zasnovani na vjerojatnosti nalaska karcinoma nakon kirurškog odstranjenja.

Slijedeći ta načela, a na osnovi podataka u literaturi i osobnog iskustva, primjenjujemo slijedeću dijagnostičku podjelu:

U kategoriju neadekvatnih ulaze materijali koji ne sadrže ili sadrže vrlo malo folikularnih stanica. U ovom slučaju treba ponoviti citološku punkciju.

Kategorija dobroćudnih promjena obuhvaća promjene koje se sa sigurnošću mogu citološki okarakterizirati kao dobroćudne. Češće dijagnoze u ovoj kategoriji su nodularna struma, Hashimotov tireoiditis i adenomatoidni čvor. Promjene u ovoj skupini liječe se konzervativno, a tek u slučaju povećanja čvora indicirano je ponavljanje punkcije ili kirurško odstranjenje čvora.

Kategorija neodređenih promjena u pogledu zloćudnosti obuhvaća širok spektar promjena s citološkim značajkama koje više ili manje upućuju na to da bi se moglo raditi o zloćudnom tumoru. Češće citološke dijagnoze u ovoj kategoriji su celularna folikularna promjena, folikularni tumor, tumor Hürthleovih stanica i suspektni papilarni karcinom. Dvije promjene s malom vjerojatnošću (manje od 5%) za zloćudni tumor, celularna folikularna promjena i suspektni folikularni tumor, mogu se liječiti konzervativno uz pažljivo praćenje. Folikularni tumor i tumor Hürthleovih stanica koji imaju veću vjerojatnost (10%-30%) za zloćudni tumor trebali bi se kirurški odstraniti kao i suspektni papilarni karcinomi koji imaju najveću vjerojatnost (55%-84%) za zloćudni tumor.

Kategorija zloćudnih tumora uključuje sve materijale u kojima se može postaviti nedvosmislena citološka dijagnoza zloćudnog tumora. Velika većina tumora u ovoj kategoriji su papilarni karcinomi (75%-90%), zatim slijede medularni karcinomi (5%-10%) i anaplastični kar-



ferentiated follicular carcinoma, primary thyroid lymphoma or thyroid metastasis are made.

The others category includes lesions when the specimen shows material without any suspect cellular features but the lack or paucity of follicular cells makes it insufficient to comfortably make a diagnosis of a benign lesion. The most common lesions from this category are pseudocystic lesions and colloid cysts. Cytological diagnosis of these lesions indicates close follow up or repeat FNAB.

Ultrasound-guided FNAB is strongly recommended not only to obtain better and sufficient material but also to ensure that the material is obtained from the correct site.

Ancillary methods in thyroid FNAB are somewhat controversial. Immunocytochemistry and molecular methods, mainly because of their high sensitivity (but relatively low specificity) can improve the accuracy of thyroid FNAB when dealing with cytologically indeterminate lesions.

For the most part, the state-of-the-art of thyroid malignancy diagnosis relies on clinical risk assessment, ultrasound and cytological data. The final pathological outcome is therefore dependent on the intrinsic quality of each of these methods.

cinomi (1%-3%). Znatno rjeđe postavljaju se citološke dijagnoze slabo diferenciranog folikularnog karcinoma, primarnog limfoma štitnjače ili metastatskog tumora.

U kategoriji ostalih uključene su promjene kod kojih se u materijalu ne nalaze promjene sumnjive na zloćudnost, ali odsutnost ili slaba prisutnost folikularnih stanica ne omogućuje sigurno razvrstavanje promjene u skupinu dobroćudnih promjena. Najčešće citološke dijagnoze u ovoj skupini su pseudocistična promjena i koloidna cista. Ovakve citološke dijagnoze upućuju na pažljivo praćenje ili ponavljanje citološke punkcije.

Preporučuje se citološka punkcija pod kontrolom ultrazvuka, ne samo zato da bi se dobio kvalitetniji materijal za citološku analizu, nego i zbog toga da bi se osiguralo uzimanje materijala s ispravnog mjesta.

Uporaba dodatnih metoda u citologiji štitnjače malo je proturječna. Ipak, primjena imunocitokemijskih metoda i molekularnih metoda, prvenstveno zbog njihove visoke osjetljivosti (usprkos njihove relativno niske specifičnosti), može poboljšati pouzdanost citološke punkcije štitnjače u slučajevima kad se radi o citološki neodređenim nalazima u pogledu zloćudnosti.

Većim dijelom, umijeće dijagnostike raka štitnjača zasniva se na kombinaciji procjene kliničke slike, nalaza ultrazvuka i nalaza citologije. Stoga će konačni patohistološki nalaz biti odraz pojedinačne kvalitete svake od ovih metoda.

## CYTOMORPHOLOGICAL CHARACTERISTICS OF PAPILLARY THYROID CARCINOMA AND THEIR PROGNOSTIC VALUE

### CITOMORFOLOŠKE KARAKTERISTIKE PAPILARNOG KARCINOMA ŠTITNJAČE I NJIHOV PROGNOSTIČKI ZNAČAJ

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Thyroid cancer accounts for 1.5% of the total number of cancer cases and 0.4% of the total number of cancer-related deaths *per* year. Palpable thyroid nodule can be found in 4% to 7% of adult individuals, whereas ultrasonographic (US) examination of the thyroid reveals

Karcinomi štitnjače čine 1,5% u ukupnom broju karcinoma, a kao uzrok smrti od karcinoma pojavljuju se u svega 0,4% na godinu. U odrasloj populaciji palpabilni čvor u štitnjači nalazi se u 4%-7%, dok se ultrazvučnim (UZV) pregledom štitnjače čvor može otkriti u 70%





nodules in 70% of adult individuals. Introducing of various examination techniques of the neck region (computed tomography of the neck, US of carotid arteries, etc.) often reveals thyroid nodules of less than 1 cm in diameter and asymptomatic, which are then called incidentalomas. Most of them are benign, and so are 90% to 95% of all thyroid nodules.

Using US guided fine needle aspiration biopsy (FNAB) to evaluate thyroid nodules reduces the number of patients requiring thyroid surgery by 50%, increases the yield of thyroid malignancies at thyroidectomy two to three times, and decreases the cost of thyroid nodule management by more than 25%.

Thyroid tumors account for 5% to 10% of the nodules analyzed. Papillary carcinoma is most common, accounting for 60% to 80% of all thyroid malignancies. In regions with adequate dietary iodine intake, there are less follicular carcinomas and consequentially a greater proportion of papillary carcinomas of the thyroid gland.

At Department of Nuclear Medicine and Radiation Protection, Zagreb University Hospital Center, 5000 FNAB procedures of thyroid and neck nodules are performed in 2000 patients *per* year. Approximately 130 carcinomas are found, with papillary carcinoma accounting for approximately 80%.

Like other thyroid diseases, papillary carcinoma is more often found in women. The incidence of thyroid cancer peaks at age 30-50. It is often found to be multifocal and it metastasizes to lymph nodes of the neck.

Papillary carcinoma of the thyroid has very distinctive cytologic characteristics, provided that the material for cytologic analysis is adequate. General classification of cytologic smears includes the following categories: inadequate, insufficient, benign, suspect and malignant. Inadequate smears do not contain cellular elements of the thyroid or the material is destroyed in the process of smear preparation. Their portion in the overall smears analyzed is 5% to 20%. A portion of more than 20% of inadequate smears calls for quality control of the laboratory that performs FNAB and smear preparation. Insufficient smears contain cellular elements of the thyroid but their number is too small for appropriate analysis (less than 5 groups of follicular cells containing 10 cells each).

Very cellular specimens are characteristic of papillary carcinoma of the thyroid. Predominantly cystic papillary carcinoma accounts for 10% of all cases and only few are predominantly colloid. Cytologic characteristics of the classic papillary carcinoma are: monolayered

odrasle populacije. Uvođenjem različitih dijagnostičkih metoda vratne regije (CT vrata, UZV krvnih žila vrata i sl.) često se kao usputni nalaz opisuje čvor u štitnjači, manji od 1 cm, asimptomatski, za koji se uvriježilo naziv incidentalom. U većini slučajeva radi se o benignim promjenama. Jednako tako 90%-95% čvorova u štitnjači otkrivenih ciljanom dijagnostikom štitnjače su benigne naravi.

Primjena ultrazvukom vođene punkcije čvorova štitnjače smanjuje broj bolesnika kod kojih je potrebna kirurška intervencija za 50%, nalaz maligne promjene kod učinjene tireoidektomije povećava dva do tri puta, a troškove obrade i liječenja čvorova u štitnjači smanjuje za 25%.

Tumori štitnjače čine 5%-10% punktiranih čvorova u štitnjači. Papilarni karcinom čini 60%-80% karcinoma štitnjače. U područjima s dostatnim unosom joda u prehrani smanjuje se broj folikularnih karcinoma, a posljedično se povećava udio (postotak) papilarnih karcinoma.

U Zavodu za nuklearnu medicinu i zaštitu od zračenja, KBC Zagreb, na godinu se učini oko 5000 punkcija čvorova štitnjače i čvorova na vratu kod oko 2000 bolesnika. Prosječno se nađe oko 130 karcinoma, od kojih oko 80% čine papilarni karcinomi.

Kao i ostale bolesti štitnjače, papilarni je karcinom češći u žena i zahvaća sve dobne skupine s najvećom učestalošću u dobi između trideset i pedeset godina. Često se javlja multifokalno, a metastazira u limfne čvorove vrata.

Papilarni karcinom štitnjače ima lako prepoznatljive citološke značajke, uz uvjet da je materijal dobiven za citološku analizu adekvatan. U općoj podjeli razmaza dijelimo na: neadekvatne, nedostatne, benigne, suspektne i maligne. Neadekvatni razmazi ne sadrže stanične elemente štitnjače ili je kod razmazivanja materijal uništen. Njihov postotak se kreće od 5% do 20%. Postotak neadekvatnih razmaza veći od 20% zahtijeva kontrolu kvalitete laboratorija u kojem se pretraga izvodi. Nedostatni razmazi sadrže stanične elemente štitnjače, ali u premalom broju za adekvatnu analizu (manje od pet nakupina od po deset tireocita).

Jaka celularnost razmaza je značajka papilarnog karcinoma štitnjače. Pretežito cistični papilarni karcinom nalazi se u 10% slučajeva, a samo je mali broj onih koji spadaju u skupinu pretežito koloidnih. Citološke značajke klasičnog papilarnog karcinoma su: jednoslojni tračci, palisade i papili slične formacije s nepravilnom orijentacijom, grupiranjem i prekrivanjem jezgara. Cito-



sheets, palisades, papillae without fibrovascular cores, often with disorganized, crowded and overlapping nuclei. Cell cytoplasm within the group lacks distinct borders while solitary cells have a well bordered, small, basophilic cytoplasm. The nuclei are oval and enlarged with fine, pale chromatin and visible intranuclear inclusions. Nuclear grooves are not visible on MGG stain. Dense, hyperchromatic colloid can be seen in papillary carcinoma. Multinucleated giant cells, psammoma bodies, hyalinized stroma and endothelial cells are associated but not specific for thyroid papillary carcinoma. A specific immunocytochemical marker of papillary carcinoma is cytokeratin 19, which is not positive in other thyroid carcinomas. Galectin-3 is highly positive in papillary carcinoma, but also in follicular tumors of the thyroid. TTF-1 is positive in all thyroid carcinomas except for anaplastic carcinoma and thyroglobulin is positive in one third of papillary carcinomas.

The following subtypes of thyroid papillary carcinoma have been differentiated:

- 1) follicular – the overall appearance looks like follicular cancer but the nuclei are typical of papillary cancer,
- 2) tall cell – cells are twice as tall as wide,
- 3) columnar – cells are columnar and show nuclear stratification,
- 4) solid – solid islands of cells with reduced colloid; it has been found in children in particular after radiation exposure,
- 5) diffuse sclerosing – dense fibrous stroma,
- 6) oncocytic – looks like Hürthle cell lesion but nuclei have typical appearance of papillary cancer, and
- 7) hyalinizing trabecular tumor – has cytologic characteristics of follicular, papillary even medullary cancer with hyalinizing sheets between cells; genetic analyses showed it to a subtype of papillary carcinoma.

Classification of a tumor to each subtype is possible if cytologic smear contains at least 50% of cells with morphological characteristics of the respective subtype. Only a minor portion of thyroid papillary carcinomas can be classified to a certain subtype while the majority of papillary carcinomas have only the usual characteristics of classic papillary carcinoma mentioned above. Tall cell, columnar, solid and diffuse sclerosing papillary carcinomas are more malignant forms of thyroid papillary carcinoma.

In European countries, total thyroidectomy is the accepted therapeutic approach to the cytologically veri-

plazne unutar nakupina su neoštro ograničene, dok su kod pojedinačnih stanica dobro ograničene, oskudne i bazofilne. Jezgre su monomorfne, povećane, ovalne, fine strukture kromatina, s vidljivim intranuklearnim inkluzijama i uzdužnim brazdama koje se ne vide na pripravcima bojenim po MGG. Koloid se obično nalazi u globulama. Multinuklearne orijaške stanice, psamomska tjelešca, endotel krvnih kapilara i hijalini tračci su često prisutni u papilarnom karcinomu, ali nisu za njega patognomonični. Imunocitokemijski, za papilarni karcinom je specifičan keratin 19, galektin 3 se nalazi u visokom postotku kod papilarnih karcinoma, ali i u folikularnim karcinomima. TTF se nalazi u svim karcinomima štitnjače osim anaplastičnog karcinoma, a tiroglobulin je pozitivan kod jedne trećine papilarnih karcinoma.

Razlikuje se nekoliko podtipova papilarnog karcinoma štitnjače:

1. folikularni tip – nakupine stanica čine mikrofolikule, ali stanice imaju sve značajke klasičnog papilarnog karcinoma
2. velikostanični tip – stanice su dvostruko više nego šire
3. tip cilindričnih stanica – stanice su cilindrične i pokazuju uslojavanje jezgara
4. solidni tip – guste nakupine stanica s oskudnim koloidom; najčešće ga nalazimo u djece nakon izlaganja zračenju
5. difuzni sklerozirajući tip – nalazi se gusta fibrozna stroma; u citološkom razmazu stanice najčešće dolaze pojedinačno, a prisutna su i brojna psamomska tjelešca; i ovaj tip tumora češće se nalazi u djece
6. onkocitni tip – stanice izgledaju poput Hürthleovih, ali su im jezgre tipične za papilarni karcinom
7. hijalinizirani trabekularni tumor – sadrži citološke značajke folikularnog, papilarnog, pa čak i medularnog karcinoma s hijalinim tračcima koji se provlače između stanica; genskim analizama dokazano je da se radi o podvrsti papilarnog karcinoma, a ne o adenomu kao što se ranije mislilo.

Klasifikacija tumora u pojedini podtip papilarnog karcinoma moguća je ako se u citološkom razmazu nađe barem 50% stanica s morfološkim značajkama određenog podtipa.

Samo manji broj tumora može se razvrstati u pojedine podtipove, dok većina papilarnih karcinoma štitnjače ima samo uobičajene, prethodno opisane morfološke značajke. Velikostanični tip, tip cilindričnih stanica, solidni i difuzni sklerozirajući tip dokazano su maligniji oblici papilarnog karcinoma štitnjače.



fied papillary carcinoma of the thyroid gland, regardless of the nodule size and presence of intraglandular dissemination. Although it is known that some subtypes of papillary carcinoma are more malignant forms, in classic papillary carcinoma, for now, there are no morphological markers that could point to a tumor with a higher malignant potential.

In a sample of 100 patients treated at Department of Nuclear Medicine and Radiation Protection, Zagreb University Hospital Center, the diagnosis of papillary carcinoma was made by cytology and verified by histology. We performed semiquantitative analysis of all the previously mentioned morphological characteristics of classic thyroid papillary carcinoma, and of the size and US characteristics of thyroid nodules. Statistical analysis showed no correlation of any of the cytomorphological characteristics, size or US characteristic of thyroid nodule with intraglandular and/or paraglandular dissemination of the disease. Since literature data and our own results indicate rather common intraglandular and paraglandular dissemination of the disease, and no marker has yet been identified to point to a higher or lower possibility of intraglandular and paraglandular dissemination of thyroid papillary carcinoma, it is advisable to perform total thyroidectomy when papillary carcinoma is diagnosed by cytologic examination, regardless of the nodule size or tumor subtype.

Totalna tiroidektomija je, u europskim okvirima, prihvaćen terapijski pristup kod citološki dokazanog papilarnog karcinoma štitnjače, bez obzira na veličinu čvora ili dokazanu intraglandularnu diseminaciju. Iako je poznata veća agresivnost pojedinih podtipova papilarnog karcinoma, za klasični papilarni karcinom zasad se ne nalazi morfoloških značajka koje bi ukazivale na veći maligni potencijal, tj. sklonost intraglandularnoj ili paraglandularnoj diseminaciji.

Na uzorku od 100 bolesnika obrađenih u Zavodu za nuklearnu medicinu i zaštitu od zračenja, KBC Zagreb, kod kojih je citološki postavljena i histološki potvrđena dijagnoza papilarnog karcinoma, semikvantitativno smo analizirali sve prethodno navedene morfološke značajke klasičnog papilarnog karcinoma, te veličinu i UZV značajke punktiranih čvorova. Statističkom obradom nije ustanovljena povezanost između bilo kojeg morfološkog parametra, veličine, lokalizacije i UZV značajka čvora s prisutnošću intraglandularne i/ili paraglandularne diseminacije bolesti. Kako je iz literaturnih podataka, a i iz našeg materijala razvidno da je intraglandularna diseminacija bolesti relativno česta, a nismo utvrdili pokazatelj koji bi ukazivao na veću ili pak manju vjerojatnost intraglandularne diseminacije, i dalje stoji preporuka o totalnoj tiroidektomiji kod citološki postavljene dijagnoze papilarnog karcinoma bez obzira na veličinu čvora i citološki podtip tumora.

## MOLECULAR DIAGNOSTICS OF THYROID CANCER

## MOLEKULARNA DIJAGNOSTIKA RAKA ŠTITNJAČE

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New insights into the molecular-genetic basis of thyroid cancer can be applied in diagnosis to discover new molecular markers and diagnostic procedures. Molecular markers and methods have several different applications in the treatment of patients with thyroid cancer. They can serve for screening, making diagnosis, determining prognosis, and for early detection of residual and recurrent disease in postoperative follow up of patients.

Spoznaje o molekularno-genetskoj osnovi raka štitnjače imaju svoju primjenu i u dijagnostici za otkrivanje novih molekularnih biljega i dijagnostičkih postupaka. Molekularne metode i biljezi imaju različite primjene u zbrinjavanju bolesnika s rakom štitnjače. Upotrebljavaju se kod probira, za postavljanje dijagnoze, za određivanje prognoze te za praćenje bolesnika nakon operacije kako bi se rano otkrio recidiv ili ostatna bolest.



Mutations in the *RET* gene, which are associated with inherited medullary carcinoma of the thyroid, are analyzed for screening. Mutations in the *RET* gene have been found in more than 90% of patients with inherited medullary carcinoma of the thyroid, and they are associated with a very high risk of development of medullary carcinoma of the thyroid. All first-degree relatives (parents, siblings, and children) of a person known to have inherited medullary carcinoma of the thyroid are tested for mutations in the *RET* gene. If mutations are found they can be offered prophylactic thyroidectomy or regular controls.

Analysis of molecular markers in fine-needle aspiration samples of thyroid nodules could help in making preoperative diagnosis in cases in which decisive diagnosis regarding malignancy cannot be made on the basis of cytologic analysis. Patients with indeterminate cytologic diagnosis regarding malignancy are being surgically treated for diagnostic purposes although most of them have benign thyroid lesions. The introduction of reliable molecular markers which would increase the accuracy of preoperative diagnosis could spare some of these patients unnecessary surgery. Numerous markers have been studied: galectin-3, CD44v6, human telomerase reverse transcriptase (hTERT), oncofetal fibronectin, *RET/PTC* gene rearrangements, mucin-1, high mobility group I(Y) (HMGI(Y)), HBME-1, and others. The expression of these markers has been analyzed by immunocytochemical methods and by reverse transcription-polymerase chain reaction (RT-PCR). Analysis of these markers has not yet been included in the routine protocols for treatment of patients with thyroid cancer. Nevertheless, some of these markers (e.g., galectin-3 detected immunocytochemically) have shown high diagnostic accuracy in identification of malignant thyroid lesions. In an attempt to improve diagnostic accuracy, a combined use of a panel of markers has been analyzed in several studies. Recently published results of transcriptomic analyses (cDNA microarrays) identified new potential markers that could show higher diagnostic accuracy than the markers studied so far.

It has also been studied whether analysis of the expression of certain markers in thyroid tissue samples after thyroidectomy or fine-needle aspiration samples can help determine prognosis. The markers studied for this purpose are: p53, p27, cyclin D1, vascular endothelial growth factor (VEGF), mucin-1, pituitary tumor transforming gene (PTTG), mutations in *BRAF* gene, *RET/PTC* gene rearrangements, and others. It has been

U svrhu probira određuju se mutacije gena *RET* koje su povezane s nasljednim medularnim karcinomom štitnjače. Mutacije gena *RET* nađene su u više od 90% osoba s nasljednim medularnim karcinomom štitnjače i povezane su s vrlo visokim rizikom za razvoj medularnog karcinoma. Mutacije gena *RET* određuju se roditeljima, braći i djeci osoba s dijagnosticiranim nasljednim medularnim karcinomom štitnjače, kako bi im se u slučaju potvrđenih mutacija mogla ponuditi profilaktična tireoidektomija ili redovite kontrole.

Analiza molekularnih biljega u punktatima čvorova štitnjače mogla bi pomoći pri postavljanju prijeoperacijske dijagnoze u slučajevima kada se citološkom analizom punktata ne može postaviti jasna dijagnoza glede malignosti. Bolesnici s nejasnom citološkom dijagnozom glede malignosti podvrgavaju se operaciji štitnjače u dijagnostičke svrhe, iako većina njih ima benigne promjene štitnjače. Uvođenje pouzdanih molekularnih biljega koji bi povećali točnost prijeoperacijske dijagnostike promjena štitnjače moglo bi poštediti dio tih bolesnika nepotrebne operacije. Istraživalo se brojne biljege (galektin-3, CD44v6, katalitičku (reverzno-transkriptaznu) komponentu humane telomerase (hTERT), onkofetalni fibronektin, *RET/PTC* genske pregradnje, mucin-1, HMGI(Y) (*high mobility group I(Y)*), HBME-1 i druge), čija se ekspresija određivala imunocitokemijskim metodama i lančanom reakcijom polimerazom nakon reverzne transkripcije (RT-PCR). Određivanje ovih biljega zasad nije uključeno u rutinske protokole zbrinjavanja bolesnika s rakom štitnjače, iako su neki od njih (npr. galektin-3 određen imunocitokemijski) pokazali obećavajuće rezultate u smislu visoke dijagnostičke točnosti pri identifikaciji malignih promjena štitnjače. Istraživalo se i određivanje više biljega na pojedinim uzorcima kako bi se povećala dijagnostička točnost. Na temelju rezultata transkriptomskih analiza (cDNA čipovi) objavljenih u novije vrijeme izdvojeni su novi potencijalni biljezi koji bi mogli pokazati veću dijagnostičku točnost od dosad istraživanih biljega.

Istraživalo se i može li analiza ekspresije pojedinih biljega u uzorcima tkiva štitnjače nakon tireoidektomije ili u punktatima pomoći pri određivanju prognoze. U tu svrhu se kao biljege istraživalo p53, p27, ciklin D1, vaskularni endotelni faktor rasta (VEGF), mucin-1, PTTG (*pituitary tumor transforming gene*), mutacije u genu *BRAF*, *RET/PTC* genske pregradnje i druge. Tako se, na primjer, pokazalo da je povećana ekspresija biljega mucin-1 u uzorcima tumorskog tkiva statistički značajno povezana s kraćim razdobljem bez znakova bolesti u

shown, for example, that overexpression of mucin-1 is statistically significantly associated with shorter relapse-free survival in patients with papillary carcinoma of the thyroid. But, none of the markers studied so far has been included in the routine protocols for treatment of patients with thyroid cancer due to the lack of clinically relevant results repeated in different studies on a large sample.

Measurement of serum thyroglobulin as a marker of recurrent or residual disease is part of routine postoperative follow up in patients with differentiated thyroid cancer. But this method has some limitations. Circulating antithyroglobulin antibodies, if present, can interfere with serum thyroglobulin measurement. Also, the measurement of serum thyroglobulin requires previous thyroxine withdrawal or administration of expensive recombinant human thyrotropin (TSH). Detection of circulating thyroid cells by RT-PCR or real-time RT-PCR has been studied as a potential more reliable marker that could replace serum thyroglobulin measurement. In most of these studies, thyroglobulin mRNA has been studied as a specific marker for the presence of circulating thyroid cells. Results of different studies regarding the value of this marker are conflicting. The value of this marker is significantly diminished by positive finding of thyroglobulin mRNA in healthy persons reported in several studies. In a smaller number of studies other markers in addition to thyroglobulin (thyrotropin receptor, thyroid peroxidase (TPO), and sodium/iodide symporter (NIS)) have been studied. Detection of circulating tumor cells as a marker of local relapse or presence of distant metastases in patients with medullary carcinoma of the thyroid has been investigated in only few studies. As markers in these studies, CK20, calcitonin, and carcinoembryonic antigen (CEA) have been analyzed by RT-PCR.

bolesnika s papilarnim karcinomom štitnjače. Međutim, dosad niti jedan od istraživanih biljega nije pokazao u većem broju studija na velikom broju uzoraka dovoljno dobre i klinički relevantne rezultate da bi ga se uvrstilo u rutinske protokole zbrinjavanja bolesnika s rakom štitnjače.

Određivanje serumskog tireoglobulina rutinski se primjenjuje u poslijeoperacijskom praćenju bolesnika s diferenciranim rakom štitnjače kao biljeg recidiva ili ostatne bolesti. Međutim, ovaj biljeg ima neke nedostatke kao što su utjecaj cirkulirajućih antitireoglobulinskih protutijela na izmjerenu vrijednost serumskog tireoglobulina i nužnost uskraćivanja tiroksina ili primjene skupog rekombinantnog humanog tireotropina (TSH) prije određivanja serumskog tireoglobulina. Kao pouzdaniji biljeg koji bi mogao zamijeniti određivanje serumskog tireoglobulina istražuje se otkrivanje cirkulirajućih stanica štitnjače metodom RT-PCR i metodom *real time* RT-PCR. U većini ovih istraživanja kao specifični biljeg prisutnosti cirkulirajućih stanica štitnjače određivala se mRNA za tireoglobulin. Rezultati različitih istraživanja su dali oprečne rezultate glede vrijednosti ovoga biljega. Vrijednost ovoga biljega najviše umanjuju pozitivni nalazi mRNA za tireoglobulin u zdravih osoba dobiveni u nekim istraživanjima. U manjem broju istraživanja određivalo se i druge biljege uz tireoglobulin: receptor za tireotropin, tireoidnu peroksidazu (TPO) i natrij-jodid-simporter (NIS). Određivanje cirkulirajućih tumorskih stanica kao biljeg lokalnog recidiva ili prisutnosti udaljenih metastaza u bolesnika s medularnim karcinomom štitnjače ispitalo se u tek nekoliko istraživanja. Kao biljege u tim se istraživanjima određivalo CK20, kalcitonin i karcinoembrijski antigen (CEA) metodom RT-PCR.



## SURGICAL TREATMENT OF DIFFERENTIATED THYROID CARCINOMA

### KIRURŠKO LIJEČENJE DIFERENCIRANOG KARCINOMA ŠTITNJAČE

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According to prognostic factors, thyroid cancer patients could be classified into several risk groups, however, the principles of surgical radicality should be first considered, as is the case in other types of cancer surgery. The choice of surgical approach primarily depends on the surgeon's skills and capability to precisely determine what surgery extent is optimal in a particular case. Cytology, ultrasonography and intraoperative biopsy are the most reliable tools when deciding on the extent of the procedure. The efficacy of surgical treatment is evident through a number of numerical parameters recorded over lifetime of both the patient and the surgeon. Mortality rate, local cancer recurrence, regional metastases, reoperation and postoperative complications all are indicators of the surgeon's efficiency. On the other hand, each cancer patient should be referred to as an "individual with a tumor disease", which follows the patient from the diagnosis to the very end of his/her life. The disease has an enormous effect on the patient's life, and makes it significantly different.

Papillary cancer is the most common type of thyroid cancer. According to the literature, surgical treatment of papillary cancer may be classified into two groups. Group 1 includes minimal papillary cancer of less than 1 cm in diameter, with no invasion of the thyroid capsule and no metastases. Cancer may be detected as an occult lesion in younger persons during surgery for some other type of lesion. Lobectomy is a preferable procedure, especially if the lesion is unicentric with less than 5 mm in diameter.

Group 2 includes all other types of papillary cancer. The signs of multicentricity are seen in over 80% of papillary cancers, lymph node metastases are common, both local and regional, and lung metastases are common in the advanced stage of the disease. In some cases local invasion of the trachea and esophagus is observed. Total thyroidectomy with neck dissection is the method of

Unatoč tomu što se s obzirom na prognostičke čimbenike bolesnici s rakom štitnjače mogu podijeliti u nekoliko rizičnih skupina, smatramo da se u kirurgiji raka štitnjače mora slijediti načelo radikalnosti, kao i u kirurgiji drugih tumora. Kako se u tom slučaju postaviti, ovisi o individualnosti kirurga, što obuhvaća njegovu dobru kiruršku izobrazbu i sposobnost neposrednog donošenja odluke o opsegu operacijskog zahvata u svakom pojedinom slučaju. Za donošenje odluke nemjerljivo su značajni pouzdan citološki nalaz, ultrazvučni prikaz, kao i nalaz intraoperacijske biopsije. Konačan rezultat vidljiv je u brojčanom prikazu brojnih parametara koji se mogu pratiti tijekom životnoga vijeka bolesnika, odnosno radnoga vijeka kirurga. Rezultate rada kirurga moguće je pratiti kroz broj smrtnih ishoda bolesnika, lokalnih recidiva, regionalnih metastaza, ponovnih operacija i poslijeoperacijskih komplikacija. S druge strane, svakog bolesnika treba promatrati kao osobu s tumorskom bolešću koja ga prati do kraja života od trenutka potvrde dijagnoze. Sigurno je da bolest kao takva utječe na njegov život i mijenja njegove dotadašnje stavove.

Prema podacima iz svjetske literature, kirurško liječenje najčešćeg papilarnog karcinoma se prema kliničkim značajkama bolesti može podijeliti u dvije skupine.

U prvu skupinu spada liječenje minimalnog papilarnog karcinoma, manjeg od 1 cm u promjeru, koji ne pokazuje znakove invazije tiroidne kapsule i koji nije metastazirao, a nađe se u mlađih osoba kao okultna lezija tijekom kirurškog zahvata na štitnjači zbog nekog drugog benignog razloga. U takvu slučaju, osobito ako je lezija unicentrična i manja od 5 mm u promjeru, smatra se da je možda dovoljna lobektomija, uz redovito praćenje daljnjeg tijeka bolesti.

U drugu skupinu spada liječenje većine papilarnih karcinoma koji nisu ni minimalni ni okultni. Poznato je da papilarni karcinom u više od 80 posto slučajeva pokazuje mikroskopske znakove multicentričnosti, često

choice. The neurovascular and muscular structures that are free of tumor remain preserved with surgery. Elective neck dissection is not indicated. The richer the experience of the surgeon, the lower the complication rate, e.g., the incidence of recurrent nerve injury and hypoparathyroidism.

The treatment of low-risk types of papillary cancer (depending on prognostic factors according to AGES, AMES and MACIS criteria) remains controversial. Although salvage surgery is favored for low mortality and surgical complication rates, the principle of surgical radicality should be considered first, for a couple of reasons. Mortality rate is significantly decreased despite a higher incidence of cancer occurrence, and this may in part be due to a more efficient and earlier diagnosis of cancer disease. On the other hand, thanks to the nature of the papillary cancer and long duration of the disease, the advanced stages of the disease with a poor prognosis rarely develop. Salvage surgery is, however, associated with thyroid recurrence requiring reoperation, which leads to a more complex surgical orientation and an increase in surgical complications. Higher recurrence and metastasis rates lead to a higher mortality rate, therefore regular and careful follow up is needed. Patients are unable to handle their disease and often insist on a “radical” surgical approach, to totally remove the remnants of the disease. Total removal of cancer makes it possible to explore other non-surgical methods of treatment with radioactive iodine.

Follicular cancer is a rarer type of thyroid cancer. The highest incidence of this type of cancer is found in females and elderly patients. Microscopic diagnosis is confirmed either through vascular or capsular invasion. Multicentricity and lymph node metastases occur rarely but the lungs, bones and other tissues are often invaded by the disease. Follicular cancer with capsular microinvasion has a good prognosis. According to the literature, lobectomy is a good method of choice. Yet, total thyroidectomy is the method of choice in the majority of cases.

Hürthle cell carcinoma is considered a variant of follicular carcinoma, and causes difficulty in the treatment for a couple of reasons. Metastases may appear in 2% to 3% of benign types, and unlike follicular variant, iodine intake by carcinoma is poorer, which causes difficulty in the treatment of metastatic disease. Total thyroidectomy is the method of choice.

metastazira u limfne čvorove lokalno i regionalno, poslije može metastazirati u pluća i ostale organe, a u pojedinim slučajevima lokalno invadira dušnik i jednjak. U navedenim slučajevima najbolji izbor kirurškog liječenja je totalna tireoidektomija s disekcijom limfnih čvorova prednje i lateralnih regija vrata kad su evidentne metastaze u vratnim limfnim čvorovima. Pritom se štede sve živčane, krvožilne i mišićne strukture koje nisu neposredno zahvaćene tumorom. U tim slučajevima nije indicirana elektivna disekcija vrata. S iskustvom kirurga opada i broj neposrednih komplikacija operacijskog zahvata, u prvom redu ozljeda povratnog živca i slučajeva trajnog hipoparatiroidizma.

U liječenju pojedinih skupina bolesnika s papilarnim karcinomom niskog rizika (ovisno o prognostičkim čimbenicima prema kriterijima AGES, AMES ili MACIS) stavovi su i danas kontroverzni. Unatoč tomu što se poštena kirurgija opravdava činjenicom niske stope smrtnosti i nižom učestalošću kirurških komplikacija, smatramo da načelo radikalnosti u kirurgiji karcinoma i dalje treba poštovati, i to zbog nekoliko činjenica. Iako je učestalost karcinoma u porastu, smrtnost opada, što se s jedne strane može objasniti boljom i ranijom dijagnostikom, zbog čega je sve više bolesnika u ranijem stadiju bolesti. S druge pak strane, s obzirom na narav papilarnog karcinoma i dug tijek bolesti, ne stignu se razviti uznapredovali oblici bolesti s lošijom prognozom. Ipak, uz poštenju kirurgiju raste broj recidiva u ležištu štitnjače i limfnim čvorovima, što zahtijeva drugi operacijski zahvat koji sa sobom nosi otežanu kiruršku orijentaciju i veći broj komplikacija. Uz to, s brojem recidiva i metastaza raste i smrtnost bolesnika, pa je uz pravodobni pristup liječenju neophodna redovita i dobra kontrola (praćenje) bolesnika. Bolesnici su opterećeni svojom bolešću i pokazuju znakove anksioznosti te često inzistiraju na “kompletnoj operaciji”, jer se ne mogu pomiriti s činjenicom da je unatoč dobroj prognozi još nešto ostalo. S druge strane, potpuno odstranjenje štitnjače omogućuje primjenu nekirurških metoda liječenja radioaktivnim jodom.

Rjeđi od papilarnog je folikularni karcinom. Oboljeli pripadaju starijim dobnim skupinama, uz prevladavanje ženskog spola. Mikroskopska dijagnoza postavlja se dokazom vaskularne ili kapsularne invazije. Rijetka je multicentričnost i limfogeno metastaziranje, dok je učestala hematogena diseminacija bolesti u pluća, kosti i ostala tkiva. Folikularni karcinom s mikroinvazijom kapsule ima dobru prognozu, a prema podacima iz svjetske literature u takvom slučaju lobektomija je možda dovoljna. Ipak,

za većinu bolesnika metoda izbora je totalna tiroidektomija.

Benigni tumor Hürthleovih stanica i karcinom varijante su folikularnoga karcinoma koje se teže liječe zbog nekoliko razloga. U 2 do 3 posto slučajeva benigni oblici poslije mogu metastazirati, a za razliku od čiste folikularne varijante karcinomi slabije kumuliraju jod, zbog čega je otežano liječenje metastatske bolesti. I u tom slučaju totalna tiroidektomija je metoda izbora.

## UP TO DATE PROCEDURES IN THYROID GLAND SURGERY SUVREMENI POSTUPCI U KIRURGIJI ŠTITNJAČE

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### Introduction

Surgical treatment of thyroid gland has dramatically changed by the introduction of advanced technologies like high-resolution endoscopy devices and harmonic scalpel.

### Aim

The goal of this presentation is to present our experience in more than 150 patients with thyroid gland disease that were operated on with harmonic scalpel and/or using minimally invasive video-assisted approach. The emphasis of the presentation will be on: (1) comparison of technology-powered thyroidectomies with conventional thyroid surgery; (2) advantages of hemostasis with harmonic scalpel when compared to electrocauterization or CO2 laser; (3) values of endoscopic visualization of operative field in the neck; (4) cosmetic gain with the use of both of these technologies; and (5) algorithm for rational implementation of endoscopic thyroidectomy in modern surgical practice. Both of these sophisticated technologies have been routinely implemented for thyroid surgery at University Department of ENT, Head and Neck Surgery, Zagreb University Hospital Center.

### Uvod

Kirurgija štitnjače u posljednjih nekoliko godina doživjela je značajne promjene uvođenjem naprednih tehnologija poput visokorezolucijske endoskopije i upotrebe ultrazvučnog noža.

### Cilj

Cilj predavanja je prikazati naša iskustva u primjeni ultrazvučnog noža i minimalno invazivne video-asistirane tiroidektomije kod više od 150 tiroidektomija, s naglaskom na: 1) usporedbu iskustava stečenih u primjeni ovih metoda s onima stečenim klasičnim tiroidektomijama, 2) prednosti hemostaze ultrazvučnim nožem u odnosu na elektrokoagulaciju i primjenu ligatura, 3) vrijednosti intraoperacijske vizualizacije endoskopskim uređajima, 4) estetske prednosti primjene naprednih tehnologija i 5) algoritam za racionalnu provedbu endoskopske tiroidektomije u suvremenoj kirurškoj praksi. Obje ove tehnologije s uspjehom se primjenjuju u našoj Klinici unazad godinu dana.

### Materijal i metode

Minimalno invazivna video-asistirana tiroidektomija (MIVAT, *minimally invasive video-assisted thyroidectomy*)

## Material and Methods

The initial endoscopic experience developed with minimally invasive parathyroidectomy prompted some authors to try a similar surgical approach for thyroid surgery. They have called the procedure MIVAT, minimally invasive video assisted thyroidectomy. Since the majority of patients affected by thyroid disease are women and cosmetic result becomes very important, the first idea that moved to MIVAT was the “almost invisible” scar, with an incision of no more than 1.5-2 cm. Further experience with MIVAT has demonstrated that this procedure enables similar results as traditional thyroidectomy, with less trauma to the tissue, better postoperative recovery, and shorter hospital stay. Furthermore, there is less postoperative pain owing to limited dissection and less tissue destruction. MIVAT is indicated for correct selection of patients (approximately 10% of all surgical thyroid cases). It is a minimally invasive procedure that requires good experience in classic “open-neck” thyroid surgery and right conduction of the endoscopic “gassless” procedure management. Indications for this procedure are nodule <3 cm in diameter, thyroid volume <25 mL, benign or low-grade follicular lesions, and papillary carcinoma. Absolute contraindications are previous neck surgery, large goiters and local metastases, while relative contraindications are previous neck irradiation, hyperthyroidism and thyroiditis.

Harmonic scalpel cuts and coagulates simultaneously using mechanical vibration. This instrument was developed in the 1990s, and since then has been successfully used for several years in general and laparoscopic surgery, otorhinolaryngology, cardiac surgery, oral surgery and gynecologic surgery. The generator of the harmonic scalpel produces a natural harmonic frequency of 55000 Hz. When the active blade contacts tissues, the transmitted acoustic waves cause cavitation fragmentation and cavitation cutting rather than electrical or thermal coagulation, as with standard cautery. The harmonic scalpel uses mechanical vibration to produce hemostasis at low temperature (80 °C), which has an advantage of producing less tissue thermal injury. The possibility of simultaneous cutting and coagulation significantly reduces surgical time in thyroid surgery. The harmonic scalpel has been shown to effectively seal and cut a vessel up to 3 mm in diameter. When compared with electro-surgery and CO2 laser, the harmonic scalpel causes approximately half the size of thermal injury. Nevertheless, for safe recurrent nerve surgery, active blade has to be at least 5 mm distant from structures that are in danger

tehnika je koja se razvila nekoliko godina nakon uvođenja endoskopskog instrumentarija u kirurgiju paratiroidnih žlijezda. Kako većinu bolesnika s bolestima štitnjače čine žene, prvobitna zamisao koja je dovela do primjene MIVAT bio je bolji kozmetički rezultat (incizija od 1,5-2 cm). S većim brojem operiranih bolesnika pokazalo se da MIVAT omogućuje iste rezultate kao i tradicionalna tiroidektomija, uza značajno manju traumu, bolji poslijeoperacijski tijek, kraću hospitalizaciju i bolje estetske rezultate. Također, zbog ograničene disekcije i manje destrukcije tkiva bolesnici se žale na manju poslijeoperacijsku bol. Ova se tehnika razlikuje od ostalih (npr. abdominalnih) endoskopskih metoda na način da se prilikom operacije ne insuflira plin u operacijsko područje. MIVAT je minimalno invazivan zahvat koji zahtijeva prethodno dobro iskustvo u konzervativnoj kirurgiji štitnjače, te ispravno rukovanje endoskopskim instrumentima u uskom operacijskom polju bez insuflacije plina. Zahvat je prikladan za oko 10% bolesnika s kirurškim bolestima štitnjače. Indikacije za MIVAT su solitarni čvor manji od 3 cm, volumen štitnjače manji od 25 mL, dobroćudne folikularne lezije ili folikularne lezije niskog maligniteta, te papilarni karcinom. Apsolutne kontraindikacije za primjenu ove metode su prethodni operacijski zahvati na vratu, prisutnost metastaza ili velike strume, dok se u relativne kontraindikacije mogu svrstati prethodno ozračivanje vrata, hipertiroidizam i tiroiditis.

Ultrazvučni nož koristi mehaničke vibracije za istodobnu koagulaciju i rezanje tkiva. Upotreba ovog instrumenta prvi je put opisana 1990. i od tada se uspješno primjenjuje u općoj i laparoskopskoj kirurgiji, otorinolaringologiji, kardijalnoj kirurgiji, oralnoj kirurgiji i ginekologiji. Ultrazvučni se nož sastoji od generatora koji stvara akustični val frekvencije 55000 Hz, koji se prenosi na aktivni rezač koji harmonično vibrira na istoj frekvenciji. Tako preneseni ultrazvučni valovi uzrokuju kavitacijsku fragmentaciju i rezanje tkiva, za razliku od električne ili toplinske koagulacije kod konvencionalnih instrumenata. Nadalje, pri radu s ultrazvučnim nožem stvara se manje toplinske energije (do 80 °C), što smanjuje toplinsko oštećenje okolnog tkiva. Mogućnost istodobnog rezanja i koagulacije značajno skraćuje vrijeme potrebno za operacije štitnjače. Ultrazvučnim nožem može se učiniti hemostaza krvnih žila promjera do 3 mm. Iako su istraživanja pokazala da se upotrebom ovog instrumenta oštećuje dvostruko manja površina okolnog zdravog tkiva u usporedbi s elektrokauterom ili laserom, za sigurno očuvanje povratnog živca preporuka

of injury. At the end, the use of harmonic scalpel in thyroid surgery enables better cosmetic result, as well as avoidance of postoperative drainage tube placement.

### Conclusion

MIVAT enables similar results as traditional thyroidectomy, with less trauma to the tissue, better postoperative recovery, shorter hospital stay, better cosmetic result, and less postoperative pain. The use of harmonic scalpel in thyroid surgery enables less tissue destruction, avoidance of drainage tube placement, and significantly shorter operative time.

je da aktivna rezna ploha noža mora biti udaljena bar 5 mm. Naposljetku, upotreba ultrazvučnog noža u kirurgiji štitnjače omogućuje izvođenje zahvata kroz manji kožni rez na vratu, te pouzdanu hemostazu nakon koje nije potrebno postavljanje drenaže.

### Zaključak

MIVAT omogućuje iste rezultate kao i tradicionalna tiroidektomija, uza značajno manju traumu, bolji poslijeoperacijski tijek, kraću hospitalizaciju, bolje estetske rezultate i manju poslijeoperacijsku bol. Upotreba ultrazvučnog noža u kirurgiji štitnjače omogućuje izvođenje zahvata kroz manji kožni rez na vratu, pouzdanu hemostazu nakon koje nije potrebno postavljanje drenaže i značajno kraće trajanje operacije.

## POSTOPERATIVE COMPLICATIONS OF THYROID CANCER SURGERY

## POSTOPERACIJSKE KOMPLIKACIJE KIRURŠKOG LIJEČENJA RAKA ŠTITNJAČE

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During their lifetime, every other person will develop one or multiple thyroid nodules. Clinically evident thyroid cancer is diagnosed in about 40 persons *per* million inhabitants, and it accounts for 0.6% to 1.6% of all malignancies.

Total thyroidectomy with anterior neck dissection (which includes complete removal of the thyroid gland, lymph nodes and fat tissue in the anterior lower neck triangle, anatomic region IV) is the surgical treatment of choice. Total thyroidectomy with unilateral or bilateral neck dissection is indicated in patients with thyroid cancer metastasizing to the lateral side of the neck.

Thyroid surgery was founded by Theodor Kocher who treated 2000 patients during the period from 1872 to 1896. Thyroid surgery has evolved with time in terms of technique as well as in reduction of the rate of com-

U svakog drugog čovjeka tijekom života razviju se veći ili manji pojedinačni ili višestruki čvorovi u štitnjači, češće u žena nego u muškaraca. Klinički manifestni karcinom štitnjače dijagnosticira se u otprilike 40 osoba na milijun stanovnika. Rak štitnjače čini od 0,6% do 1,6% svih zloćudnih tumora.

U liječenju karcinoma štitnjače totalna tiroidektomija s prednjom disekcijom vrata (podrazumijeva odstranjenje čitave štitnjače, limfnih čvorova i masnog tkiva u prednjem donjem trokutu vrata, odnosno regije VI) je kirurška metoda izbora. Totalna tiroidektomija s jednostranom ili obostranom disekcijom vrata je kirurški zahvat indiciran u bolesnika s karcinomom štitnjače i metastazama u lateralnim stranama vrata.

Temelje današnje kirurgije štitnjače postavio je Theodor Kocher. On je od 1872. do 1896. godine uspješno





plications. Improved surgical technique, and better knowledge of the anatomy and pathology have led to safe thyroid surgery with minimal postoperative complications.

Thyroid surgery is a field involving different specialties, e.g., general surgeons, thoracic surgeons, ENT specialists, cervicofacial surgeons and endocrine surgeons. At the beginning of the 20<sup>th</sup> century, according to the literature, the most common complications of thyroid surgery were postoperative bleeding, formation of hematoma, infections, and high postoperative mortality, the latter being extremely low in current practice.

However, total thyroidectomy is associated with a high risk of potential complications. The most common complications of total thyroidectomy are as follows:

- unilateral or bilateral injury of the recurrent laryngeal nerve
- injury of the superior laryngeal nerve
- transitory or permanent hypoparathyroidism
- postoperative bleeding
- wound infection

Occasional postoperative complications of total thyroidectomy include:

- injury of the thoracic duct
- Horner's syndrome
- injury of the trachea

Injury of the recurrent laryngeal nerve occurs in the immediate postoperative period and can be transitory or permanent. The patient talks harshly because of vocal cord paresis: in case of transitory paresis, vocal cords are located paramedially, while in case of permanent paresis (paralysis) vocal cords are located intermedially.

Transitory paresis lasts for 6 to 8 months and requires follow up by an ENT specialist. In bilateral paralysis accompanied by breathing disorders tracheotomy is a provisory solution, while cordopexy of the displaced vocal cord is a definitive one. Permanent injury of the recurrent laryngeal nerve is a very rare complication and occurs in less than 1% of cases.

Injury of the external superior laryngeal nerve is encountered in 3.7% of patients. Clinical symptoms include speech fatigue, voice tonality disorder and restriction in high tone production.

Injury of the main internal superior laryngeal nerve with ipsilateral lesion of the recurrent laryngeal nerve causes dysphagia. It occurs in less than 0.4% of cases.

Hypoparathyroidism is the result of the removal, injury or disrupted vascularization of parathyroid glands. It manifests on postoperative day 2 or 3, or exceptional-

izveo preko 2000 operacija štitnjače. Kirurgija štitnjače doživljavala je značajne promjene u samoj tehnici, a time i u popratnim komplikacijama. Usavršavanjem kirurške tehnike te boljim poznavanjem kirurške anatomije i patologije štitnjače kirurgija štitnjače postaje sigurna s minimalnim poslijeoperacijskim komplikacijama. Danas se kirurgijom štitnjače bave kirurzi različite izobrazbe i profila: opći kirurzi, torakalni kirurzi, otorinolaringolozi, onkikirurzi, kirurzi glave i vrata te endokrini kirurzi.

Na početku 20. stoljeća, prema objavljenim radovima, najčešće komplikacije kirurgije štitnjače bila su poslijeoperacijska krvarenja, hematomi, infekcije i poslijeoperacijska smrtnost. Poslijeoperacijska smrtnost u kirurgiji štitnjače danas je vrlo niska. Nedostatak totalne tireoidektomije podrazumijeva visok rizik od mogućih komplikacija. Najčešće komplikacije totalne tireoidektomije su :

- jednostrana ili obostrana lezija povratnog živca
- lezija gornjeg laringalnog živca
- prolazni ili trajni hipoparatiroidizam
- poslijeoperacijsko krvarenje
- infekcija rane

Rjeđe poslijeoperacijske komplikacije totalne tireoidektomije su:

- lezija torakalnog duktusa
- Hornerov sindrom
- lezija traheje.

Ozljeda povratnog živca javlja se kao trajna i prolazna pareza neposredno nakon operacije. Bolesnik je promukao, glasiljka je u prolaznim parezama u paramedijalnom položaju, a kod trajne u intermedijalnom položaju. Prolazna pareza iščezava nakon šest do osam mjeseci i zahtijeva kontrolu otorinolaringologa. Kod bilateralne paralize je zbog smetnji disanja potrebna traheotomija, a kao konačno rješenje kordopeksija jedne glasnice. Trajna ozljeda povratnog živca danas je svedena na najmanju mjeru, do 1% slučajeva.

Lezija vanjske grane gornjeg laringalnog živca je suspektna u 3,7% slučajeva. Klinički simptomi su govorna zamorljivost, teškoće u tonalitetu glasa i ograničenju visokih tonova.

Lezija gornjeg laringalnog živca s istostranim oštećenjem povratnog živca dovodi do smetnji gutanja tekućine. Oštećenje gornjeg laringalnog živca je ispod 0,4% slučajeva.

Hipoparatiroidizam nastaje kao posljedica odstranjenja, ozljede ili poremećene vaskularizacije paratiroidnih žlijezda. Pojavljuje se drugog do trećeg dana nakon operacije, a iznimno nakon petog dana. Klinički

ly postoperative day 5. Clinical symptoms include hypocalcemia with consequentially increased neuromuscular excitation with hand and foot paresthesia, Chvostek's sign, muscular spasms that may progress to carpopedal tetany, laryngospasm and bronchospasm. Transitory hypoparathyroidism as the result of disrupted vascularization is more frequent. According to most experts, normal function of only one parathyroid gland is sufficient for physiological PTH levels, while others believe that at least three functional parathyroid glands are needed. Low calcium and high phosphate blood levels indicate the possibility of permanent hypoparathyroidism and the need for D3 or AT-10 drops. After 6 months of substitution calcium therapy, hypoparathyroidism is considered permanent. The incidence of permanent hypoparathyroidism above 3% after total thyroidectomy is considered extremely high.

Postoperative bleeding most commonly occurs immediately after awaking of the patient or after a few hours because of the strain and blood pressure increase. Slipping of the ligature of a great artery or vein is the most dangerous complication. Heavy bleeding can cause suffocation, so in such cases urgent wound revision is mandatory. Blood transfusion is needed in 1% of these patients. Currently, 80% of surgeons do not require blood doses prepared for thyroidectomy.

Wound infections are extremely rare nowadays. There is no need for antibiotic prophylaxis or therapy in thyroid surgery, except for patients with diabetes, heart disease or immunodeficiency.

Literature is abundant in studies performed in large patient series (Rosato 14,934; Thomusch 4000; Tartaglia 1636; Muller 1031; Rios 301 patients), without any systematic analysis of risk factors in thyroid surgery. According to some authors, surgical experience is an important factor for complication development (Acun), whereas others believe that the problem lies in the size, weight or intrathoracic location of the thyroid gland, patient age, duration of the procedure, etc. A paper by Thomusch and Herman implies that injury of the recurrent laryngeal nerve and hypoparathyroidism are more frequent in male patients.

Thanks to preoperative preparation of the patient, anesthesia, surgical technique and better knowledge of thyroid anatomy, the incidence of postoperative complications in total thyroidectomy is constantly decreasing. Two most serious complications have been diminished: recurrent laryngeal nerve injury occurs in 1% and hypoparathyroidism in 3% of patients.

simptomi su znakovi hipokalcemije, a rezultat su povećane neuromuskularne podražljivosti. To su parestezije u rukama i nogama, Chvostekov znak, a mišićni grčevi se mogu pogoršati do karpopedalnog spazma, laringospazma i bronhospazma. Prolazni hipoparatiroidizam je češći od trajnog oblika, a posljedica je narušavanja vaskularizacije žlijezda. Za normalnu funkciju parathormona, prema većini autora, dovoljna je funkcija jednog paratiroidnog tjelešca, dok drugi smatraju da je potrebno sačuvati tri tjelešca. Niska razina kalcija i visoka razina fosfata u krvi nakon operacije je mogući znak da će nastati trajni hipoparatiroidizam koji zahtijeva liječenje pomoću D3 ili AT-10 kapi. Ako nakon šest mjeseci ostaje potreba za nadomjesnom terapijom kalcija, prolazni hipoparatiroidizam se smatra trajnim. Incidencija trajnog hipoparatiroidizma iznad 3% nakon totalne tireoidektomije se smatra znatno visokom.

Poslijeoperacijsko krvarenje najčešće se pojavljuje neposredno nakon buđenja iz anestezije ili nekoliko sati poslije zbog napinjanja i porasta krvnog tlaka. Najveća je opasnost skliznuće podveza s arterije ili vene većeg lumena. Jača krvarenja mogu dovesti do gušenja, pa je prijeko potrebna hitna revizija rane. Transfuzija krvi potrebna je u 1% slučajeva krvarenja. Danas 80% kirurga ne potražuje krv prije tireoidektomije.

Infekcije rane danas su iznimno rijetke. Većina kirurga ne rabi antibiotsku profilaksu ili terapiju u kirurgiji štitnjače. Antibiotska terapija potrebna je u slučajevima kada se radi o bolesnicima s manifestnim dijabetesom, srčanim bolestima i imunodeficijenciji.

U literaturi se navode mnoge analize na velikim serijama bolesnika (Rosato 14,934; Thomusch 4000; Tartaglia 1636; Muller 1031; Rios 301 bolesnik), koje nesusstavno analiziraju rizične čimbenike u nastajanju komplikacija u kirurgiji štitnjače. Prema nekima kirurško iskustvo je važan čimbenik u nastajanju komplikacija u kirurgiji štitnjače (Acun). Prema drugima uzrok treba tražiti u veličini, težini, intratorakalnom položaju štitnjače, dobi bolesnika, trajanju samog zahvata. Radovi Thomuscha i Hermana ukazuju na to da su kod muškaraca češće komplikacije povezane s lezijom povratnog živca i hipoparatiroidizma.

Zahvaljujući prijeoperacijskoj pripremi bolesnika, anesteziji, kirurškoj tehnici i boljem poznavanju kirurške anatomije štitnjače, danas su poslijeoperacijske komplikacije kod totalne tireoidektomije u stalnom padu. Dvije najozbiljnije komplikacije totalne tireoidektomije su svedene su na najmanju mjeru, a to su ozljeda povratnog živca na 1% te hipoparatiroidizam na 3% slučajeva.



## TREATMENT OF POSTOPERATIVE HYPOCALCEMIA

### LIJEČENJE POSTOPERACIJSKE HIPOKALCEMIJE

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Postoperative hypocalcemia is one of the most common complications of thyroid surgery. It is related to the type of disease (malignant or benign), number of parathyroid glands identified during surgical procedure, reoperation and the surgeon's experience.

Postoperative hypoparathyroidism can be temporary or permanent. The incidence of permanent hypoparathyroidism has been reported to range from as high as more than 20%, when total thyroidectomy and radical neck dissection are performed, to as low as 0.9%; however, there are reports on an even lower incidence of permanent hypoparathyroidism.

Operative strategies to prevent postoperative hypoparathyroidism include preservation of parathyroid glands *in situ* and autotransplantation of parathyroid glands during total thyroidectomy.

Postoperative hypoparathyroidism results in hypocalcemia, hyperphosphatemia, and low parathyroid hormone (PTH) level. Intraoperative PTH at 20 to 30 minutes after total thyroidectomy can predict impending postoperative hypocalcemia.

Acute hypocalcemia directly causes increased neuromuscular irritability, and this pathophysiology underlies the most prominent symptoms. Tetany is seen in more severe hypocalcemia.

If there is any doubt, the presence of hypocalcemia needs to be confirmed by the measurement of serum ionized calcium. The diagnosis is confirmed by a finding of serum calcium  $< 2.05$  mmol/L or ionized calcium  $< 1.1$  mmol/L.

Patients with acute symptomatic hypocalcemia (serum calcium  $< 0.8$  mmol/L) should be treated promptly with IV calcium. Calcium gluconate is preferred to calcium chloride because it causes less tissue necrosis if extravasated. The first 100 to 200 mg of elemental calcium (1 to 2 g calcium gluconate) should be given over 10 to 20 minutes. Faster administration may result in cardiac dysfunction, or even arrest. This should be followed by slow

Postoperacijska hipokalcemija jedna je od čestih komplikacija operacijskog zahvata na štitnjače. Njena učestalost ovisi o vrsti bolesti (zloćudna ili dobroćudna), broju identificiranih paratireoidnih žlijezda tijekom operacijskog zahvata, reoperaciji i iskustvu operatera.

Postoperacijski hipoparatireoidizam može biti privremeni i trajni. Učestalost trajnog hipoparatireoidizma po podacima iz literature iznosi i preko 20% kod totalne tireoidektomije i radikalne disekcije vrata pa do niskih 0.9%. Neki vrsni operateri izvješćuju o vrlo maloj učestalosti trajnog hipoparatireoidizma nakon operacijskog zahvata.

Operacijska strategija prevencije postoperacijskog hipoparatireoidizma uključuje čuvanje paratireoidnih žlijezda „in situ“ i autotransplantaciju paratireoidnih žlijezda tijekom totalne tireoidektomije.

Postoperacijski hipoapatireoidizam se očituje hipokalcemijom, hiperfosfatemijom i niskom koncentracijom paratireoidnog hormona. Vrijednost intraoperacijskog PTH određivanog između 20 i 30 min. nakon totalne tireoidektomije može biti važan predkazatelj predstojeće postoperacijske hipokalcemije.

Za utvrđivanje hipokalcemije potrebno je određivanje koncentracije ioniziranog kalcija u serumu. Ukoliko je serumska koncentracija ukupnog kalcija  $< 2.05$  ili ioniziranog  $< 1.1$  mmol/L, dijagnoza hipokalcemije sigurno je potvrđena.

Bolesnici sa akutnim znacima hipokalcemije (serumski kalcij  $< 0.8$  mmol/L) moraju biti odmah liječeni i.v. davanjem kalcija. Kalcijev karbonat ima prednost nad kalcijevim kloridom zbog manje učestalosti izvanžilne nekroze. Prvih 100 do 200 mg elementarnog kalcija (1 do 2 g kalcijevog glukonata) treba dati kroz 10 do 20 min. Brža aplikacija može uzrokovati srčane poremećaje sve do zastoja rada srca. Nakon toga daje se lagano u infuziji kalcij od 0.5 do 1.5 mg/kg/h. Infuzija kalcija daje se kontinuirano sve do postizanja zadovoljavajuće doze oralnog kalcija i preparata D vitamina.

calcium infusion at 0.5 to 1.5 mg/kg/h. Calcium infusion should be continued until the patient can receive effective doses of oral calcium and vitamin D.

Chronic hypocalcemia is treated by the administration of oral calcium and, if it is insufficient, vitamin D supplementation (0.25 to 0.50 mg of 1,25-(OH) vitamin D is the usual initial daily dose). Appropriate doses of calcium and vitamin D are established by gradual titration. The serum calcium level should be targeted to about 2.0 mmol/L. Most patients will be entirely asymptomatic at this level, and further elevation will lead to hypercalciuria because of the lack of PTH effect on the renal tubules. Chronic hypercalciuria may lead to the development of nephrocalcinosis, nephrolithiasis, renal impairment, and should be avoided.

With the recent availability of synthetic PTH preparations (1-34 PTH, teriparatide), several reports have described successful control of hypocalcemia with a lower risk of hypercalciuria using twice-daily subcutaneous administration.

Kronična hipokalcemija liječi se davanjem peroralnog kalcija a ukoliko je to nedostavno dodaje se D vitamin u početnoj dnevnoj dozi od 0.25 do 0.50 mcg 1,25-(OH) vitamin D.

Odgovarajuća doza kalcija i vitamina D određuje se postupnim titriranjem doze. Ciljna vrijednost serumskog kalcija treba se kretati oko 2.0 mmol/L. Mnogi bolesnici nemaju znakova hipokalcemije kod tih vrijednosti serumskoga kalcija pa veće terapijske doze mogu uzrokovati hiperkalciuriju zbog izostanka učinka PTH na tubule bubrega. Kronična hiperkalciurija može biti podloga za razvoj nefrokalcinoze, nefrolitijaze i oštećenja bubrežne funkcije.

Nekoliko novijih izvješća opisuje korisnost davanja sintetskog preparata PTH (1-34 PTH, teriparatide) uz dobru kontrolu hipokalcemije i uz niski rizik od nastanka hiperakcemije. Preparat se daje subkutano u dvije dnevne doze.

## CURRENT CONTROVERSIES IN TREATMENT AND FOLLOW-UP OF PATIENTS WITH THYROID CANCER

### RAZLIČITI PRISTUPI U LIJEČENJU I PRAĆENJU BOLESNIKA S RAKOM ŠTITNJAČE

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#### Background

Although rare among human malignancies, thyroid cancer is the most frequent endocrine cancer, occurring in about 5% of patients with thyroid nodules, and is among the three human cancers showing a continuous increase year by year. Thyroid cancer is treated by different specialists (including endocrinology, internal medicine, nuclear medicine, oncology, surgery and even general practice), operating in different settings and thus too often the same disease is managed in different ways. As a consequence, both diagnostic and therapeutic controversies still exist. Diagnostic and treatment tools have

#### Uvod

Iako rijetka maligna bolest, rak štitnjače najčešći je rak endokrinih organa i javlja se u otprilike 5% bolesnika sa čvorovima u štitnjači. Jedan je od tri vrste raka u ljudi incidencija kojih se svake godine povećava. Rakom štitnjače bave se specijalisti različitih profila (endokrinolozi, internisti, specijalisti nuklearne medicine, onkolozi, kirurzi pa čak i obiteljski liječnici) pa se često istoj bolesti pristupa na različite načine. Posljedica toga su postojeći sporovi u dijagnostici i liječenju. Dijagnostičke i terapijske metode su tijekom proteklih godina napredovale (osjetljivi imunoenzimski testovi za mje-



improved in recent years (sensitive assays for serum Thyroglobulin (Tg) measurement, neck ultrasonography (US), recombinant human TSH), thus allowing less invasive and less uncomfortable procedures for patients. Altogether, these considerations dictate the need of applying more appropriate, less invasive and less expensive procedures able to guarantee the best management and the best quality of life for a disease that in view of its intrinsic low mortality has to face lifelong follow up. Several societies have developed thyroid cancer guidelines in Europe and America, based on the experience and cultural attitude of the country. However, they differ in several, sometimes important, respects. The main controversies are focused on surgical treatment, postoperative administration of radioiodine, and follow up.

### Surgical treatment

Surgery of thyroid cancer should be performed by experienced surgeons embedded in multidisciplinary teams specifically trained in thyroid cancer surgery. Whenever the diagnosis of thyroid cancer has been made by FNAC, the standard surgical treatment is total (or near-total) thyroidectomy. This procedure decreases the risk of local recurrence and is performed with almost no morbidity under expert hands. More limited thyroidectomy should not be performed, and if a patient is referred after less than near total thyroidectomy, completion thyroidectomy should be proposed in case of large tumor, multifocality, extrathyroidal extension and/or vascular invasion evidence of local or distant metastases, previous history of radiation exposure or unfavorable histology. Depending on the size of the thyroid remnant, an effective alternative to completion thyroidectomy when the risk of persistent disease is low, may be radioiodine ablation of the residual thyroid tissue. Compartment-oriented microdissection of lymph nodes should be performed in cases with preoperative suspected and/or intraoperatively proven lymph node metastases. Children and adolescents should be treated with the same surgical procedure as the adults, provided they are treated by an experienced surgeon.

### Postoperative radioiodine administration (Thyroid ablation)

Thyroid ablation refers to the postoperative administration of  $^{131}\text{I}$  aimed to destroy any thyroid residue in the thyroid bed. Three groups of patients can be individualized according to the surgeon's and pathologist's reports:

renje serumske razine tireoglobulina, ultrazvuk vrata, rhTSH) te postale manje invazivne i neugodne za bolesnike. Sve to ukazuje na nužnost odgovarajućih, manje invazivnih i jeftinijih metoda koje bi osigurale najkvalitetnije liječenje i najbolju kvalitetu života za bolesnike u kojih su, s obzirom na nisku stopu smrtnosti raka štitnjače, kontrole doživotne. Neke europske i američke organizacije izradile su smjernice za rak štitnjače utemeljene na iskustvu i kulturološkim značajkama pojedinih zemalja. Međutim, one se razlikuju u nekim, ponekad vrlo važnim stavovima. Najspornije su smjernice vezane uz kirurško liječenje, poslijeoperacijsku primjenu radioaktivnog joda i sustavno praćenje.

### Kirurško liječenje

Kirurškim liječenjem raka štitnjače trebali bi se baviti iskusni kirurzi uključeni u primjereno obrazovane multidisciplinarnih timove. U slučaju citološkom punkcijom utvrđene dijagnoze raka štitnjače, totalna (ili subtotalna) tireoidektomija je standardni zahvat izbora kojim se smanjuje rizik od lokalnog recidiva, a smrtnost je gotovo nikakva ako ga izvode iskusni stručnjaci. Poštedni zahvat nije preporučljiv, a u bolesnika u kojih je učinjena djelomična tireoidektomija, odstranjenje ostatnog tkiva štitnjače potrebno je u slučaju velikog tumora, multifokalnih žarišta, širenja tumora izvan štitnjače, invazije krvnih žila, lokalnih ili udaljenih metastaza, prethodne izloženosti zračenju ili nepovoljne histološke dijagnoze. Ovisno o količini ostatnog tkiva štitnjače, u slučaju male vjerojatnosti zaostataka tumorskog tkiva alternativa ponovnoj operaciji može biti radiojodna ablacija preostalog tkiva štitnjače. Mikrodisekcija određenih skupina limfnih čvorova nužna je u slučajevima prijeoperacijski sumnjivih i/ili intraoperacijski dokazanih metastaza u limfnim čvorovima. Djecu i adolescente potrebno je liječiti na isti način kao i odrasle osobe, pod uvjetom da ih operiraju iskusni kirurzi.

### Poslijeoperacijska primjena radioaktivnog joda (ablacija štitnjače)

Ablacija štitnjače je postupak poslijeoperacijske primjene  $^{131}\text{I}$  s ciljem uništavanja ostatnog tkiva štitnjače u samom ležištu. Prema nalazima kirurga i patologa moguće je razlikovati tri skupine bolesnika:

**Skupina s vrlo niskim rizikom:** bolesnici s unifokalnim mikrokarcinomom ( $\leq 1$  cm) koji ne probija čahuru štitnjače, bez metastaza u limfnim čvorovima. U ovoj skupini nema dokaza o koristi od poslijeoperacijske primjene  $^{131}\text{I}$  te ju ne treba provoditi.





**Very low risk group:** patients with unifocal microcarcinoma ( $\leq 1$  cm) with no extension beyond the thyroid capsule and without lymph node metastases. In this group there is no evidence of any benefits from postoperative  $^{131}\text{I}$  administration that should not be performed.

**High risk group:** patients with documented persistent disease or at a high risk of persistent or recurrent disease. In this group postoperative  $^{131}\text{I}$  administration reduces the recurrence rate and possibly prolongs survival; it also permits early detection of persistent disease. A high activity of radioiodine is indicated.

**Low risk group:** includes all other patients. The benefits of thyroid ablation are controversial and there are still uncertainties whether it should be administered to all patients or only to selected patients.

In any case, the value of a diagnostic scan before thyroid ablation has been questioned based on its low clinical utility, the possibility of a stunning effect on the subsequent therapeutic activity of  $^{131}\text{I}$ , and the consideration that post-therapy WBS performed 3-5 days after the radioiodine administration is much more sensitive than diagnostic WBS. Thus, this procedure may be avoided without loss of information. The administered  $^{131}\text{I}$  activity ranges among centers between 1110 MBq (30 mCi) (low activity) and 3700 MBq (100 mCi) or even more (high activity). A post-ablation WBS should be performed 3 to 5 days after the administration of  $^{131}\text{I}$ .

## Follow-up after initial treatment

### *Physical examination and neck ultrasonography*

Physical examination is poorly sensitive for the detection of persistent or recurrent disease in the neck. Neck US is more sensitive than neck palpation and is routinely used for assessing lymph node chains as well as the thyroid bed. The specificity of neck US is improved by performing US guided FNA for cytology and Tg measurement in the aspirate fluid.

### *Serum thyroglobulin (Tg) determination*

Tg is a specific and extremely useful tumor marker for the follow up of patients with papillary and follicular thyroid carcinoma. Serum Tg should be measured using a sensitive IRMA assay (functional sensitivity  $< 1.0$  ng/mL) standardized on the European reference standard (CRM 457). When using such methods, the presence of anti-Tg antibodies in the circulation may interfere with the assay, leading to false negative serum Tg determination. Thus, the presence of anti-Tg antibodies must

**Visokorizična skupina:** bolesnici koji imaju potvrđenu stalno prisutnu bolest ili visok rizik stalno prisutne bolesti ili recidiva bolesti. U ovoj skupini poslijeoperacijska primjena  $^{131}\text{I}$  smanjuje postotak recidiva i vjerojatno produžuje preživljenje; također omogućuje rano otkrivanje tumorskog tkiva odnosno recidiva bolesti. Indicirana je primjena visoke doze radioaktivnog joda.

**Niskorizična skupina:** uključuje sve preostale bolesnike. Pozitivni učinci ablacije štitnjače su upitni i još uvijek postoje dvojbe je li ona potrebna svim bolesnicima ili samo pomno odabranima.

Vrijednost dijagnostičke scintigrafije prije radiojodne ablacije ostatnog tkiva štitnjače još uvijek je upitna s obzirom na njenu malu kliničku važnost, mogućnost smanjivanja učinka terapijske primjene  $^{131}\text{I}$  i činjenicu da je poslijeterapijska scintigrafija cijelog tijela učinjena 3-5 dana nakon primjene radioaktivnog joda znatno osjetljivija od dijagnostičke scintigrafije cijelog tijela. Dakle, bez primjene te metode nema značajnijeg gubitka podataka. Doza primijenjenog  $^{131}\text{I}$  iznosi od 1110 MBq (30 mCi) (mala aktivnost) do 3700 MBq (100 mCi) ili više (visoka aktivnost), ovisno o centru. Poslijeablacijsku scintigrafiju cijelog tijela potrebno je učiniti 3 do 5 dana nakon primjene  $^{131}\text{I}$ .

## Praćenje bolesnika nakon primarnog liječenja

### *Fizikalni pregled i ultrazvuk vrata*

Osjetljivost fizikalnog pregleda u otkrivanju zaostale bolesti ili recidiva je vrlo mala. Ultrazvuk vrata je osjetljiviji od palpacije i redovito se rabi za pregled limfnih čvorova vrata i ležišta štitnjače. Specifičnost ultrazvuka vrata povećana je primjenom citološke punkcije pod kontrolom ultrazvuka te mjerenjem razine tireoglobulina u aspiratu.

### *Određivanje serumske razine tireoglobulina*

Tireoglobulin (Tg) je specifičan i vrlo koristan tumorski biljeg u praćenju bolesnika s papilarnim ili folikularnim karcinomom štitnjače. Serumsku razinu Tg potrebno je mjeriti osjetljivim imunoenzimskim testom IRMA (osjetljivost  $< 1,0$  ng/mL) standardiziranim prema Europskim standardnim preporukama (CRM 457). Kod primjene takvih metoda prisutnost anti-Tg protutijela može prouzročiti lažno negativan nalaz Tg u serumu. Zbog toga je prisutnost anti-Tg protutijela potrebno isključiti izravnim mjerenjem njihove razine, a ne "recovery" testom.

Nakon totalne ablacije štitnjače operacijskim odstranjenjem i primjenom radioaktivnog joda razina Tg mora

be ruled out by direct measurement of anti-Tg antibodies to be preferred to the Tg recovery test.

After total thyroid ablation by surgery and radioiodine, the Tg level should be undetectable and any detectable level should alert the clinician. The rare false negative serum Tg determinations are mainly due to small lymph node metastases that are demonstrated by neck US. TSH stimulation increases the sensitivity of serum Tg determination for the detection of persistent or recurrent disease. TSH stimulation can be achieved by thyroid hormone withdrawal or recombinant human TSH (rhTSH) injections.

Complementary imaging modalities include CT scan of the neck and lungs, MRI of bones and brain, as indicated.

At 6-12 months after initial treatment, disease status is assessed by physical examination, neck US, and serum Tg determination after stimulation with rhTSH. Low risk patients with a normal US and an undetectable serum Tg following rhTSH are considered cured as subsequent recurrences are very rare (<1% at 10 years). Diagnostic WBS is indicated by some authors in high risk patients or when the post-ablation WBS was poorly informative due to the high uptake in thyroid remnants or when it disclosed suspected uptake. Suspected findings at neck US should be submitted to further testing. Patients with detectable serum Tg following rhTSH stimulation in the range of 1-2 ng/mL should be submitted to an additional Tg stimulation test with rhTSH 1-2 years later. If serum Tg becomes undetectable, the patient is considered cured. If serum Tg increases above its previous level, recurrent disease should be sought, and CT scan of the neck and chest is performed and therapeutic activity of <sup>131</sup>I is administered. Very low risk patients, eventually treated with lobectomy are followed periodically by neck US and serum Tg measurement on LT4 treatment.

In low risk patients with no evidence of disease at the 9- to 12-month assessment, the LT4 dose is decreased, with the goal of obtaining a TSH level within a lower normal range. In patients initially considered at a high risk, it may be safer to maintain serum TSH at a low level for 3-5 years. Even in these patients, the risk of recurrence is low when there is no evidence of disease and they can be reclassified as low risk. Follow up should be continued for life.

biti nemjerljiva, a bilo koja mjerljiva razina Tg je važan znak za kliničare. Rijetka pojava lažno negativnog nalaza Tg u serumu uglavnom je rezultat metastaza u malim limfnim čvorovima vrata, koje se registriju ultrazvukom. Stimulacija tireotropinom (TSH) povisuje osjetljivost određivanja serumske razine Tg za otkrivanje stalno prisutne bolesti ili recidiva bolesti. Stimulacija pomoću TSH može se postići prekidom liječenja hormonima štitnjače ili primjenom rekombinantnog humanog TSH (rhTSH). Dodatni slikovni prikazi uključuju CT vrata i pluća, MR kostiju i mozga, ovisno o indikaciji.

Šest do dvanaest mjeseci nakon inicijalnog liječenja stadij bolesti procjenjuje se fizikalnim pregledom, ultrazvukom vrata i određivanjem serumske razine Tg nakon rhTSH stimulacije. Niskorizični bolesnici s urednim ultrazvučnim nalazom i nemjerljivom serumskom razinom Tg smatraju se izliječenima i recidivi su kod njih vrlo rijetki (<1% u 10 godina). Prema nekim autorima dijagnostička scintigrafija cijelog tijela je indicirana u visokorizičnih bolesnika i u slučaju velikog nakupljanja u ostatnom tkivu štitnjače ili sumnjivog nakupljanja na poslijeablaćijskim scintigramima. Sumnjiv ultrazvučni nalaz potrebno je dodatno istražiti. U bolesnika u kojih serumska razina Tg nakon TSH stimulacije iznosi 1-2 ng/mL potrebno je ponoviti test stimulacije nakon 1-2 godine. Ako serumska razina Tg postane nemjerljiva, bolesnik se smatra izliječen. Ako serumska razina Tg poraste u odnosu na prethodnu vrijednost, potrebno je potražiti recidiv, učiniti CT vrata i toraksa i terapijski primijeniti <sup>131</sup>I. Bolesnike s vrlo niskim rizikom u kojih je učinjena lobektomija potrebne su periodične kontrole ultrazvukom vrata i mjerenjem serumske razine Tg uza supstitucijsku terapiju.

U niskorizičnih bolesnika bez dokaza bolesti nakon 9-12 mjeseci potrebna doza T4 se smanjuje s ciljem održavanja razine TSH na donjoj granici normale. U bolesnika koji su smatrani visokorizičnima sigurnije je održavati serumsku razinu TSH niskom tijekom 3-5 godina. Čak u i tih bolesnika rizik recidiva je nizak ako nema dokaza bolesti te ih se može tada smatrati niskorizičnima. Nužno je doživotno praćenje.

## RADIOIODINE ABLATION OF THYROID REMNANT RADIOJODNA ABLACIJA OSTATNOG TKIVA ŠTITNJAČE

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Ablation of thyroid remnants or metabolically active metastases with radioiodine is a usual procedure after surgical ablation of the thyroid in patients with differentiated thyroid carcinoma.

There are five categories of thyroid cancer patients who are candidates for radioiodine treatment. Group 1 are patients with normal thyroid remnants. The aim of treatment is to reduce normal tissue function. Group 2 are patients with a very small amount of thyroid tissue, which is now the case after surgical treatment by an experienced surgeon. In some cases, the application of I-131 is questionable. Group 3 patients are those with metastases in lymph nodes. Group 4 are patients with distant metastases, and group 5 are patients without scintigraphic evidence of thyroid tissue but elevated serum thyroglobulin concentration.

There are two approaches to determine the radioiodine ablation dose. One is empirical and the dose may vary from 30 to 300 mCi. Patients with only thyroid remnants, groups 1 and 2, receive 30-100 mCi. For patients with local lymph node metastases, the recommended dose is 100-150 mCi. For patients with distant metastases and those without evidence of thyroid tissue on the scan but elevated thyroglobulin the recommended dose is 100-300 mCi.

Second approach to determine the radioiodine ablation dose is dosimetric. For a particular patient the dose is calculated according to dosimetric calculations.

Therapy with I-131, even with large doses, is safe. Some patients develop anorexia, nausea and very rarely vomiting. Radiation thyroiditis is uncommon because of surgical removal of thyroid tissue. In about 10% of patients sialoadenitis is observed. Radiation pneumonitis occurs in some patients with diffuse pulmonary metastases. The effect on hematopoietic tissue is transient. However, large doses of up to 37 GBq (1Ci) can produce pancytopenia and leukemia.

Absolute contraindications for I-131 treatment are: pregnancy, lactation in a nursing mother, and insufficient uptake of I-131. Questionable contraindications are age and ophthalmopathy.

Ablacija ostatnog tkiva ili metabolički aktivnih metastaza radioaktivnim jodom je uobičajen postupak nakon kirurške ablacije štitnjače kod bolesnika s diferenciranim karcinomom štitnjače.

Postoji 5 kategorija bolesnika s karcinomom štitnjače koji su kandidati za terapiju radioaktivnim jodom. Prvu skupinu čine bolesnici s normalnim ostatnim tkivom. Liječenjem se želi smanjiti funkcija normalnog tkiva. Drugu skupinu čine bolesnici s vrlo malom količinom tkiva štitnjače, što je danas slučaj nakon kirurškog zahvata iskusnih kirurga. U nekim je slučajevima primjena I-131 dvojbena. Treću skupinu bolesnika čine oni s metastazama u limfnim čvorovima. Četvrtu skupinu čine bolesnici s udaljenim metastazama, a petu oni bez scintigrafskih dokaza o tkivu štitnjače, no kod kojih je povišena koncentracija seruma tireoglobulina.

Postoje dva pristupa za određivanje doze kod radiojodne ablacije. Prvi je empirijski, a doza se kreće između 30 i 300 mCi. Bolesnici prve i druge skupine s ostatnim tkivom primaju 30-100 mCi. Za bolesnike s lokalnim metastazama u limfnim čvorovima preporučena doza je 100-150 mCi. Preporučena doza od 100-300 mCi odnosi se na bolesnike s udaljenim metastazama i one kod kojih nema dokaza o tkivu štitnjače, ali imaju povišen tireoglobulin.

Drugi pristup za određivanje doze kod radiojodne ablacije je dozimetrijski. Za dotičnog bolesnika doza se izračunava prema dozimetrijskim proračunima.

Terapija pomoću I-131 je sigurna i kod velikih doza. Neki bolesnici imaju anoreksiju, mučninu, a rijetko i povraćanje. Radijacijski tireoiditis je neuobičajen, jer je tkivo štitnjače kirurški uklonjeno. Kod 10% bolesnika primijećen je sialoadenitis. Radijacijski pneumonitis je primijećen kod nekih bolesnika s raširenim plućnim metastazama. Utjecaj na krvotvorno tkivo je prolazan. Međutim, velike doze do 37 GBq (1Ci) mogu prouzročiti pancitopeniju i leukemiju.

Apsolutne kontraindikacije za liječenje pomoću I-131 su: trudnoća, dojenje i niska akumulacija I-131. Relativne kontraindikacije su dob i oftalmopatija.



## RADIOIODINE TREATMENT OF METASTATIC THYROID CARCINOMA

### LIJEČENJE METASTATSKOG RAKA ŠTITNJAČE RADIOAKTIVNIM JODOM

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Radioiodine has been used in the treatment of metastatic thyroid cancer for more than fifty years. About two thirds of metastases from papillary and follicular thyroid cancer concentrate and retain radioiodine. This ability is fundamental for radioiodine ( $^{131}\text{I}$ ) therapy. The metabolism of  $^{131}\text{I}$  in thyroid cancer cells is profoundly altered. Cancer cells have a diminished ability to concentrate and retain  $^{131}\text{I}$  as compared with normal thyroid tissue, especially in elderly patients, patients with advanced disease and those with more aggressive thyroid cancer. Several defects have been identified at cellular level: decreased expression of sodium-iodide symporter, markedly reduced organification and shorter effective half life of iodine in tumor tissue. Unlike many tumor types, removal of thyroid as well as primary tumor in patients with metastatic differentiated cancer is necessary to enable treatment with  $^{131}\text{I}$ . Lungs and bones, especially spine are the most common distant metastatic sites in patients with differentiated thyroid cancer. There are three approaches to  $^{131}\text{I}$  therapy: empiric fixed doses, upper bound limits that are set by blood and whole body dosimetry, and the third approach is quantitative tumor dosimetry. At the present time there is no evidence that one approach is better than the other. The most widely used and simplest method is the application of empiric fixed doses in a range from 3.7 to 11.1 GBq (100-300 mCi). Cervical nodal and mediastinal metastases, if surgical treatment is not possible, are treated with doses from 100 to 175 mCi. Distant metastases are treated with doses from 200 to 300 mCi. Diffuse pulmonary metastases are treated with doses of 150 mCi or less to avoid lung fibrosis that may occur if  $^{131}\text{I}$  retention in the whole body 48 hours after administration is higher than 80 mCi. The aim of whole body and blood  $^{131}\text{I}$  dosimetry is to use the largest safe dose of  $^{131}\text{I}$  without exceeding safety limits set by blood (bone mar-

Radioaktivni jod se rabi u liječenju metastaza diferenciranog karcinoma štitnjače više od 50 godina. Oko dvije trećine metastaza papilarnog i folikularnog karcinoma štitnjače ima sposobnost nakupljanja i zadržavanja joda, što je osnovni preduvjet za liječenje jodom-131. Stanice diferenciranog karcinoma štitnjače znatno slabije nakupljaju i zadržavaju jod u odnosu na normalno tkivo štitnjače, osobito u starijih bolesnika, bolesnika s uznapredovalim tumorom i agresivnijim oblikom diferenciranog karcinoma štitnjače. Na staničnoj razini utvrđeno je nekoliko poremećaja od kojih su najvažniji slabija izraženost natrij-jodid kotransportne molekule, slabija organifikacija i kraći efektivni poluzivot joda u tumoru. Za razliku od drugih tumora, neophodno je kod metastaza diferenciranog karcinoma štitnjače odstraniti štitnjaču zajedno s primarnim tumorom kako bi se omogućila terapijska primjena joda-131. Kod diferenciranog karcinoma štitnjače najčešće nalazimo plućne i koštane metastaze, osobito metastaze u kralježnicu. Razlikujemo tri pristupa terapiji jodom-131: empirijske fiksne doze, najveće sigurne doze temeljene na dozimetriji cijelog tijela i krvi, a treći pristup je kvantitativna tumorska dozimetrija. Do danas nema sigurnih dokaza da je jedan pristup bolji od drugog. Danas se najčešće rabe empirijske fiksne doze u rasponu od 3,7 do 11,1 GBq (100-300 mCi). Sekundarizmi u limfnim čvorovima vrata i mediastinuma, ako nisu pogodni za operacijski zahvat, liječe se dozama od 100 do 175 mCi, a udaljene metastaze od 200 do 300 mCi. Difuzne plućne metastaze diferenciranog karcinoma štitnjače liječe se dozom od 150 mCi ili manje kako bi se izbjegla plućna fibroza koja može nastati ako je zadržavanje joda-131 u cijelom tijelu 48 sati nakon primjene veće od 80 mCi. Svrha metode dozimetrije krvi i cijelog tijela koju je uspostavio Benua prije više od četiri desetljeća temelji se na primjeni najveće sigurne doze joda-131, a da se ne prekorači sigurna grani-





row). The method was introduced by Benua forty years ago. The currently accepted upper dose limit is calculated to deliver a maximum of 200 cGy to the whole blood while keeping the whole body  $^{131}\text{I}$  retention less than 120 mCi at 48 hours or less than 80 mCi when there is diffuse pulmonary uptake to avoid lung fibrosis. Quantitative tumor dosimetry estimates uptake and retention of  $^{131}\text{I}$  in tumor tissue to determine radiation dose to each lesion (the ratio between total uptake in the lesion and the mass of the lesion) integrated over time during which it remains in the lesion. The estimation of the mass of the lesion is often difficult and determination of the uptake with time requires multiple measurements. The data are collected one or more times daily during 72 to 96 hours. The aim of quantitative dosimetry is to deliver an acceptable radiation dose to the metastatic lesion without exceeding safety limits that are set by blood (bone marrow) and whole body. The cancer is unlikely to respond to  $^{131}\text{I}$  therapy if the tumor dose is less than 35 Gy while keeping the applied dose within safety limits. Radiation dose that is necessary to cure most of metastatic lesions should be around 80 to 120 Gy. Quantitative tumor dosimetry is a very complicated procedure that can only be applied in specialized medical centers, usually in patients with distant metastases with low uptake of  $^{131}\text{I}$ , in patients with renal failure or when therapy with recombinant human TSH (rhTSH) is deemed necessary. Diffuse pulmonary metastases in young patients are successfully treated with  $^{131}\text{I}$ , especially those seen only on whole body scintigraphy with  $^{131}\text{I}$ , and not with radiological methods. Bone metastases are generally resistant to treatment with  $^{131}\text{I}$ , especially large metastases. Older age and multiple metastases are usually associated with worse prognosis. The standard preparation for treatment with  $^{131}\text{I}$  involves thyroid hormone withdrawal for four to six weeks before treatment with  $^{131}\text{I}$  to elevate TSH level, usually  $>30$  mU/L. In order to augment the efficacy of  $^{131}\text{I}$  treatment, the patient is instructed to be on low iodine diet with restriction of daily iodine intake of about 50  $\mu\text{g}$ . It can be achieved by restriction of iodized salt, dairy products, eggs, sea food, especially shells, vitamins and medications that contain iodine. With restriction of iodine intake, the uptake of  $^{131}\text{I}$  in tumor tissue can double, but it may increase total body radiation as a result of delayed clearance. The diet should be started two weeks before  $^{131}\text{I}$  therapy and continued for several days thereafter. When there is doubt in iodine contamination, the measurement of urinary iodine excretion is recommend-

ca za krv odnosno koštanu moždinu koja danas iznosi 200 cGy, uz uvjet da zadržavanje joda-131 u cijelom tijelu 48 sati nakon primjene bude manje od 120 mCi ili manje od 80 mCi u slučaju difuznih plućnih metastaza kako bi se izbjegla plućna fibroza. Kvantitativnom dozimetrijom nakupljanja i zadržavanja joda-131 u tumoru određuje se radijacijska doza na svaku metastazu, što označava koncentraciju joda-131 u tumoru (kvocijent ukupnog nakupljanja joda-131 u tumoru i mase tumora) integriranu kao funkciju vremena u kojem se zadržava u tumoru. Procjena mase pojedine metastaze često je teška, a određivanje nakupljanja joda-131 u vremenu zahtijeva ponavljana mjerenja. Podaci se prikupljaju jednom ili više puta na dan tijekom 72 do 96 sati. Cilj kvantitativne tumorske dozimetrije je primjena dostatne doze radijacije na pojedinu metastatsku leziju, a da se pritom ne prekorače sigurne granice za krv (koštanu srž) i cijelo tijelo. Ako je izračunata radijacijska doza na pojedinu metastatsku leziju manja od 35 Gy, a dosegnuta je sigurnosna granica za krv odnosno cijelo tijelo, tada jod-131 vjerojatno neće imati terapijski učinak i treba razmotriti drugu mogućnost liječenja metastatske bolesti. Radijacijska doza neophodna za razaranje većine metastaza mora biti oko 80 do 120 Gy. Kvantitativna tumorska dozimetrija je vrlo složen postupak koji se može primjenjivati samo u specijaliziranim centrima, a najčešće se primjenjuje u bolesnika s udaljenim metastazama koje slabije nakupljaju  $^{131}\text{I}$ , u bolesnika sa zatajenjem bubrega ili u bolesnika u kojih se primjenjuje rekombinantni humani TSH (rhTSH). Radioaktivnim jodom osobito se dobro liječe difuzne milijarne plućne metastaze u mlađih bolesnika, koje se mogu zabilježiti samo scintigrafijom cijelog tijela jodom-131, a ne radiološkim metodama. Koštane metastaze su često otporne na liječenje jodom-131, osobito veće metastaze. Općenito lošu prognozu imaju stariji bolesnici i bolesnici s višestrukim metastazama. Uobičajeni postupak pripreme bolesnika za liječenje jodom-131 sastoji se od prekida hormonske supresijske terapije L-tiroksinom u trajanju od četiri do šest tjedana prije primjene kako bi se postigao porast TSH, obično iznad 30 mU/L. Kako bi se povećao učinak terapijske primjene joda-131 bolesniku se savjetuje pridržavanje dijete s malo joda kojom se ograničava dnevni unos joda na oko 50  $\mu\text{g}$ . Preporuča se smanjiti unos jodirane soli, izbjegavati mlijeko i mliječne proizvode, jaja, suhomesnate proizvode, hranu podijetlom iz mora, osobito školjke, te vitamine i lijekove koji sadrže jod. Ograničenim unosom joda nakupljanje joda-131 u tumoru može se čak udvostručiti, ali to može povećati dozu radi-





ed. If urinary iodine concentration is elevated  $>200 \text{ }\mu\text{g/L}$ , then  $^{131}\text{I}$  therapy should be postponed until urinary iodine level returns to normal. If there is a possibility for routine urinary iodine measurement, this procedure is recommended in all patients before treatment with  $^{131}\text{I}$ . The application of rhTSH as preparation for  $^{131}\text{I}$  therapy is also possible in patients with distant metastases, in which case they do not need thyroid hormone withdrawal. rhTSH mediated therapy may be indicated in selected patients unable to raise their serum TSH level after thyroid hormone withdrawal because of large remnant tissue or massive functional metastases, pituitary or hypothalamic disease, in patients with underlying comorbidities making iatrogenic hypothyroidism potentially risky, or if the patient needs urgent treatment. Lithium can increase retention of  $^{131}\text{I}$  in tumor tissue making treatment with  $^{131}\text{I}$  more effective. Lithium inhibits iodine release from the thyroid without impairing iodine release. Radiation dose to metastatic lesion is on an average twofold with the use of lithium, especially in those tumors that rapidly clear iodine. The drug should be started a week before  $^{131}\text{I}$  treatment and continue several days thereafter. However, it is necessary to continuously measure lithium levels in blood because of lithium toxicity.

In patients with elevated thyroglobulin (Tg) level and negative diagnostic whole body scan there has been a trend toward using  $^{131}\text{I}$  therapy, usually 100 mCi, because some metastases can only be detected on scans after therapy. In some patients with elevated Tg level occult disease can be detected with this strategy as confirmed by pathologic findings on scans after therapy, and beneficial therapeutic effect of  $^{131}\text{I}$  has also been reported. If there is no pathologic accumulation of  $^{131}\text{I}$  on scans after therapy, further diagnostic studies should be done (computed tomography, nuclear magnetic resonance, and positron emission tomography (PET) with  $^{18}\text{F-FDG}$ ). Metastases of differentiated thyroid cancer that are PET positive are less differentiated, with worse prognosis and usually do not accumulate  $^{131}\text{I}$ . In some patients with metastases of differentiated thyroid cancer that do not accumulate  $^{131}\text{I}$  there were attempts to restore accumulation of  $^{131}\text{I}$  in metastatic lesion with retinoic acid that has redifferentiating properties. However, most patients did not benefit from this approach.

jacije na cijelo tijelo kao rezultat produženog klirensa. Dijetu s malo joda treba započeti dva tjedna prije primjene joda-131 i nastaviti nekoliko dana nakon primjene. U slučaju sumnje na kontaminaciju jodom savjetuje se određivanje izlučivanja joda u mokraći. Ako koncentracija joda u mokraći iznosi više od  $200 \text{ }\mu\text{g/L}$ , tada se liječenje jodom-131 treba odgoditi sve dok izlučivanje ne bude u granicama normale. Ako postoji mogućnost rutinskog određivanja joda u mokraći, poželjno je to učiniti u svih bolesnika prije liječenja jodom-131. Primjena rhTSH kao priprema za liječenje jodom-131 također je moguća u bolesnika s udaljenim metastazama, pri čemu oni tada ne prekidaju hormonsku supresivnu terapiju L-T4, a može se primijeniti u bolesnika u kojih se nakon prekida hormonske supresivne terapije L-T4 ne može postići dostatno povišena razina TSH zbog velikog ostatnog tkiva štitnjače ili masivnih funkcionalnih metastaza, bolesti hipofize ili hipotalamusa, zatim u bolesnika u kojih postoji kontraindikacija za prekid liječenja L-T4 zbog prateće teške bolesti ili je terapiju potrebno provesti što prije. Primjenom litija može se produžiti zadržavanje joda-131 u tumoru i time povećati učinak liječenja. Litij ne utječe na nakupljanje joda u tumoru, nego koči njegovo otpuštanje pa su radijacijske doze na metastatsku leziju čak dvostruko više, osobito kod tumora koji brzo metaboliziraju jod. Primjenu litija treba započeti tjedan dana prije liječenja jodom-131 i nastaviti nekoliko dana nakon primjene uz praćenje njegove razine u krvi zbog potencijalne toksičnosti.

U bolesnika s porastom tumorskog biljega tireoglobulina (Tg), a negativnom dijagnostičkom scintigrafijom cijelog tijela vrlo često se primjenjuje terapijska doza joda-131, obično 100 mCi, jer se neke metastaze mogu zabilježiti samo na poslijeterapijskim scintigramima. Ovim pristupom može se u nekih bolesnika s povišenom razinom Tg otkriti okultna bolest nalazom patološkog nakupljanja joda-131 na poslijeterapijskim scintigramima, a uočen je i terapijski učinak. Ako na poslijeterapijskim scintigramima nema patološkog nakupljanja joda-131, tada je potrebna daljnja obrada (kompjutorizirana tomografija, magnetna rezonancija, pozitronska emisijska tomografija,  $^{18}\text{F-FDG-PET}$ ). Metastaze karcinoma štitnjače koje su PET pozitivne obično su slabije diferencirane, imaju lošiju prognozu i ne nakupljaju jod-131. U rijetkih bolesnika s metastazama diferenciranog karcinoma štitnjače koje ne nakupljaju jod-131 primjenom retinoične kiseline kao rediferencijacijskog sredstva uspjelo se postići naznačeno nakupljanje joda-131, ali u većine bolesnika taj postupak nije bio uspješan.



## ULTRASONOGRAPHY IN FOLLOW-UP OF THYROID CANCER PATIENTS

## ULTRAZVUK U PRAĆENJU BOLESNIKA S RAKOM ŠTITNJAČE

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Neck ultrasonography in the postoperative follow up of thyroid cancer patients has become a mandatory standard procedure for detecting the spread of the disease because of its high sensitivity in the early detection of local tumor recurrence as well as secondary changes in cervical lymph nodes, independently of thyroid hormone substitution and accumulation of radioactive iodine (J 131)<sup>1</sup>. This mostly refers to patients with papillary thyroid cancer that most frequently metastasizes to the lymph nodes of the neck, and to medullary thyroid cancer. Detection of cervical lymph node metastases is important for the disease prognosis and for decision on further treatment. Ultrasound has proven to be considerably better in detecting lymph node metastases from palpation, and in many studies also better than CT and MRI. Its advantages are low cost and ease of use, without limitations.

The literature describes many echographic criteria to distinguish lymph node metastases from benign ones<sup>2</sup>. Hyperplastic lymph nodes are almost always elongated, with a longitudinal to transverse diameter ratio (L/T) greater than 2, and most frequently present a central hyperechoic hilum. In contrast, round lymph nodes with an L/T ratio less than 2 are suspected of metastasis. Metastatic lymph nodes are on an average larger than benign ones. Most frequently, they show up as hypoechogenic, without a hilum, but they may sometimes be echogenic and heterogeneously presented. In necrosis, coarse echoes can be seen. In thyroid cancer, the position of lymph nodes in the neck is also important. Metastases are by far more frequent in lower areas of the neck, in the pretracheal area and in the jugulum than in the upper areas of the neck. The presence of cystic changes in lymph nodes is considered highly suggestive of metastatic papillary cancer (of all cystic metastases in the neck, 43% are metastases of papillary thyroid cancer). Cystic metastasis appears in 20%-24% of patients

Ultrazvučna pretraga vrata u poslijeoperacijskom praćenju bolesnika s rakom štitnjače postala je obvezna rutinska metoda za otkrivanje širenja bolesti zbog visoke osjetljivosti u ranom otkrivanju lokalnog recidiva, kao i sekundarnih promjena u limfnim čvorovima vrata neovisno o nadomjesnim hormonima štitnjače i akumulaciji radioaktivnog joda (J 131)<sup>1</sup>. To se najviše odnosi na bolesnike s papilarnim rakom štitnjače koji najčešće metastazira u limfne čvorove vrata, te na one s medularnim rakom štitnjače. Otkrivanje metastatskih limfnih čvorova važno je radi prognoze bolesti i izbora liječenja. Ultrazvuk se pokazao znatno superiornijim u otkrivanju metastatskih limfnih čvorova od palpacije, a u mnogim studijama i od CT i MRI. Prednosti su jednostavnost izvođenja pretrage bez ograničenja i niska cijena.

U literaturi su opisani mnogi ehografski kriteriji za razlikovanje metastatskih od benignih limfnih čvorova vrata<sup>2</sup>. Reaktivno promijenjeni limfni čvorovi gotovo uvijek su duguljasti s omjerom uzdužnog i poprečnog promjera (omjer L/T) većim od 2 i najčešće pokazuju centralni hilus. Nasuprot tome okruglasti limfni čvorovi s omjerom L/T manjim od 2 sumnjivi su na metastazu. Metastatski limfni čvorovi u prosjeku su veći od benignih. Najčešće su hipoehogeno prikazani, bez hilusa, ali mogu biti i ehogeni, te nehomogeno prikazani. Kod nekroze se vide grublji odjeci. Također je važan i položaj limfnog čvora na vratu. Daleko su češće metastaze u donjim dijelovima vrata i pretrahealno, te u jugulumu nego u gornjim dijelovima vrata. Prisutnost cističnih promjena u limfnom čvoru na vratu izrazito je sumnjiva na metastazu papilarnog raka štitnjače (od svih cističnih metastaza na vratu 43% otpada na papilarni rak štitnjače). Cistične metastaze javljaju se kod 20%-24% bolesnika s papilarnim rakom, dok su kalcifikati u metastatskom limfnom čvoru izrazito rijetki (u oko 1%-5% metastaza, nešto češće kod medularnog raka štitnjače), ali visoko specifični. Primjena obojenog i Power Dopplera koji daju



with papillary cancer while calcifications in metastatic lymph nodes are extremely rare (in about 1%-5% of metastases, somewhat more frequently in medullary carcinoma), but highly specific. The use of color and Power Doppler gives additional information on the blood flow into the lymph node. Enhanced vascularization is a reason to suspect malignancy.

However, in the appearance of a lymph node with benign and malignant changes there are many overlaps, so that many small lymph nodes can be metastatic and large lymph nodes in the upper parts of the neck can be reactively changed. Round lymph nodes are frequently found in toxoplasmosis and calcifications in tuberculosis. No matter how sensitive an ultrasound examination may be in detecting the potentially metastatic lymph nodes, the diagnosis cannot be made solely on this basis. Instead, ultrasound examination helps in the selection of suspect lymph nodes for ultrasound guided fine needle aspiration biopsy (FNAB) and cytological analysis. Cytological diagnosis is highly specific (95%-100% for papillary and medullary cancer), so that a combination of ultrasound and FNAB achieves high accuracy in the diagnosis of thyroid cancer metastases. Besides cytological analysis in case of negative cytology (inadequate material, cystic content without cell elements, or peripheral blood in the sample), it is possible to determine from the acquired aspirate thyroglobulin and calcitonin in medullary cancer. For differential diagnosis from other tumor metastasis, various cytochemical analyses can be performed.

In patients who have been operated on for thyroid cancer, it is also necessary to closely examine thyroid bed. In the early postoperative period, the examination can be difficult because of the presence of granulation tissue, both pretracheal and, in case of lateral neck dissection, behind the surgical scar. In later examinations fibrotic scars can imitate metastatic changes (hypoechoic nodes with coarse central echoes).

In well performed total thyroidectomies, only granular tissue is visible at the site of the thyroid gland at the first examination after surgery. The minimal quantities of remaining tissue are not echographically visible (in this case scintigraphy with J 131 is much more sensitive). The presence of thyroid tissue in its anatomical position immediately points to an inadequately performed operation, which complicates treatment and monitoring with radioactive iodine, and frequently requires new surgery. Local recurrences in the thyroid bed rarely appear in papillary carcinoma; they are frequent-

informaciju o prokrvljenosti limfnog čvora također je važna za otkrivanje metastaza, jer je pojačana prokrvljenost limfnog čvora sumnjiva na malignitet.

Međutim, u izgledu limfog čvora kod benignih i malignih promjena ima dosta preklapanja, pa tako i vrlo mali limfni čvorovi mogu biti metastatski, a veliki limfni čvorovi u donjim dijelovima vrata mogu biti reaktivno promijenjeni. Okrugli limfni čvorovi često se nađu kod toksoplazmoze, a kalcifikati kod tuberkuloze. Prema tome, koliko je god ultrazvučni pregled osjetljiv za otkrivanje potencijalnih metastatskih limfnih čvorova, ne može se dati dijagnoza samo na osnovi nalaza ultrazvuka, već ultrazvučni pregled služi za izbor sumnjivog limfnog čvora koji tada treba ciljano punktirati pod kontrolom ultrazvuka. Citološka dijagnoza je visoko specifična (95%-100% za papilarni i medularni rak štitnjače), tako da kombinacija ultrazvuka i citološke punkcije postiže veliku točnost u dijagnozi metastaza raka štitnjače. Uz citološku analizu u slučaju negativne citologije (oskudan materijal, cistična tvorba bez staničnih elemenata ili periferna krv u punktatu) moguće je iz dobivenog aspirata odrediti tireoglobulin odnosno kalcitonin kod medularnog raka. Radi diferencijalne dijagnoze prema drugim sekundarnim promjenama na vratu mogu se raditi i razne citokemijske analize.

Uz otkrivanje metastaza u limfnim čvorovima vrata u bolesnika s operiranim rakom štitnjače treba pažljivo pregledati i ležište štitnjače. U ranom poslijeoperacijskom razdoblju pregled može biti otežan opsežnim granulacijskim tkivom, kako predtrachealno, tako i u slučaju lateralne disekcije vrata, oko operacijskog ožiljka. U kasnijim kontrolama fibrozni ožiljci mogu oponašati metastatske promjene (hipoehogeni čvorovi s grubljim centralnim odjecima).

Kod dobro izvedene totalne tireoidektomije, pri prvom pregledu nakon operacije u ležištu štitnjače vidi se samo granulacijsko tkivo. Minimalne količine ostatnog tkiva ehografski se ne vide (u ovom slučaju scintigrafija pomoću J 131 je puno osjetljivija metoda). Prikaz tkiva štitnjače u njenom anatomskom ležištu odmah nakon operacije upućuje na neprimjereno izveden operacijski zahvat, što otežava liječenje i praćenje radioaktivnim jodom, a nerijetko zahtijeva i ponovnu operaciju. Kasniji lokalni recidivi u ležištu štitnjače rijetko se javljaju kod papilarnog raka štitnjače, oni su čest nalaz kod invazivnijih tumora, naročito kod anaplastičnog raka štitnjače. Ultrazvukom se prikazuju kao hipoehogene mase u ležištu štitnjače, nepravilnog oblika, ponekad s grubljim odjecima.



ly found in more invasive tumors, especially in anaplastic thyroid. Echographically, they are present as hypoechogenic masses in the thyroid bed, irregular in form, sometimes with coarse echoes.

Later local recurrences and metastatic changes usually follow the growth of serum thyroglobulin, which requires a more detailed ultrasound examination of the neck and FNAB of very small changes but also of lymph nodes that appear echographically benign.

In addition to diagnosis, ultrasound can be used for carrying out therapeutic treatments. The simplest is the method of sclerozation with 95% alcohol, which has already been proven in the treatment of hepatocellular carcinoma and liver metastasis and in the neck for the treatment of parathyroid glands, thyroid cysts and toxic adenomas. The technique is simple and noninvasive. It is carried out by the injection of 95% sterile alcohol into a previously diagnosed metastasis. It is recommended as an alternative intervention when there are solitary metastases in the neck that do not accumulate J 131, and in patients with contraindications for reoperation. The first results reported in the literature are encouraging, the method is well accepted by patients, and surgery is always an option if the disease progresses. In this way, tumor mass and serum level of thyroglobulin can be significantly reduced. Besides percutaneous injection of alcohol under ultrasound guidance, there are many other more aggressive and expensive treatment methods such as radiofrequency ablation and laser techniques<sup>3</sup>.

Thanks to better ultrasound equipment, more experienced examiners and routine use of ultrasound for monitoring postoperative thyroid cancer patients, local tumor recurrences and cervical lymph node metastases are more frequently found. This poses new dilemmas and challenges in the treatment of thyroid cancer (especially papillary), the prognosis of which is relatively good, even in case of metastases in the neck.

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## TUMOR MARKERS IN THYROID CANCER TUMORSKI BILJEZI RAKA ŠTITNJAČE

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Determination of tumour markers (TM) is a routine procedure in oncology. These noninvasive tests are useful in the diagnosis, tumour bulk assessment and, most important, postoperative and post-in the follow-up of patients after surgery and therapy. Generally, very few TM are highly sensitive and specific, and among them there are two markers relevant for thyroid cancer. Thyroglobulin (Tg) is used as a marker in patients with differentiated thyroid cancer (DTC), and calcitonin (CT) in patients with medullary thyroid cancer (MTC).

Serum Tg concentration is not of value preoperatively but it is very useful in monitoring patients after surgery. In contrast, preoperative serum CT concentration can point to the diagnosis of MTC, evaluate the mass of tumour tissue, and occasionally serve in screening for the familial type of MTC.

In patients with total thyroidectomy and <sup>131</sup>I ablation, serum Tg level should be undetectable. One gram of residual thyroid tissue corresponds to a Tg concentration of approximately 1 ng/mL. A normal, well differentiated thyroid remnant, after TSH stimulation by recombinant human TSH (rhTSH), is increasing Tg level 6-8 times above the baseline value. In patients with less differentiated thyroid tumour, Tg increases only 3 times or not at all if TgA are positive. Therefore, Tg concentration should be measured, either during suppression L-thyroxine therapy (on T4) or during TSH stimulation (off-T4, rh-TSH). Both of these conditions have different Tg cut-off values (on T4: Tg < 1 ng/mL, off-T4, rh-TSH: Tg < 2 ng/mL). Consequently, any Tg value higher than 2 ng/mL, if measured by a sensitive Tg method, suggests the presence of recurrence or metastases. Several follow up studies of DTC patients have confirmed that the Tg measurement is a more reliable parameter than the whole body scintigraphy (<sup>131</sup>I WBS) to detect recurrence or metastases.

At the beginning, Tg methods were based on radio-immunological measurements (RIA, IRMA) and after

Određivanje tumorskih biljega (TB) u onkoloških bolesnika postala je uobičajena rutina. Te neinvazivne pretrage rabe se u dijagnostičke svrhe, za procjenu tumorske mase i najčešće za praćenje tijeka bolesti nakon operacije i terapije. Danas se relativno mali broj TB smatra visoko specifičnim, a od njih su čak dva povezana s karcinomom štitnjače. Bolesnicima s diferenciranim karcinomom štitnjače (DKŠ) određuje se tireoglobulin (Tg), a u onih s medularnim karcinomom (MKŠ) kalcitonin (CT). Dok se koncentracija Tg u serumu rabi samo za poslijeoperacijsko praćenje bolesnika, serumski CT određuje se i prijeoperacijski za potvrdu dijagnoze MKŠ, procjenu tumorske mase, a ponekad i sa svrhom probiranja radi otkrivanja MKŠ obiteljskog tipa.

U bolesnika kojima je operacijski potpuno odstranjena štitnjača i provedena ablacija pomoću <sup>131</sup>I razina Tg serumu morala bi biti nemjerljiva. Smatra se da jednom gramu ostatnog tkiva štitnjače odgovara vrijednost Tg od oko 1 ng/mL. Normalni odgovor ostatnog tkiva štitnjače ili dobro diferenciranog tumora na endogeni TSH ili rekombinirani TSH (rhTSH) povećava razinu Tg oko 6-10 puta iznad osnovne vrijednosti. U bolesnika sa slabije diferenciranim tumorima porast Tg manji je i do tri puta, a u bolesnika s pozitivnim tireoglobulinskim protutijelima (TgA) može se dogoditi da Tg uopće ne poraste.

Razina Tg određena za vrijeme supstitucije L-tiroksinom (Tg-on T4), uspoređuje se s graničnom vrijednosti Tg < 1 ng/mL, dok se Tg određen za vrijeme stimulacije pomoću TSH (> 30 mU/L) uspoređuje s graničnom vrijednosti od Tg < 2 ng/mL. Uz uvjet da se radi o visoko osjetljivoj Tg metodi, rezultati Tg viši od 2 ng/mL s velikom vjerojatnošću ukazuju na pojavu recidiva ili metastaza.

Mnoge studije su pokazale da je u praćenju bolesnika s DKŠ Tg pouzdaniji parametar od scintigrafije cijelog tijela (<sup>131</sup>I WBS). Stoga se određivanju Tg poklanja osobita pozornost. U početku su Tg metode bile radio-



including the non-isotopic labels, the methods have changed to immunometric assay (IMA) of different sorts like: chemiluminometric (ICLA), enzymometric (IEMA) or immunofluorometric (IFMA) assays. These new tests are mostly automated, quick, give a wide concentration range and have a long shelf-life. Nevertheless, very few Tg methods satisfy stringent clinical criteria for the determination of serum Tg, demanding a very low functional sensitivity (ideally  $<0,2$  ng/mL) and high precision in the lower concentration range ( $< 2$  ng/mL). The majority of Tg methods are still influenced by TgA in spite of using monoclonal autoantibodies as well as recovery testing, so Tg value remains imprecise. As a result of TgA interference, Tg results can be falsely low (mostly by IMA methods) or falsely high (with RIA/IRMA methods).

Methodological problems may be provoked by heterophilic autoantibodies (HAMA), Hook effect, and with different types of Tg standards. Methods have been found to be variable in spite of using a reference Tg standard (CRM 457). Discrepancy depends on the quality of Tg- matrix, used for Tg standards preparation and serum samples dilution, and on the type of TgA that reacts in the assay. All of these are reflecting on the Tg value that sometimes can be positively or negatively biased. A great variability of the Tg methods has been reported by external quality control assessment. As a result of the bias inherent in these methods, unreliable Tg results are obtained and this causes problems in clinical interpretation of the results. Therefore, now an accepted rule for the quality of patient monitoring is: during a longitudinal monitoring it is better to use even a less sensitive Tg assay than to periodically introduce a new sensitive Tg procedure. Any change of the diagnostic kit inevitably modifies Tg value and a comparison with the previous results becomes impossible if the samples are not measured by the old as well as by the new method.

To provide a successful follow-up study of DTC patients, it is obligatory that every Tg method be evaluated through the internal and external quality control procedures by checking the whole Tg concentration range (low, median, high). Unfortunately, very few manufacturers include into their Tg kits a control serum of great clinical importance (0,5-1,0 ng/mL). So, a laboratory is advised to prepare its own serum pool sample of low Tg concentration that must be tested regularly. In fact, a precision of low concentration control sample measurements (reproducibility) gives an answer on reliability of

imunološke (RIA/IRMA), a nakon uvođenja različitih neizotopskih obilježivača postale su imunometrijske (IMA), najčešće luminometrijske (ICLA) i enzimometrijske (IEMA) ili fluorometrijske (IFMA). Suvremene metode su automatizirane, kratkotrajne, širokog raspona koncentracije i s reagensima produžene trajnosti. Unatoč tome, danas manji broj tržišnih kompleta zadovoljava stroge kliničke zahtjeve u mjerenju koncentracije Tg. To su niska funkcijska osjetljivost (idealna  $< 0.2$  ng/mL) i visoka preciznost, naročito u niskom koncentracijskom području. Mnogi kompleti, unatoč primjeni monoklonskih protutijela i pokusa "recovery", ne omogućavaju pouzdano mjerenje Tg ako su TgA pozitivna. Zbog TgA interferencije vrijednosti Tg mogu biti lažno snižene, najčešće uz IMA metode, ili lažno povišene ako se primjenjuju RIA/IRMA metode. Metodološki problemi nastaju i zbog heterofilnih protutijela (HAMA), Hookova učinka te zbog primjene različitih Tg standarda. Pokazano je da se unatoč uporabi referentnog Tg standarda (CRM 457) Tg metode ponekad razlikuju. Odstupanja među metodama nastaju i zbog različitosti Tg-matriksa koji se upotrebljava za otapanje Tg standarda i razrjeđivanje seruma bolesnika, kao i zbog primjene različitih vrsta reakcijskih Tg protutijela. Sve navedeno odražava se na rezultatu Tg koji može imati pomak prema višim ili nižim koncentracijama (pozitivni ili negativni pomak; *bias*). Velika varijabilnost u koncentraciji Tg nekog uzorka određene u većem broju laboratorija potvrđena je u nekim međunarodnim izvješćima o vanjskoj provjeri kakvoće. A nepouzdana vrijednost Tg, dakako, stvara problem u kliničkoj interpretaciji nalaza. Stoga je, za dobrobit bolesnika, korisnije da se Tg određuje istom, mada i manje osjetljivom metodom kroz što duže razdoblje, nego da se rabi više osjetljivih metoda u kraćim razdobljima. Naime, svaka promjena postupka uglavnom mijenja vrijednost Tg i onemogućuje usporedivost zadnjeg rezultata s prethodnima ako se posljednji uzorak seruma ne odrediti objema metodama. Da bi sustavno praćenje bolesnika bilo pouzdano i djelotvorno, primijenjenu metodu obvezno treba valorizirati provođenjem redovite unutarnje i vanjske kontrole kvalitete (kontrolni serumi). Kako većina proizvođača kompleta Tg ne uključuje kontrolni serum niske koncentracije, bilo bi uputno da se u laboratoriju pripravi takav uzorak (mješavina seruma oko 0,5-1 ng/mL) i da ga se određuje u svakom testu, jer će o pouzdanosti mjerenja Tg u tom klinički značajnom području zavisiti i daljnji tijek liječenja bolesnika s DKŠ. Ponekad se radi potvrde nastanka regionalnih metastaza Tg može

Tg result and further patient therapy. Suspected lymph nodes metastases in patients with DTC can be confirmed by measuring Tg in the fine needle aspirate.

In case of MTC, a stimulation test with calcium or pentagastrin (Pg) can also be used (Pg-test) in addition to baseline CT. In the Pg-test, a blood sample is obtained before i.v. application of Pg (time zero) and then after 2min, 5min, 10min, and 15min. In patients with MTC, a stimulated CT value further increases in relation to an already increased baseline CT value (in healthy individuals baseline CT must be less than 10 pg/mL and stimulated CT less than 30 pg/mL). For patients with MTC after thyroidectomy, CT is the first line laboratory test in looking for recurrence or metastases. According to a stimulated CT value it is possible to assess the present tumour volume.

Up to 1988, the concentration of CT was measured by RIA methods using polyclonal antibodies that failed to identify the complete CT monomer from the precursors or degradation products. The outcome was too many false negative results, and therefore, an assay protocol with extraction was introduced. Monoclonal antibodies allowed the development of more sensitive and specific IRMA-CT tests that were able to detect the complete 32- amino acid CT monomer. Nowadays, different CT methods (IRMA, IFMA, CLIA, EIA) on the market are required to be highly sensitive (detection limit of 1 pg/mL). Although using the reference CT standard (WHO 2<sup>nd</sup> IRP 89/620), some CT methods have an analytical sensitivity around 2 pg/mL and rarely around 0.5 pg/mL. In a two-site IFMA kit the monoclonal antibodies, coated by biotin, are bound to the microtitration plate wells coated by streptavidin. The polyclonal antibodies bind from one side to an antigen and from the other to a label (europium, Eu). Such a combination provides much higher sensitivity (detection limit of 0,3 pmol/L). During monitoring of MTC patients, in parallel to CT concentration, a less specific TM carcinoembryonic antigen (CEA) can also be measured.

Generally, the thyroid related TM are able to confirm a recurrence or metastases but not yet the presence of micrometastases. More sensitive and precise Tg and CT kits are needed for monitoring of patients with DTC and MTC.

određivati i u punktatu limfnog čvora bolesnika s DKŠ.

Za dijagnosticiranje MKŠ osim određivanja osnovne razine CT može se primijeniti i stimulacijski test CT pomoću kalcija ili pentagastrina (Pg). Pentagastrinski test (Pg-test) uključuje mjerenje CT u serumu prije i poslije i.v. aplikacije Pg (nulto vrijeme, 2min, 5min, 10min i 15min). U bolesnika s MKŠ stimulacijski CT pokazuje daljnji porast u odnosu na povišenu osnovnu razinu (u zdravih ispitanika osnovna koncentracija CT iznosi manje od 10 pg/mL, a porast poslije opterećenja Pg manji je od 30 pg/mL). Nakon tiroidektomije CT se smatra izbornim tumorskim biljegom u praćenju pojave recidiva ili metastaza, a prema osnovnoj i stimuliranoj koncentraciji CT potvrđuje se masa ostatnog tumorskog tkiva.

Do 1988. godine koncentracija CT određivala se metodama RIA u kojima su se primjenjivala poliklonska protutijela koja nisu razlikovala potpuni CT monomer od preteča ili degradacijskih proizvoda. Rezultati dobiveni direktnom RIA analizom, često su bili lažno negativni, pa je uveden RIA postupak s ekstrakcijom koji se u dijagnosticiranju MKŠ pokazao pouzdanijim testom. Nakon što su proizvedena monoklonska CT protutijela bilo je moguće razviti IRMA-CT test povećane osjetljivosti i specifičnosti kojim se mogao određivati potpuni 32-aminokiselinski CT monomer. Od metoda koje se danas primjenjuju (IRMA, IFMA, ICLA, IEMA) traži se što veća osjetljivost mjerenja, od oko 1 pg/mL. Analitička osjetljivost nekih metoda, unatoč primjeni referentnog CT standarda (WHO 2<sup>nd</sup> IRP 89/620), iznosi oko 2 pg/mL. U tzv. dvostranom IFMA kompletu upotrebljavaju se monoklonska protutijela koja su preparirana biotinom prije dodavanja u jažice (mikrotitracijska pločica) stjenke kojih su obložene streptavidinom. Ista vrsta poliklonskih protutijela služi jednim dijelom za vezanje s antigenom, a drugim s obilježivačem (europij, Eu). Takvom kombinacijom protutijela postiže se još veća osjetljivost metode koja ima granicu detekcije od oko 0,3 pmol/L. U praćenju bolesnika s MKŠ može se u istom uzorku seruma uz CT određivati i nespecifični TB, karcinoembrijski antigen (CEA).

Velika većina postojećih TB, pa tako i Tg i CT mogu s priličnom sigurnošću ukazivati na pojavu recidiva i metastaza ali ne i mikrometastaza. Stoga bi metode određivanja Tg i CT trebale bi postati još osjetljivije i preciznije.

## FOLLOW-UP OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

### PRAĆENJE BOLESNIKA S DIFERENCIRANIM KARCINOMOM ŠTITNJAČE

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Although patients with differentiated thyroid carcinoma (DTC) have a low mortality rate (8%/30 yrs), they require lifelong monitoring because of a high recurrence rate (30%/30 yrs)<sup>1</sup>. Initial management is total thyroidectomy and I-131 remnant ablation. The main methods in the follow up of patients with DTC are measurement of serum thyroglobulin (Tg), I-131 whole body scintigraphy (WBS) and neck ultrasonography (US).

**Thyroglobulin** is one of the most sensitive and specific tumor markers in oncology. After successful thyroidectomy and radioiodine ablation, Tg should be undetectable (<0.5 ng/mL) under T4 suppression therapy (Tg/T4) or thyrotropin (TSH) stimulation (Tg/TSH). The sensitivity of Tg/T4 is 78% and of Tg/TSH 96%<sup>2</sup>. To avoid hypothyroidism after T4 withdrawal, rhTSH is increasingly used in recent years. The sensitivity of Tg/rhTSH is 92%<sup>2</sup>. Serum Tg measurement is seriously affected by the presence of serum anti-Tg antibodies (TgAb). Positive TgAb are detected in 25% of patients with DTC, which can mask the presence of recurrent or persistent thyroid carcinoma<sup>3</sup>. In case of elevated Tg, the question is: recurrence or metastases, were are they and are they iodine positive or negative?

**I-131** is the most specific radionuclide to image well differentiated local recurrences, lymph node metastases or distant metastases. To perform I-131 WBS, the patient needs to be under TSH stimulation (TSH >30 mU/L) after 3-4 weeks of T4 withdrawal or 2-week T3 withdrawal, or after i.m. injection (2x0.9 mg) of rhTSH while on T4. For routine follow up diagnosis I-131 WBS (d-WBS) with 185 MBq of I-131 is appropriate but in case of elevated Tg and if high dose therapy is intended, d-WBS can be omitted or only 74 MBq I-131 should be given to avoid thyroid stunning. The sensitivity of d-WBS for detection of recurrent disease or metastases is only 49%, while the sensitivity of pt-WBS is 79%<sup>4</sup>. Be-

Iako bolesnici s diferenciranim rakom štitnjače (DRŠ) imaju nisku stopu smrtnosti (8%/30 g), potrebno je njihovo doživotno praćenje budući da imaju i visoku stopu recidiva bolesti (30%/30 g)<sup>1</sup>. Osnovno liječenje podrazumijeva totalnu tireoidektomiju i radiojodnu ablaciju ostatka štitnjače pomoću I-131. Glavne metode u praćenju bolesnika s DRŠ su serumski tireoglobulin (Tg), scintigrafija cijelog tijela pomoću I-131 i ultrazvuk vrata (UZ).

**Tireoglobulin** je jedan od najosjetljivijih i najspecifičnijih tumorskih biljega u onkologiji. Nakon uspješne tireoidektomije i radiojodne ablacije, Tg uz supresivnu terapiju pomoću T4 (Tg/T4) i uz stimulaciju tireotropinom (Tg/TSH) treba biti nedetektabilan, odnosno negativan (<0,5 ng/mL). Osjetljivost Tg/T4 je 78%, a Tg/TSH 96%<sup>2</sup>. Da bi se izbjegli simptomi hipotireoze nakon obustavljanja tiroksina, posljednjih godina se sve češće rabi rekombinantni ljudski TSH (rhTSH). Osjetljivost Tg/rhTSH je 92%<sup>2</sup>. Na vrijednosti Tg utječe prisutnost tireoglobulinskih antitijela (TgAb) u serumu. Pozitivna TgAb se mogu naći u 25% bolesnika s DRŠ, što onda može prikriti postojanje ustrajnog ili recidivirajućeg raka štitnjače<sup>3</sup>. U slučaju povećane vrijednosti Tg (>2 ng/mL) postavlja se pitanje: recidiv ili metastaze, gdje su, te jesu li na jod pozitivni ili negativni?

**I-131** je najspecifičniji radionuklid za prikaz recidiva dobro diferenciranih karcinoma štitnjače, metastaza u limfne čvorove ili udaljenih metastaza. Da bi se učinila scintigrafija cijelog tijela pomoću I-131 bolesnik mora biti pod TSH stimulacijom (TSH >30 mU/L) nakon prekida T4 tijekom 3-4 tjedna ili nakon dva tjedna prekida T3, odnosno nakon i.m. injekcije rhTSH (2x0,9 mg), a bez prekida hormona štitnjače. Za uobičajeni dijagnostički scintigram cijelog tijela pomoću I-131 dovoljno je 185 MBq I-131, ali u slučaju povišene vrijednosti Tg i ako se planira dati terapijsku dozu I-131, di-

cause of the high sensitivity of Tg/TSH and low sensitivity of d-WBS, the new definition of successful ablation is now considered when serum Tg level following TSH stimulation is negative ( $<0.5$  ng/mL), while formerly successful ablation was considered when Tg/TSH and d-WBS were negative<sup>5</sup>.

DTC involves cervical lymph nodes in 20%-50% of patients whether at the diagnosis or at follow up<sup>3</sup>. **Neck US** is the most sensitive tool to detect it<sup>6</sup>. In suspected cases, US guided FNA for cytology and Tg measurement in aspirate should be performed. Tg in metastatic lymph node is always higher than Tg in serum. The sensitivity of cytology is 85%-91%, and combined with Tg measurement in aspirate it approaches 100%<sup>7,8</sup>.

Only 2/3 of recurrences and metastases show I-131 uptake. In case of iodine positive metastases repeat treatment with radioiodine every 6-12 months is the treatment of choice. After several courses of radioiodine treatment, dedifferentiation of recurrences and metastases may occur. In case of elevated Tg and negative I-131 WBS, or in case with marked elevation of Tg, but only faint uptake on I-131 WBS, when additional I-131 negative metastases are suspected, imaging methods using nonspecific tracers are needed to detect I-131 negative metastases. According to local circumstances and feasibility, F-18-FDG PET, Tl-201 WBS, Tc-99m Sestamibi WBS, Tc-99m tetrofosfin WBS, bone scintigraphy; CT, MR or x-ray can be performed.

The important issue is how to treat iodine negative metastases? In iodine negative metastases surgery may be curable if metastases are completely resectable. In case of nonresectable, single bone metastases or nodular macrometastases of the lung, external radiation therapy is helpful. Elevated Tg may be the only indication of metastases and these patients can be treated empirically with I-131. The rate of lung metastases on pt-WBS in these patients ranges from 6% to 9%<sup>9,10</sup>.

In case of inoperable multiple I-131 negative metastases, redifferentiation using retinoic acid and radioiodine therapy can be applied after TSH stimulation. However, results with these treatments are not very encouraging, only 26% of patients have a significant increase in radioiodine uptake, and 16% have a reduced tumor volume<sup>11</sup>. Another ineffective option is chemotherapy (doxorubicin) with no more than 25% of partial response rate<sup>3</sup>.

Besides improvement in the follow up methods, improvement in follow up **strategies** has been achieved by better definition of risk groups. Although there are several, slightly different staging systems (AJCC, UICC,

jagnostički scintigram pomoću I-131 se može izostaviti ili se isti može učiniti uz dozu od samo 74 MBq I-131 kako bi se izbjegao učinak omamljivanja. Osjetljivost dijagnostičkog scintigrama cijelog tijela pomoću I-131 za otkrivanje recidiva ili metastaza iznosi samo 49%, dok je osjetljivost poslijeterapijskog scintigrama 79%<sup>4</sup>. Zbog visoke osjetljivosti Tg/TSH, a niske osjetljivosti dijagnostičkog scintigrama cijelog tijela pomoću I-131 nova definicija uspješne ablacije podrazumijeva negativan Tg/TSH ( $<0,5$  ng/mL), dok je nekada ta definicija podrazumijevala uz negativan Tg/TSH i negativan dijagnostički jodni scintigram<sup>5</sup>.

U 20%-50% bolesnika s DRŠ mogu se naći metastaze u limfne čvorove vrata, bilo u vrijeme postavljanja dijagnoze ili kasnije tijekom praćenja bolesnika<sup>3</sup>. **UZ vrata** je najosjetljivija metoda za njihovo otkrivanje<sup>6</sup>. U sumnjivim slučajevima treba napraviti citološku punkciju pod kontrolom UZ, kao i određivanje Tg u punktatu. Kod metastatskih limfnih čvorova Tg u punktatu je uvijek veći nego Tg u serumu tih bolesnika. Osjetljivost citologije je 85%-91%, a zajedno s određivanjem Tg u punktatu dostiže 100%<sup>7,8</sup>.

Samo dvije trećine recidiva ili metastaza DRŠ akumulira I-131. U slučaju na jod pozitivnih metastaza tretman izbora je I-131 svakih 6-12 mjeseci. Poslije nekoliko tretmana radioaktivnim jodom može nastati dediferencijacija stanica raka štitnjače. U slučaju povećanog Tg, a negativnog jodnog dijagnostičkog scintigrama ili u slučaju jako povećanog Tg, a minimalnog nakupljanja I-131 na dijagnostičkom scintigramu, odnosno kada se očekuju dodatne na jod negativne metastaze mogu se rabiti druge, manje specifične dijagnostičke metode. Prema lokalnim okolnostima i mogućnostima mogu se učiniti F-18-FDG PET, scintigrafija cijelog tijela pomoću Tl-201, Tc-99m-sestamibijem, Tc-99m-tetrofosminom, scintigrafija skeleta Tc-99m difosfonatom, CT, MR ili rtg.

Važno pitanje je kako liječiti na jod negativne metastaze? Ako je metastaza potpuno resektabilna, kirurška resekcija je metoda izbora koja u tom slučaju može dovesti do izlječenja. U slučaju solitarne, inoperabilne, koštane metastaze ili makronodularne plućne metastaze može se primijeniti vanjsko zračenje. Ponekad će jedino povećan Tg ukazivati na postojanje metastaza, te se u tom slučaju može primijeniti terapijska doza I-131. U 6%-9% ovih slučajeva naći će se plućne metastaze na poslijeterapijskom scintigramu cijelog tijela<sup>9,10</sup>.

U slučaju višestrukih, inoperabilnih, na jod negativnih metastaza može se pokušati provesti rediferencijaciju retinoičnom kiselinom, te nakon stimulacije po-



AGES, AMES, MACIS, NTCTCS, etc.), each of them allows for accurate identification of the majority of **patients at low risk** of recurrence or mortality (80%). These stagings enable less intensive follow up and management of low-risk patients compared to the higher risk minority (20%), who may benefit from a more aggressive management strategy.

To facilitate follow up and management of patients, the term **disease free patients** has been introduced. Most of them are patients after total thyroidectomy and radioiodine ablation, without clinical and imaging evidence of tumor, undetectable serum Tg level during TSH suppression and stimulation, and negative neck US<sup>3</sup>. These patients are followed-up on Tg/T4 basis and neck US. Because the sensitivity of d-WBS (49%) is lower than the sensitivity of Tg/T4 (78%), these patients do not require routine d-WBS. **High-risk patients** are followed-up with more aggressive management strategies and in case of recurrence or metastatic disease, the following therapeutic procedures are applied, depending on iodine positive or negative recurrences or metastases: curative or palliative surgery, I-131 therapy, external beam radiation, experimental chemotherapeutic trial or watchful waiting in patients with stable, asymptomatic and slow progressing disease.

Suppression of TSH with supraphysiological doses of T4 is used in an effort to decrease the risk of recurrence or metastases. Retrospective studies have demonstrated that TSH suppression below 0.1 mU/L may improve outcomes in high-risk patients, although such evidence has not been documented in low-risk patients. Because suppression therapy is in fact subclinical thyrotoxicosis, in disease free and low-risk patients TSH may be kept within the low-normal range (0.3-2 mU/L). In disease free patients who presented as high-risk patients, TSH may be kept in the range of 0.1-0.5 mU/L, while in patients with persistent disease TSH should be maintained below 0.1 mU/L<sup>3</sup>.

The recent explosion of knowledge regarding the molecular and cellular pathogenesis of cancer has led to the development of a range of different therapeutic methods which are currently evaluated: oncogene inhibitors, modulators of growth or apoptosis, angiogenesis inhibitors, immunomodulators and gene therapy<sup>3</sup>.

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moću TSH provesti radiojodnu terapiju. Međutim, uspjehnost ove terapije nije ohrabrujuća, samo kod 26% bolesnika je potaknuta akumulacija joda, a kod 16% je zabilježeno smanjenje metastaza<sup>11</sup>. Jednako skroman, djelomičan odgovor od 25% može se očekivati nakon kemoterapije doksorubicinom<sup>3</sup>.

Uz poboljšanje metoda kontrole u bolesnika postignuta su i poboljšanja **strategije** praćenja bolesnika boljim definiranjem rizičnih skupina. Iako ima nekoliko, ponešto različitih sustava za stupnjevanje rizika recidiva ili smrtnosti od DRŠ (AJCC, UICC, AGES, AMES, MACIS itd.), svaki od njih omogućava identificiranje većine niskorizičnih bolesnika (80%), omogućavajući da praćenje i zbrinjavanje ovih bolesnika bude manje intenzivno nego kod manjine visokorizičnih bolesnika (20%) kod kojih je potrebna intenzivnija kontrola<sup>3</sup>.

Da bi se olakšalo praćenje i zbrinjavanje bolesnika uveden je pojam „**disease free patients**“ (bolesnici bez znakova bolesti). Većinu čine bolesnici nakon totalne tireoidektomije i radiojodne ablacije, bez kliničkih i scintigrafskih znakova bolesti, negativnim Tg, bilo pod TSH supresijom ili stimulacijom, te s negativnim UZ vrata<sup>3</sup>. Praćenje ovih bolesnika se provodi određivanjem Tg/T4 i UZ vrata. Kod ovih bolesnika nije potrebno činiti dijagnostički scintigram pomoću I-131, budući da je osjetljivost Tg pod supresijom (78%) veća od osjetljivosti dijagnostičkog scintigrama cijelog tijela pomoću I-131 (49%). Strategija kontroliranja visokorizičnih bolesnika je mnogo intenzivnija, te se u slučaju recidiva ili metastaza primjenjuju slijedeći postupci, ovisno o tome jesu li recidivi ili metastaze na jod pozitivni ili negativni: kurativna ili palijativna kirurgija, terapija I-131, vanjsko zračenje, eksperimentalni kemoterapijski pokušaj ili samo pomno praćenje bolesnika ako je u stabilnoj, asimptomatskoj i sporo progresivnoj fazi bolesti.

Supresija TSH sa suprafiziološkim količinama T4 provodi se radi smanjenja rizika pojave recidiva ili metastaza. Retrospektivne studije su pokazale kako supresija TSH ispod 0,1 mU/L poboljšava ishod u visokorizičnih bolesnika, dok dokaza za isti učinak kod niskorizičnih bolesnika nema. Budući da supresivna terapija znači supkliničku tireotoksikozu, u niskorizičnih bolesnika bez znakova bolesti TSH se može održavati na “nisko normalnim vrijednostima” (0,3-2 mU/L). U visokorizičnih bolesnika koji su bez znakova bolesti TSH se može održavati na razini od 0,1-0,5 mU/L, a u bolesnika s ustrajnom bolesti TSH treba suzbijati, tj. ispod 0,1 mU/L<sup>3</sup>.

Ubrzani razvoj znanja o molekularnoj i staničnoj patogenezi tumora doveo je do razvoja niza novih terapi-





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## CHANGING TRENDS IN LABORATORY EVALUATION OF THYROID CANCER PATIENTS

### NOVI PRISTUPI U LABORATORIJSKOJ OBRADI BOLESNIKA S RAKOM ŠTITNJAČE

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In the past, when TSH measurements were not sufficiently sensitive to distinguish patients with hyperthyroidism from those without it, the strategy for treatment with levothyroxine (L-thyroxine) after surgery for differentiated thyroid carcinoma (DTC) with or without ablation was to suppress TSH to undetectable lev-

Dok mjerenje razine TSH nije postalo dovoljno osjetljivo za dijagnosticiranje hipertireoze, levotiroksin (L-tiroksin) se je primjenjivao nakon operacije diferenciranog karcinoma štitnjače (DKŠ) s ablacijom ili bez nje, kako bi suprimirao TSH na nemjerljivu razinu i spriječio rast preostalih stanica raka. Danas je to zastarjela meto-

els in order to avoid any growth promotion of remaining cancerous cells. This is now an obsolete approach with development of very sensitive TSH methods, since it has never been proved that complete suppression of TSH is necessary for a favorable survival in patients with low-risk DTC. On the contrary, data from a co-operative study in US did not support the concept that suppressing TSH to undetectable, thyrotoxic ranges was required to prevent disease progression. There is an increasing awareness of the possible long-term damaging effects such as cardiac arrhythmias, cardiovascular deaths and osteoporosis, if survivors are treated life-long to a mild to moderate hyperthyroidism, in particular in postmenopausal women. As a practical matter, the most appropriate L-thyroxine dose is that which reduces serum TSH to just below the lower limit of the normal range for the assay being used (typically 0.1-0.4 mU/L).

Thyroglobulin (Tg) is almost the ideal tumor marker for DTC since it is only produced in thyroid cells, and it is measurable in serum with high precision and sensitivity. There are, however, a number of caveats in the interpretation of serum Tg values during follow up of patients with thyroid carcinomas. Tg is produced in the thyroid gland proportional to the size of the gland and its functional state. It is stimulated physiologically by TSH and is therefore elevated during hyperthyroidism, but also in partly compensated or subclinical hypothyroidism or any other situation with a high glandular turnover and borderline or overt insufficient thyroid hormone production. Tg is stored with the thyroid hormones within the colloid and is released in large quantities when the thyroid is undergoing destruction such as in thyroiditis, radioiodine therapy and surgery. Serum Tg levels should be undetectable if a patient with DTC has had total thyroidectomy performed, in which case persistence or reappearance of Tg indicates recurrence. The values after lobectomy are about half that of a person with an intact gland, and therefore the prediction of relapse from serum Tg measurements is much poorer in those patients, as is also whole body scintigraphy (WBS). The follow up strategy for these patients is therefore not yet quite clear. Recent studies have found neck ultrasonography valuable. The usefulness of serum Tg measurements in routine clinical practice depends on how they are interpreted. Serum Tg can be assessed correctly only in TgAb-negative sera. These autoantibodies are present in approximately 25% of patients with DTC compared with about 10% in the general population. Recently, NACB has presented in-

da, kako zbog razvoja osjetljivijih metoda mjerenja TSH, tako i zbog činjenice da nikad nije potvrđen utjecaj potpune supresije TSH na preživljenje bolesnika s niskorizičnim DKŠ. Nasuprot tome, američkom studijom nije potvrđena hipoteza da je supresija TSH na nemjerljivu, tireotoksičnu razinu nužna za sprječavanje progresije bolesti. Javljaju se spoznaje o potencijalnim dugotrajnim štetnim utjecajima, npr. srčanoj aritmiji, kardiovaskularnoj smrti i osteoporozi u bolesnika koji se održavaju u stanju blage do umjerene hipotireoze, osobito u žena u postmenopauzi. U praksi je najprimjerenija doza L-tiroksina ona koja smanjuje razinu TSH malo ispod donje granice normalnih vrijednosti (tipično 0,1-0,4 mU/L).

Tireoglobulin (Tg) je gotovo idealan tumorski biljeg za DKŠ budući da ga proizvode samo stanice štitnjače, a njegova se razina može izmjeriti vrlo precizno i s velikom osjetljivošću. Međutim, postoje neke nedoumice što se tiče interpretacije vrijednosti Tg tijekom praćenja bolesnika s rakom štitnjače. Proizvodnja Tg proporcionalna je veličini i aktivnosti štitnjače. Fiziološki je stimulirana putem TSH i time povišena u hipertireozu, ali i u djelomice kompenziranoj ili subkliničkoj hipotireozu ili u bilo kojem drugom stanju pojačanog rada štitnjače i graničnog ili nedostatnog stvaranja hormona štitnjače. Tg je pohranjen u koloidu, kao i hormoni štitnjače i otpušta se u velikim količinama tijekom razaranja tkiva štitnjače kod tireoiditisa, radiojodne terapije ili operacijskog zahvata. Razina Tg trebala bi biti nemjerljiva u bolesnika s DKŠ u kojih je izvršena totalna tireoidektomija, a njegova i dalje mjerljiva razina ili ponovna pojava ukazuje na recidiv. Nakon lobektomije vrijednosti su upola manje nego kod osoba koje imaju cijelu štitnjaču pa je predviđanje recidiva mjerenjem razine Tg manje korisno, kao i scintigrafija cijelog tijela. U tih bolesnika još nije utvrđena optimalna strategija praćenja. Nedavno provedene studije govore u prilog dijagnostičke vrijednosti ultrazvuka. Značenje mjerenja razine Tg u kliničkoj praksi ovisi o tome kako se nalaz tumači: vrijednost Tg se može točno procijeniti samo u serumu negativnom na TgAb. Navedena protutijela prisutna su u 25% bolesnika s DKŠ te u 10% opće populacije. Nedavno je Nacionalna akademija za kliničku biokemiju (NACB) predstavila internacionalne smjernice za primjenu mjerenja razine Tg i TgAb s analitičkog i kliničkog stajališta. Dvije temeljno različite metode mjerenja Tg su u uporabi:

- Imunometrijske metode u kojima prisutnost TgAB može lažno smanjiti koncentraciju Tg. Nemjerljiva razina Tg ne može ukazivati na nepostojanje tumora

ternational guidelines for the use of serum Tg and TgAb from both an analytical and clinical point of view. Two principally different Tg methods are used:

- immunometric methods where presence of TgAb may artificially lower the Tg concentration. Undetectable serum Tg results therefore cannot be used to indicate the absence of tumor in a TgAb-positive serum sample. A detectable Tg indicates that Tg is present, but the concentration may be underestimated; and
- radioimmunoassay (RIA) values may be either falsely low or falsely high in the presence of TgAb. Detectable serum Tg results by RIA should therefore not be the sole factor in determining the presence of residual tumor or recurrence. The presence of TgAb should be measured by a very sensitive method as even very low levels may induce false results.

Measurements of TgAb should be performed in every single sample, and the sole use of Tg recovery as evidence for interference from TgAb as recommended by some manufacturers cannot be advised. Cut-off levels for serum Tg values to be used as an indicator of recurrence depend on the particular assay, typically 1-2 mg/L (but only in patients who have had complete thyroid ablation). The functional assay sensitivity should be below 1 mg/L. The first serum Tg value on L-thyroxine replacement after surgery is usually a good prognosticator, although Tg may remain detectable for up to one year after treatment before becoming undetectable. The first serum Tg is recommended after six months due to gradual destruction of the remnant after radioablation and the half-life of Tg. Thereafter, serum Tg should be measured during stimulation with TSH either by L-thyroxine withdrawal or rhTSH stimulation, which lowers the false negative rate well below that of WBS. The disadvantage of rhTSH is the expense for the clinic and/or the health authorities, but the overall calculation shows very good cost effectiveness when considering the economic burden of work absenteeism. Furthermore, if routine performance of WBS in long-term management can be reduced, the financial outcome becomes very much in favor of using rhTSH. Recent results demonstrate that rhTSH stimulated serum Tg and neck ultrasound are superior to WBS in long-term follow up of patients with low-risk DTC. A new algorithm is therefore advised, but it must be recognized that this algorithm is not useful in more limited ablation of the thyroid gland, in the presence of TgAb in serum and in high-risk patients.

kod pozitivnih TgAb. Mjerljiva razina Tg ukazuje na njegovu prisutnost, ali koncentracija može biti podcijenjena.

- Radioimunoenzimski test može dati lažno niske ili lažno visoke rezultate u prisutnosti TgAb. Mjerljiva serumska razina Tg dobivena radioimunoenzimskim testom ne može biti jedini čimbenik utvrđivanja prisutnosti ostatnog tumora ili recidiva. Prisutnost TgAb trebalo bi mjeriti vrlo osjetljivom metodom budući da i vrlo niske razine protutijela mogu prouzročiti lažne rezultate.

TgAb treba određivati u svakom uzorku, a sam pronalazak Tg nije dovoljan dokaz njegove interferencije s TgAb, bez obzira na preporuke nekih proizvođača. Razina Tg koju možemo smatrati dokazom recidiva ovisi o samoj metodi mjerenja i najčešće iznosi 1-2  $\mu$ g/L (ali samo u bolesnika u kojih je učinjena potpuna ablacija štitnjače). Osjetljivost testa trebala bi biti ispod 1  $\mu$ g/L. Prva izmjerena vrijednost Tg tijekom supstitucijske terapije L-tiroksinom nakon operacije je u većini slučajeva dobar prognostički čimbenik, iako Tg može biti mjerljiv do godine dana nakon operacije. Prvo mjerenje Tg preporuča se 6 mjeseci nakon operacije zbog postupnog razaranja ostatnog tkiva štitnjače radioablacijom te vremena poluživota Tg. Poslije toga Tg bi trebalo mjeriti za vrijeme stimulacije pomoću TSH, bilo putem prekida supstitucije L-tiroksinom ili primjene rhTSH. Na taj način postotak lažno negativnih nalaza postaje niži nego kod primjene scintigrafije cijelog tijela. Nedostatak primjene rhTSH je njegova cijena, iako konačne procjene pokazuju vrlo dobar omjer troška i koristi kada se uzme u obzir smanjenje radne sposobnosti bolesnika s hipotireozom za vrijeme prekida supstitucije L-tiroksinom. Nadalje, ako se scintigrafija cijelog tijela rutinski manje primjenjuje, primjena rhTSH postaje financijski opravdana. Novi podaci ukazuju na prednost rhTSH stimulacije Tg i ultrazvuka vrata u odnosu na scintigrafiju cijelog tijela u dugoročnom praćenju bolesnika s niskorizičnim DKŠ. Stoga je predložen novi algoritam, ali ni on nije koristan u bolesnika s djelomičnom ablacijom štitnjače, kod prisutnosti TgAb u serumu te u visokorizičnih bolesnika. Nove smjernice savjetuju kliničku procjenu stanja bolesnika svaka 3 mjeseca tijekom prve godine te mjerenje Tg tijekom supstitucijske terapije 6 i 12 mjeseci nakon početka liječenja. Nakon toga određivanje Tg (i TgAb) nakon stimulacije pomoću rhTSH, kao i ultrazvuk vrata preporuča se primjenjivati jednom na godinu. Nadalje, scintigrafiju cijelog tijela treba snimati jednom godišnje dok se ne dobiju dva ne-

The new guidelines advocate clinical assessment of patients every three months in the first year, and measurement of serum Tg during replacement at six and 12 months of initial therapy. Thereafter, rhTSH stimulated Tg (and TgAb) and neck ultrasound should be performed yearly. Furthermore, WBS should be performed yearly until two negative scans; thereafter, WBS is no longer necessary unless serum Tg becomes detectable and/or neck ultrasound positive. The improvement in performance of laboratory methods used in the follow up of patients with DTC has contributed to a change in the strategy for the management of these patients with DTC; it has further urged the need for multidisciplinary collaboration, since the field now not only needs contributions from surgery, pathology, radiotherapy and nuclear medicine, but also from medical endocrinology, ultrasound and clinical biochemistry.

gativna scintigrama. Nakon toga ona više nije potrebna osim u slučaju pojave ponovno mjerljive razine Tg ili pozitivnog nalaza na ultrazvuku. Unaprjeđenje laboratorijskih metoda za praćenje bolesnika s DKŠ pridonijelo je promjeni strategije liječenja; povećana je potreba za multidisciplinskom suradnjom, budući da to područje zahtijeva angažiranost kirurgije, patologije, radioterapije, nuklearne medicine, kao i medicinske endokrinologije, ultrazvuka i kliničke biokemije.

## DIFFERENCES IN EUROPEAN AND AMERICAN GUIDELINES FOR MANAGEMENT OF PATIENTS WITH THYROID NODULES AND DIFFERENTIATED THYROID CANCER

### RAZLIKE IZMEĐU EUROPSKIH I AMERIČKIH SMJERNICA U DIJAGNOSTICI I LIJEČENJU NODULARNE STRUME I DIFERENCIRANOG KARCINOMA ŠTITNJAČE

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In the year 2006, two national and two multinational organizations issued guidelines on the management of thyroid nodules and/or thyroid cancer. These organizations were the American Thyroid Association, British Thyroid Association, American Association of Clinical Endocrinologists together with the Italian Associazione Medici Endocrinologi, and European Thyroid Association. The recommendations differ considerably with respect to their character (guidelines *versus* consensus report), the task forces involved (small team of experts *versus* large group of “delegates”), implementation of a review process, the mode of literature research, and the typing of evidence and grading of recommendations.

Tijekom 2006. godine dvije su nacionalne i dvije multinacionalne organizacije izradile smjernice za dijagnosticiranje i liječenje bolesnika s čvorovima u štitnjači i/ili rakom štitnjače. To su redom: Američko društvo za štitnjaču, Britansko društvo za štitnjaču, Američko udruženje kliničkih endokrinologa zajedno s Talijanskim udruženjem endokrinologa te Europsko društvo za štitnjaču. Preporuke se znatno razlikuju ovisno o vrsti dokumenta (smjernice nasuprot konsenzusu), radnoj skupini uključenoj u njihovu izradu (mala skupina eksperata nasuprot velike skupine “izaslanika”), nadziranju tijeka izrade, načinu pretraživanja literature, klasifikaciji dokaza i stupnjevanju preporuka.



*The Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer issued by the American Thyroid Association* in 2006 address all the relevant questions for physicians involved in the diagnosis and treatment of patients with thyroid nodules and thyroid cancer. Some short statements on treatment of benign nodules are included. The chapters on treatment of differentiated thyroid cancer and especially on follow up of differentiated cancers are systematic and completed by flowcharts.

*The Guidelines for Management of Thyroid Cancer by the British Thyroid Association and the Royal College of Physicians* mainly address treatment and follow up of differentiated thyroid cancer. There is only a short paragraph on fine-needle aspiration biopsy; in patients with nodules no systematic statements on other diagnostic modalities as ultrasound or radionuclide scanning are given. On the contrary, the paragraphs related to treatment and long-term follow up address many specific issues such as pregnancy and differentiated thyroid cancer, childhood differentiated thyroid cancer, documentation and pathology reporting as well as guidelines for the primary physician.

*The Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules issued by the American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi* begin with systematic recommendations for diagnosis including the use of ultrasound, radionuclide scanning and fine-needle aspiration biopsy. Different flowcharts develop algorithms for diagnosis of thyroid cancer in patients with palpable nodules as compared to patients with incidentalomas. On the contrary, treatment and follow up of differentiated thyroid cancer is not addressed by the AACE and AME experts.

*The European Consensus for the Management of Patients with Differentiated Thyroid Carcinoma of the Follicular Epithelium issued by the European Thyroid Association* addresses the diagnosis of thyroid nodules only briefly; treatment of benign nodule is not part of this consensus report. On the other hand, treatment and follow up of differentiated thyroid cancer is addressed extensively.

The different recommendations show a considerable proportion of consensus; however, there is significant dissent related to clinically relevant issues. With respect to diagnosis, the use of ultrasound and radionuclide scanning in comparison to fine-needle aspiration biopsy and related algorithms is judged differently. In

*Smjernice za dijagnosticiranje i liječenje bolesnika sa čvorovima u štitnjači i diferenciranim karcinomom štitnjače*, koje je izradilo Američko društvo za štitnjaču 2006. godine, obrađuju sva pitanja važna za liječnike koji se bave takvim bolesnicima. Smjernice sadržavaju i upute o postupcima kod dobroćudnih čvorova u štitnjači. Poglavlja koja se odnose na liječenje bolesnika s diferenciranim karcinomom štitnjače i osobito njihovo daljnje praćenje vrlo su sustavna i upotpunjena dijagramima.

*Smjernice za postupanje kod raka štitnjače*, koje je objavilo Britansko društvo za štitnjaču i Kraljevski zbor liječnika, uglavnom se bave metodama liječenja i praćenjem diferenciranog karcinoma štitnjače. Samo se jedan kratki odlomak odnosi na citološku punkciju; nema sustavnih preporuka za primjenu drugih dijagnostičkih metoda u bolesnika sa čvorovima u štitnjači, kao što su ultrazvuk ili radionuklidne pretrage. S druge strane, odlomci u kojima se govori o postupcima liječenja i dugotrajnom praćenju obrađuju mnoge specifične probleme kao što su: diferencirani karcinom štitnjače kod trudnica i djece, problem dokumentiranja i patološke dijagnoze te smjernice za obiteljske liječnike.

*Medicinske smjernice za kliničku praksu u dijagnozi i liječenju čvorova u štitnjači*, koje je izradilo Američko društvo kliničkih endokrinologa zajedno s Talijanskim društvom endokrinologa, odmah na početku donose sustavne preporuke za dijagnostiku, uključujući uporabu ultrazvuka, radionuklidnih pretraga i citološke punkcije. Različiti dijagrami razvijaju algoritme za dijagnosticiranje raka štitnjače u bolesnika s palpabilnim čvorovima u štitnjači nasuprot onih sa slučajnim nalazom. S druge strane, postupke liječenja i praćenja diferenciranog karcinoma štitnjače AACE (American Association of Clinical Endocrinologists) i AME (Associazione Medici Endocrinologi) stručnjaci nisu uopće razmatrali.

*U Europskom konsenzusu o liječenju bolesnika s diferenciranim karcinomom štitnjače s folikularnim epitelom*, koji je objavilo Europsko društvo za štitnjaču, samo se ukratko spominje dijagnosticiranje čvorova u štitnjači; zbrinjavanje dobroćudnih čvorova u štitnjači nije dio ovoga konsenzusa. S druge strane, postupci liječenja i praćenja diferenciranog karcinoma štitnjače su opširno razmatrani.

Različite preporuke ukazuju na znatan stupanj konsenzusa; međutim, postoje razilaženja u klinički bitnim pitanjima. Što se tiče dijagnoze, uporaba ultrazvuka i radionuklidnih pretraga u usporedbi s citološkom punkcijom te tematski algoritmi različito se procjenjuju. Što se tiče bolesnika s dijagnosticiranim rakom štitnjače,



relation to patients with documented thyroid cancer, one important issue of dissent is staging and risk classification. Concerning surgery, there is no consensus for the indication of central lymph node dissection. The indications for radioiodine ablation are not consistent, and this also holds for the application of recombinant human TSH and low iodine diet for preparation for radioiodine therapy. Finally, the follow up protocols differ with respect to the implementation of radioiodine scan and its replacement by rhTSH-stimulated thyroglobulin measurements.

razilaženja postoje u određivanju stadija i klasifikaciji rizika. Ne postoji konsenzus o disekciji središnjih limfnih čvorova pri kirurškom zahvatu. Nema dosljednosti niti o pitanju indikacija za ablaciju radioaktivnim jodom, kao ni o primjeni rekombinantnog humanog TSH i dijete osiromašene jodom u pripremi za liječenje radioaktivnim jodom. Naposljetku, protokoli za praćenje oboljelih razlikuju se u preporukama o provođenju scintigrafije s radiojodom i njegove zamjene mjerenjem rhTSH-stimuliranog tireoglobulina.

## CLINICAL CHARACTERISTICS OF MEDULLARY, POORLY DIFFERENTIATED AND ANAPLASTIC THYROID CARCINOMA

### KLINIČKA OBILJEŽJA MEDULARNOG, SLABO DIFERENCIRANOG I ANAPLASTIČNOG KARCINOMA ŠTITNJAČE

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#### Medullary thyroid carcinoma (MTC)

In 1959, Hazard *et al.* were the first to describe medullary thyroid carcinoma (MTC) and its histological characteristics. In 1961, Sipple reported on the association of thyroid carcinoma and pheochromocytoma in six of his patients. In 1965, Schimke found MTC and bilateral pheochromocytoma to be inherited in an autosomal dominant fashion. In 1968, Steiner reported on hyperparathyroidism associated with MTC and pheochromocytoma, and designated it as MEN (Multiple Endocrine Neoplasia) 2A syndrome, while Williams in 1966 and Sizemore in 1974 identified MTC and pheochromocytoma without parathyroid hyperplasia, associated with a marfanoid body habitus and mucosal ganglioneuromatosis and identified it as MEN 2B syndrome. In 1986, Farndon identified MTC as having a familial association which is not associated with other endocrinopathies and identified it as FMTC. Over time, the following subtypes of MEN 2A syndrome were identified:

a) MEN 2A (1): MTC, pheochromocytoma, parathyroid disease,

#### Modularni karcinom štitnjače (MKŠ)

Hazard i suradnici 1959. prvi opisuju medularni karcinom štitnjače (MKŠ) i njegove histološke značajke. Sipple 1961. izvješćuje o udruženosti karcinoma štitnjače i feokromocitoma u šestoro svojih bolesnika. Schimke 1965. ustanovljava da se MKŠ i bilateralni feokromocitom nasljeđuju autosomno dominantno. Steiner 1968. izvješćuje o hiperparatireoidizmu udruženom s MKŠ i feokromocitomom i označuje ga kao sindrom multiple endokrine neoplazije 2A (sindrom MEN 2A), dok Williams 1966. i Sizemore 1974. izdvajaju MKŠ i feokromocitom bez paratireoidne hiperplazije, a udružen s marfanoidnim habitusom i neuronima sluznice probavnog trakta i označuju ga sindromom MEN 2B. Farndon 1986. uočava i obiteljski MKŠ koji nije udružen s ostalim endokrinopatijama i označava ga kao FMKŠ. S vremenom se prepoznaju i podvarijante sindroma MEN 2A:

a) MEN 2A (1): MKŠ, feokromocitom, bolest paratireoideje  
b) MEN 2A (2): MKŠ i feokromocitom bez paratireoidne bolesti

- b) MEN 2A (2): MTC and pheochromocytoma without parathyroid disease, and  
c) MEN 2A (3): MTC and parathyroid disease without pheochromocytoma.

In 1993, routine testing for the RET proto-oncogene mutation in members of families with MEN 2A syndrome was introduced. MTC ranks 3<sup>rd</sup> most common thyroid carcinoma and accounts for some 10% of all thyroid carcinomas. It is of a neuroectodermal origin, i.e. it comes from C cells of the thyroid belonging to the APUD system. C cells are characterized by a pluripotent ability to secrete various biological substances such as, first of all, calcitonin, chromogranin and CEA, but also by ectopic production of ACTH, CRF, MSH, VIP, NSE, serotonin, prostaglandin, somatostatin, etc. In 75% of cases MTC occurs in the sporadic and in 25% in the familial form. Sporadic MTC are mainly unifocal, whereas familiar MTC are multicentric and bilateral. Sporadic MTC usually occurs in mature age and develops slowly; however, at 10-year follow up the survival rate was about 50%. MTC in MEN 2A syndrome is manifested in early thirties and in MEN 2B syndrome in early twenties. MTC in both syndromes and especially in MEN 2B syndrome is considerably more aggressive than sporadic MTC and is prone to earlier metastasis. Clinical symptoms of the disease depend on the type of the potential ectopic production of particular hormones or substances and on associated endocrinopathies. Some patients complain of diarrhea that occurs with high calcitonin, prostaglandin and serotonin levels. The rate of parathyroid hyperplasia in MEN 2 syndrome is 20% to 40%, of bilateral pheochromocytoma about 50%, however, the incidence rate of pheochromocytoma in MEN 2B syndrome is higher.

Since the heritable MTC forms were found to be caused by activation of the RET proto-oncogene mutation, all patients with a familial form of RET proto-oncogene have to undergo testing. Specific type of the familial form of MTC (MEN 2A, MN 2B and FMTC) can be identified by a characteristic mutation of RET proto-oncogene of individual exons (10, 11, 13, 14, 15, 16) as well as by characteristic codons. All newly found MTC have to be tested. In case of positive RET mutation, all relatives have to be tested in order to establish genetic load with this disease and for further treatment and follow up. Recently, prenatal testing for RET mutation on amniocentesis has is also available.

Ultrasound-guided cytologic puncture provides a finding that is characteristic of MTC; calcitonin level

- c) MEN 2A (3): MKŠ i paratireoidna bolest bez feokromocitoma

Od 1993. započinje rutinsko ispitivanje mutacije RET protoonkogeno kod članova obitelji sa sindromom MEN 2. MKŠ je treći po učestalosti među karcinomima štitnjače, a javlja se u oko 10% svih karcinoma štitnjače. Neuroektodermalnog je podrijetla, odnosno potječe iz C stanica štitnjače koje pripadaju sustavu APUD. C stanice obilježava pluripotentna sposobnost lučenja različitih bioloških supstancija, kao što su prije svega kalcitonin, kromogranin, CEA, ali i ektopična proizvodnja ACTH, CRF, MSH, VIP, NSE, serotoninina, prostaglandina, somatostatina i dr. Oko 75% slučajeva MKŠ se javlja sporadično, a u 25% kao obiteljski oblik bolesti. Sporadični MKŠ se javlja u štitnjači najčešće kao solitarni čvor u jednom od režnjeva, dok se obiteljski oblici MKŠ javljaju multicentrično u oba režnja. Sporadični MKŠ je bolest zrelije dobi i sporije napreduje, no 10-godišnje preživljavanje je ipak oko 50%. MKŠ u sindromu MEN 2A očituje se već u ranim tridesetim, a u sindromu MEN 2B u ranim dvadesetim godinama. MKŠ u oba sindroma, a naročito u sindromu MEN 2B, je značajno prodravniji od sporadičnog MKŠ i rano metastazira. Kliničke manifestacije bolesti ovise o tipu moguće ektopične proizvodnje pojedinih hormona ili supstancija, te o udruženim endokrinopatijama. Određeni broj bolesnika prate uporni proljevi zbog kalcitoninske, prostaglandinske i serotonininske aktivnosti. Učestalost hiperplazija paratireoidne u sindromu MEN 2 je 20%-40%, bilateralnog feokromocitoma oko 50%, s time što je učestalost pojave feokromocitoma u sindromu MEN 2B veća.

Od otkrića da su nasljedni oblici MKŠ uzrokovani aktivacijom mutacije u RET protoonkogenu, testiranje RET mutacije postaje rutinskom metodom. Približno 100% nasljednih MKŠ vezani su s urođenom mutacijom RET protoonkogeno. Pojedini tipovi obiteljskih MKŠ (MEN 2A, MEN 2B i FMKŠ) mogu se prepoznati znakovitim mutacijama RET protoonkogeno pojedinih eksona (10, 11, 13, 14, 15, 16) kao i znakovitim kodovima. Analizi RET mutacije treba podvrgnuti sve novootkrivene MKŠ. U slučaju dokaza pozitivne RET mutacije treba ispitati sve srodnike zbog otkrivanja genetskog opterećenja bolešću i daljnjeg liječenja i praćenja. U posljednje vrijeme spominje se i prenatalni test RET mutacije u sklopu amniocenteze.

Citološkom punkcijom uz kontrolu ultrazvuka dobije se znakovit nalaz za MKŠ, može se mjeriti i koncentracija kalcitonina iz uzorka punktata. Histološki dokaz MKŠ postiže se pozitivnom imunohistokemijskom reakcijom na kalcitonin, kromogranin, CEA.

can be measured in the aspirate. Histological evidence of MTC is obtained by positive immunohistochemical reaction with calcitonin, chromogranin and CEA.

In the early detection and monitoring of patients with MTC, determination of the level of calcitonin as a very selective marker is highly valuable. C cells produce calcitonin that is a very strong inhibitor of osteoclastic activity. Other tumors such as small cell lung carcinoma rarely produce calcitonin. Calcitonin secretion is stimulated by pentagastrin, calcium and alcohol. Measurement of calcitonin is a standard part of the pentagastrin stimulation test. In newly detected MTC with already formed nodule, high basal calcitonin level is usually measured. Stimulation test (pentagastrin) is highly valuable in the follow up of patients operated on (occurrence of metastases) and in the follow up of newly detected members with familial MTC. Increased CEA level is also a sign of the disease propagation. Increased chromogranin level points to the association of other endocrinopathies (pheochromocytoma).

Scintigraphic testing is more or less limited: scintigraphy of the whole body with  $Tc^{99m}$  DMS (V),  $I^{131}$  MIBG and  $Tc^{99m}$  octreotide. Scintigraphy with  $Tc^{99m}$  sestamibi is useful providing evidence of parathyroid hyperplasia. PET-CT diagnostic technology is important in the detection of existing metastases.

The leading treatment method is surgical extirpation of the thyroid with removal of the neck and upper mediastinum lymph nodes. Radioiodine therapy is not indicated, and the effects of x-ray radiation and chemotherapy are poor.

The age at which younger family members with MEN 2 syndrome should be exposed to prophylactic thyroidectomy is still a subject for debate. The age range of 6-10 years is considered appropriate. Foci of MTC have been reported in the thyroid of a child operated on at the age of 7 months. Metastases have been reported in a child as young as 6 years.

#### Poorly differentiated thyroid carcinoma (PDTC)

According to the WHO classification, PDTC is defined as a tumor originating from follicular thyroid cells and with morphological and biological characteristics between differentiated adenocarcinoma and anaplastic thyroid carcinoma. However, histological definition of PDTC is still controversial and diagnostic criteria have not yet been defined. Histological subtypes of well differentiated adenocarcinoma can be found in the litera-

U ranom otkrivanju kao i praćenju bolesnika s MKŠ od velike je vrijednosti određivanje koncentracije kalcitonina kao vrlo selektivnog biljega. C stanice proizvode kalcitonin koji je vrlo snažan inhibitor osteoklastične aktivnosti. Kalcitonin vrlo rijetko proizvode i drugi tumori, npr. karcinom malih stanica pluća. Sekreciju kalcitonina stimuliraju pentagastrin, kalcij i alkohol. Rutinski se kalcitonin određuje u pentagastrinskom stimulacijskom testu. Kod novootkrivenog MKŠ s već formiranim čvorom najčešće se već mjeri visoka bazalna koncentracija kalcitonina. Stimulacijski test (pentagastrin) od velike je vrijednosti u praćenju operiranih bolesnika (pojava metastaza) i u praćenju mladih novootkrivenih članova s obiteljskim MKŠ. Povišena koncentracija CEA je također znak propagacije bolesti. Povišena koncentracija kromogranina može ukazivati na udruženost drugih endokrinopatija (feokromocitom).

Scintigrafske pretrage su više-manje ograničenog dometa: scintigrafija cijelog tijela pomoću  $Tc^{99m}$  DMS (V),  $I^{131}$  MIBG,  $Tc^{99m}$  oktreatid. Kvalitetna je scintigrafija pomoću  $Tc^{99m}$  sestamibi kod dokaza hiperplazije paratireoideja. U dokazu prisutnih metastaza važna je PET-CT dijagnostika.

Vodeća terapijska metoda je kirurška ekstirpacija štitnjače s odstranjenjem limfnih čvorova vrata i gornjeg mediastinuma. Radiojodna terapija nije indicirana, učinci ozračivanja x-zrakama i kemoterapije su vrlo slabi.

O dobi mladih članova obitelji sa sindromom MEN 2 u kojoj ih treba izložiti profilaktičnoj tireoidektomiji se još uvijek raspravlja. Prevladava da je to dob od 6-10 godina. Žarišta MKŠ su nađena u štitnjači djeteta operiranog u dobi od 7 mjeseci. Također se izvješćuje i o dokazu metastaza u djeteta od 6 godina.

#### Slabo diferencirani rak štitnjače (SDRŠ)

Prema klasifikaciji SZO slabo diferencirani karcinom štitnjače definira se kao tumor podrijetlom iz folikularnih stanica štitnjače, a s morfološkim i biološkim oznakama između diferenciranog adenokarcinoma i anaplastičnoga karcinoma štitnjače. Međutim, histološka definicija SDRŠ je još kontroverzna i nisu još definirani dijagnostični kriteriji. U literaturi se nalaze histološki podtipovi dobro diferenciranih adenokarcinoma: trabekularni, nodularni, solidni i inzularni rast folikularnog adenokarcinoma uz prikaz rabdoidnih stanica, visoke cilindrične stanice varijante papilarnog karcinoma, solidna varijanta papilarnog karcinoma u djece izložene radijododu nakon černobilske nesreće 1986, difuzno sklerozirajući

ture: trabecular, nodular, solid and insular growth of follicular adenocarcinoma with presentation of rhabdoid cells, tall columnar cells of papillary carcinoma variant, solid papillary carcinoma variant in children exposed to radioiodine after Chernobyl accident in 1986, and diffuse sclerosing variant of papillary carcinoma in young women associated with lymphocyte infiltration.

In PDTC, thyroglobulin can be determined by immunohistochemical analysis. The possible genetic load such as BRAF mutation in tall cell variant of papillary carcinoma is studied. Expression of various markers of cell proliferation and differentiation is also studied. In the treatment of PTDC, more radical treatment with exploration of the neck and upper mediastinum is suggested.

### Anaplastic thyroid carcinoma (ATC)

ATC is the most aggressive thyroid carcinoma metastasizing very quickly with the highest incidence rate in patients aged over 60 years. It is a very rare disease accounting for 1% of all thyroid malignant diseases and is the cause of over 40% of deaths due to thyroid carcinoma. Survival longer than 6 to 12 months of the onset is very rare. ATC occurs in patients with a goiter enlarging for a longer period and with previously diagnosed thyroid adenocarcinoma coming from iodine-poor regions. The main symptoms are abrupt growth of frequently painful nodular goiter with enlarged lymph nodes, with difficulties in respiration and speech. At the time of the disease detection, distant metastases are seen in 20%-50% of patients. Tumor metastasizes to many organs. ATC has easily recognizable cytological and histological characteristics.

Treatment is mainly palliative: surgical removal of tumor mass with freeing of the respiratory tract, radiation and chemotherapy.

papilarni karcinom mladih žena udružen s limfocitnom infiltracijom.

U SDRŠ se imunohistokemijski može dokazati tireoglobulin. Istražuje se moguća genetska opterećenost kao npr. BRAF mutacija kod varijante papilarnog karcinoma visokih stanica. Također se ispituje izraženost raznih biljega stanične proliferacije i diferencijacije. U liječenju SDRŠ sugerira se radikalnije liječenje s eksploracijom vrata i gornjeg medijastinuma.

### Anaplastični rak štitnjače (ARŠ)

Anaplastični rak štitnjače najagresivniji je tumor štitnjače koji napreduje vrlo brzo. Najčešći je u bolesnika starijih od 60 godina. Vrlo je rijetka bolest i javlja se u 1% svih malignoma štitnjače, a uzrokuje preko 40% smrti od karcinoma štitnjače. Rijetko je preživljenje duže od 6-12 mjeseci od pojave bolesti. ARŠ se pojavljuje u bolesnika iz jodom siromašnih područja s već prethodno duže rastućom gušom, te prethodno dokazanim adenokarcinomom štitnjače. Vodeći simptomi su nagli rast često bolne čvoraste guše s uvećanim regionalnim limfnim čvorovima uza smetnje disanja i govora. U 20%-50% bolesnika u trenutku otkrivanja bolesti se dokazuju udaljene metastaze. Tumor brzo metastazira u mnoge organe. ARŠ ima lako prepoznatljivu citološku i histološku sliku. Liječenje je najčešće palijativno: kirurško odstranjenje tumorske mase uz oslobađanje dišnih putova, zračenje i kemoterapija.



## ROLE OF ULTRASONOGRAPHY IN DIAGNOSIS OF MEDULLARY, POORLY DIFFERENTIATED AND ANAPLASTIC THYROID CARCINOMA

### ULTRAZVUČNA DIJAGNOSTIKA MEDULARNOG, SLABO DIFERENCIRANOG I ANAPLASTIČNOG KARCINOMA ŠTITNJAČE

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Medullary thyroid carcinoma originates from the parafollicular cells of the thyroid, which secrete calcitonin. Medullary thyroid carcinoma accounts for 4%-10% of all malignant thyroid tumors. Approximately 25% of medullary thyroid cancers are familial forms that can be detected by molecular screening for RET proto-oncogene mutations. The prognosis is usually poor, since lymph node involvement and distant metastases are frequently present at the time of diagnosis. In general, the strongest prognostic variable is the extent of disease at presentation. Presentation with a thyroid mass strongly correlates with regional nodal disease. The 5-year survival rate is between 78% and 91%, and 10-year survival between 61% and 75%. Early diagnosis and radical surgical treatment improve the morbidity and mortality associated with medullary thyroid carcinoma.

Ultrasound examination of thyroid gland can detect impalpable and very small nodules, but different types of cancers cannot be distinguished by ultrasound. Medullary carcinomas present a hypoechogenic echo-pattern as compared with normal thyroid follicular structure in 85% of cases, similar to papillary carcinomas (in 86% of cases). Follicular carcinomas present hypoechogenic echostructure in 56% of cases because follicular structure is more often preserved in follicular carcinoma than in papillary and medullary carcinomas. If the contour of a hypoechogenic nodule is irregular or blurred, or microcalcifications, grouped calcification or edge calcifications are present, the probability of carcinoma is high with a specificity of 97%. Characteristic findings of carcinoma are present in 44% of medullary carcinomas, 54% of papillary carcinomas and 28% of follicular carcinomas.

Ultrasound-guided cytology is a highly specific (97%) and quite sensitive (about 90%) method in the diagnosis of medullary and papillary carcinoma. The precise

Medularni rak štitnjače često se svrstava u slabije diferencirane tumore s lošijim ishodom bolesti. Nastaje iz parafolikularnih stanica štitnjače koje luče kalcitonin, javlja se u 4%-10% svih malignih tumora štitnjače, većinom sporadično, ali oko 25% slučajeva je nasljedno. Nasljedni oblik medularnog raka može se otkriti molekularnim probirom na RET proto-onkogene mutacije. Prognoza bolesti ovisi o stadiju u kojem se rak dijagnosticira. Prognoza bolesti je loša kad je tumor veći, ako je prisutno ekstraintroidno širenje tumora i kad su zahvaćeni limfni čvorovi, a pogotovo ako se pojave udaljene metastaze. Stopa 5-godišnjeg preživljavanja je 78%-91%, a 10-godišnjeg 61%-75%.

Ultrazvukom se mogu otkriti nepapilabilni i vrlo mali čvorovi u štitnjači, ali se ne mogu prepoznati različiti tipovi tumora. Medularni rak se u 85% slučajeva prikazuje hipoehogeno u odnosu na normalno tkivo štitnjače, jer tumorsko tkivo ima veću celularnost od normalne folikularne građe štitnjače, slično kao i papilarni rak (u 86% slučajeva). Folikularni rak prikazuje se hipoehogeno u manjem postotku (56%), jer češće od papilarnog i medularnog raka zadržava folikularnu građu sličnu adenomima i nodularnim strumama. Ultrazvukom se mogu prepoznati neke značajke raka kao što su infiltrativni rast (neravne konture čvora) i prisutnost sitnih kalcifikata, grupiranih ili rubno smještenih kalcifikata. Na temelju tih pokazatelja može se prepoznati rak, što je naročito važno pri odabiru čvorova za ciljanu citološku punkciju, pogotovo ako se radi o manjim čvorovima, jer veće čvorove treba punktirati bez obzira na ehostrukturu. Na temelju navedenih ultrazvučnih kriterija za rak može se prepoznati medularni rak u 44%, papilarni u 54%, a folikularni u 28% slučajeva.

Ciljana citološka punkcija pod kontrolom ultrazvuka je visoko specifična (97%) i prilično osjetljiva (oko 90%)





description of echostructure, size and localization of the nodules in the thyroid facilitates the choice of the nodules for biopsies. Subcapsular tumors have a high probability of extrathyroid spread, therefore it is important to perform ultrasound-guided biopsy of subcapsular nodules, even when they are small.

Color Doppler is an additional tool for understanding the nodule vascularity. Pathological vascularization of cancers is not always visible, but the presence of intranodal vascularity on color Doppler is a sign of malignancy if the nodule is “cold” on scintigraphy.

Small impalpable neck lymph nodes can easily be detected by ultrasound. They are presented as hypoechogenic nodules, sometimes with central echogenic hilum. Experienced examiner can recognize metastatic lymph node for its round shape, or more echogenic, irregular or cystic appearance, or small calcifications within the nodule, or abnormal peripheral vascularity using color Doppler. If lymph node metastases are diagnosed, lymph node dissection is performed at the same time with total thyroidectomy. Ultrasound helps evaluate the stage of the disease and to plan the extent of surgery. In patients with lymph node involvement at the time of diagnosis, new lymph node metastases often occur after initial surgery, especially if serum calcitonin levels remain increased.

Ultrasonography is also an important method in the investigation of the familial form of medullary thyroid cancer among family members. Although they can be detected by molecular screening for RET proto-oncogene mutations, subjects are reluctant to have total thyroidectomy which is recommended on the basis of this procedure. Precise ultrasound examination can detect small nodules of 2-3 mm in diameter. Ultrasound-guided fine-needle biopsy can reveal medullary carcinoma. Measurement of calcitonin from fine-needle biopsy material, diluted with one milliliter of normal saline, can be helpful in cases with negative cytologic findings. Calcitonin levels from such a solution can be several times higher than serum calcitonin levels if medullary cancer is punctured.

Prognostic indicators of differentiated thyroid carcinoma and outcome of the disease are analyzed in many statistical reports. However, nowadays we know that many histologic features of such cancer exist: minimally invasive follicular carcinoma, widely invasive follicular and Hürthle cell carcinoma, insular carcinoma as a morphological variant of follicular carcinoma, papillary microcarcinoma, encapsulated variant, follicular variant,

metoda u dijagnostici medularnog i papilarnog raka štitnjače. Ultrazvukom se može procijeniti veličina čvora, smještaj u štitnjači i odnos prema kapsuli štitnjače. Subkapsularno smješteni čvorovi imaju veću vjerojatnost ekstratiroidnog širenja u okolne strukture. Zato treba obratiti pozornost na subkapsularno smještene čvorove i treba ih ciljano punktirati pa makar se radilo i o manjim čvorovima. Obojeni Doppler omogućuje prikaz vaskularizacije čvora. Patološka vaskularizacija raka ne mora biti uvijek vidljiva, ali je jaka intranodalna vaskularizacija, pogotovo bez značajnije periferne vaskularizacije scintigrafski “hladnog” čvora, vrlo suspektan nalaz za rak. Ultrazvukom se dobro prikazuju limfni čvorovi, prikazuju se hipoehogeno u odnosu na štitnjaču, pravilnog su oblika, najčešće izduženi i prepoznaje se pravilan hilus. Metastatski limfni čvorovi mogu se prepoznati zbog promijenjene ehostrukture, više su ehogeni i pokazuju strukturu kao tkivo štitnjače, često su nepravilne ehostrukture s cističnim promjenama i kalcifikatima. Obojeni Doppler znatno pomaže u prepoznavanju metastatskih čvorova, pogotovo manjih kod kojih još nije narušena ehostruktura, ali je prisutna patološka periferna vaskularizacija s ruba čvora prema unutra koja nikad nije prisutna u normalnom limfnom čvoru kod kojega se vidi samo diskretna vaskularizacija u hilusu. Ultrazvuk pomaže u ocjeni proširenosti raka i u planiranju opsežnosti operacijskog zahvata. U bolesnika s medularnim rakom kad su u vrijeme postavljanja dijagnoze zahvaćeni limfni čvorovi koji su operativno odstranjeni često se pojavljuju novi metastatski limfni čvorovi, pogotovo ako su povišene vrijednosti kalcitonina u serumu i nakon operacijskog zahvata.

Ultrazvučna dijagnostika je važna i u ispitivanju nasljednog oblika medularnog raka. Iako je danas moguć molekularni probir na RET proto-onkogene mutacije na temelju kojih se može preporučiti profilaktična tiroidektomija, ispitanici se ne odlučuju lako za taj zahvat. Pomnim pretraživanjem štitnjače ultrazvukom mogu se otkriti vrlo sitni čvorići, veličine 2-3 mm, koji se mogu punktirati pod kontrolom ultrazvuka. Kod nesigurnog citološkog nalaza i urednih vrijednosti kalcitonina u serumu može pomoći i određivanje kalcitonina iz punktata, razrijeđenog s 1 mL fiziološke otopine. Kalcitonin iz punktata može biti znatno viši nego u serumu ako je punktirani čvorić medularnog raka.

Papilarni i folikularni rak spadaju u dobro diferencirane maligne tumore. U svim statistikama analiziraju se prognostični čimbenici i ishod bolesti za ove dvije skupine bolesnika, ali danas znamo da to nisu jedinstvene bolesti. Danas se dijagnosticira minimalno invazivni i invazivni



solid/trabecular variant, diffuse sclerosing variant, tall cell and columnar cell variants of papillary carcinoma, clear cell carcinoma, mucinous and squamous variant of thyroid carcinoma. It is not known whether there are different types of thyroid carcinoma with different biological behavior or stages of malignant thyroid disease. Yet, it is generally accepted that poorly differentiated carcinomas and anaplastic carcinomas arise from well-differentiated carcinomas. Poorly differentiated and anaplastic carcinomas present a rapidly enlarging neck mass, produce compression signs such as dyspnea, dysphagia, and hoarseness. Extrathyroid extension, invasion of major vessels and nerves of the region, and spread into the larynx, trachea, and esophagus are common. Lymph node and distant metastases are frequent. Ultrasound examination shows large irregular inhomogeneous mass with calcifications and necrosis, infiltration of muscles and other neck structures, and tumor relation with major vessels. Radical surgical treatment, radiotherapy and chemotherapy are not efficient. Poorly differentiated carcinoma are more frequent in elderly patients, however, children and young patients may also have advanced disease and poorly differentiated carcinoma at the time of diagnosis. Anaplastic carcinoma is rare, accounting for 1%-5% of all malignant thyroid tumors, but it is one of the most lethal human malignant tumors.

### Conclusion

Ultrasonography and ultrasound-guided fine-needle biopsy are the methods of choice in the diagnosis of thyroid cancers. Ultrasound can detect small medullary cancer during general check-up in apparently healthy individuals, and also among family members of patients with the familial form of medullary thyroid carcinoma, sized 2-3 mm in diameter. Although the prognosis of patients with thyroid carcinoma is usually excellent, a subset of patients develop a more aggressive disease. The strongest prognostic variable of medullary thyroid cancers is the extent of disease at presentation. Therapy of poorly differentiated and anaplastic carcinomas is mostly not effective. Early diagnosis and surgical treatment are the keys to improve the morbidity and mortality associated with medullary and differentiated thyroid carcinoma, preventing development of poorly differentiated and anaplastic carcinoma.

folikularni i rak Hürthleovih stanica, inzularni rak kao morfološka varijanta folikularnog raka, papilarni mikrokarcinom, inkapsulirana varijanta, folikularna varijanta, solidna trabekularna varijanta, sklerozna difuzna varijanta, varijanta papilarnog raka visokih stanica i cilindričnih stanica, rak svijetlih stanica, mucinozni i skvamozni oblici raka štitnjače. Još se ne zna jesu li to posebne vrste raka s različitim biološkim ponašanjem tumora i različitim ishodom bolesti ili samo pojedine faze maligne bolesti, no poznato je da se slabije diferencirani i anaplastični rak razvija većinom iz dobro diferenciranog raka. Anaplastični rak brzo raste, infiltrira okolne organe i ima vrlo lošu prognozu, najčešće sa smrtnim ishodom bolesti. Ultrazvukom se prikazuje kao nepravilna velika tvorba, različite ehostrukture s kalcifikatima i nekrotičnim sadržajem, može se vidjeti infiltrativni rast u mišiće i dušnik, odnos s krvnim žilama i opsežnost metastaza, što je važno u planiranju operacijskog zahvata. Slabo diferencirani rak i anaplastični rak često se ne može u potpunosti odstraniti, česti su lokalni recidivi i udaljene metastaze. Slabo diferencirani tumori ne nakupljaju radioaktivni jod, slabo reagiraju na vanjsko zračenje i kemoterapiju. Slabije diferencirani tumori češći su u starijoj dobi, ali se mogu javiti i u djece i mladih ljudi. Anaplastični rak štitnjače javlja se u 1%-5% svih malignih tumora štitnjače, a prema novijim literaturnim podacima rjeđe nego ranije, na što je vjerojatno utjecala jodna profilaksa i sve ranija dijagnostika raka štitnjače.

### Zaključak

Ultrazvučna dijagnostika štitnjače i ciljana citološka punkcija su neophodne u dijagnostici raka štitnjače. Ultrazvukom se medularni rak može otkriti na sistematskom pregledu kad još nema palpabilnog čvora i među članovima obitelji bolesnika oboljelog od nasljednog oblika medularnog raka (može se otkriti tumor veličine 2-3 mm). Iako je prognoza bolesti dobra u bolesnika s rakom štitnjače, lošiji prognostični pokazatelji i dobro diferenciranih tumora kao što su veličina tumora, dob i ekstratiroidno širenje tumora pokazuju znatno lošiju prognozu, otežano i skuplje liječenje koje zahtijeva i nekoliko operacija i radijodnih terapija, a često i sa smrtnim ishodom. Terapija medularnog raka je isključivo operacijska, radioterapija ima slab uspješ. Terapija slabo diferenciranog i anaplastičnog raka većinom je bezuspješna te jedino rana dijagnostika može poboljšati prognozu bolesti i smanjiti smrtnost bolesnika oboljelih od medularnog i slabo diferenciranog raka te spriječiti razvoj slabo diferenciranog i anaplastičnog raka štitnjače.



## SURGICAL TREATMENT OF MEDULLARY, POORLY DIFFERENTIATED AND ANAPLASTIC THYROID CARCINOMA

### KIRURŠKO LIJEČENJE MEDULARNOG, SLABO DIFERENCIRANOG I ANAPLASTIČNOG KARCINOMA ŠTITNJAČE

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Surgical treatment is therapy of choice for all types of thyroid cancer. Appropriate treatment planning depends on accurate and precise preoperative diagnostic evaluation. Preoperative evaluation is based on ultrasonography of thyroid gland and neck lymph nodes and cytological verification of all suspect nodes within thyroid gland and neck. Multidisciplinary treatment is obligatory for tumors with malignant biological characteristics, poor clinical course and bad prognosis. Depending on tumor type, stage of disease, patient's general condition and surgery performed, the treatment is continued with radioiodine ablation, radiotherapy or chemotherapy.

Treatment of medullary thyroid cancer is surgical. Minimal operation includes total thyroidectomy and central compartment neck dissection (group VI, pretracheal and bilateral paratracheal lymph nodes). Modified radical neck dissection is indicated if metastatic lymph nodes are present. Primary tumor and metastatic lymph nodes located in mediastinum are usually accessible through neck incision, in some cases it is necessary to perform upper medial sternotomy.

It is important to recognize patients with familial type (familial medullary cancer, multiple endocrine neoplasia syndrome) among patients with medullary thyroid cancer. When dealing with familial type, family members should be screened for calcitonin elevation and/or RET proto-oncogene mutation. Family members who are gene carriers for the RET proto-oncogene mutation should undergo prophylactic thyroidectomy. There are no unique recommendations for the age and minimal diagnostic evaluation necessary to perform prophylactic thyroidectomy.

The group of poorly differentiated thyroid cancers includes insular cancer, papillary and follicular cancer with poorly differentiated parts (tall cell cancer, colum-

Kirurško liječenje je metoda izbora za liječenje svih karcinoma štitnjače. Dobro planiranje liječenja omogućava točna i precizna prijeoperacijska dijagnostička obrada koja se temelji na ultrazvuku štitnjače i vrata, te citološkoj verifikaciji svih sumnjivih čvorova u štitnjači i na vratu. Primjena imunocitokemijskih metoda povećava točnost citoloških nalaza, što je osobito važno u prepoznavanju medularnog karcinoma štitnjače. Kod skupine tumora s biološki lošijim značajkama i klinički malignijim tijekom bolesti, te lošom prognozom liječenje je najčešće multidisciplinarno. Ovisno o vrsti tumora, stadiju bolesti, stanju bolesnika i učinjenoj operaciji liječenje se nastavlja radiojodnom terapijom, radioterapijom ili kemoterapijom.

Medularni karcinom štitnjače liječi se kirurški. Minimalna operacija medularnog karcinoma štitnjače uključuje totalnu tiroidektomiju i disekciju limfnih čvorova vrata skupine VI. (predtrahealni i obostrani paratrachealni limfni čvorovi). Modificirana radikalna disekcija vrata indicirana je ako su prisutne metastaze u limfnim čvorovima na vratu. Primarni tumor i metastatski limfni čvorovi smješteni u gornjem medijastinumu najčešće se mogu odstraniti kroz rez na vratu, a rijetko je potrebno učiniti gornju medijalnu sternotomiju.

U skupini bolesnika s medularnim karcinomom štitnjače važno je prepoznati bolesnike s familijarnim tipom (nasljedni medularni karcinom, sindrom multiple endokrine neoplazije). Dijagnoza familijarnog tipa medularnog karcinoma indicira probir kod članova obitelji. On uključuje mjerenje razine kalcitonina u krvi i/ili otkrivanje mutacije RET protoonkogena. Kod nosilaca mutacije RET protoonkogena indicirana je profilaktična tiroidektomija. Dosad nije jednoznačno određena dob i minimalna neophodna dijagnostička obrada potrebna kako bi se učinila profilaktična totalna tiroidektomija.

U skupinu slabo diferenciranih karcinoma štitnjače ubrajaju se inzularni karcinom, papilarni i folikularni



nar cell cancer – without insular cancer characteristics), mucinous and mucoepidermoid cancer. Prognosis for patients with poorly differentiated thyroid cancer is worse than for patients with well differentiated thyroid cancer but better than for patients with anaplastic thyroid cancer. Surgical treatment includes total thyroidectomy and central compartment neck dissection. Modified radical neck dissection is indicated if metastatic lymph nodes are present. Radioiodine therapy is applied postoperatively. Chemotherapy and radiotherapy have a palliative role.

Anaplastic thyroid cancer is rarely surgically treatable because it usually presents as advanced inoperable tumor. It is important to differentiate anaplastic thyroid cancer from thyroid gland lymphoma and de Quervain's thyroiditis because of their similar presentation and different prognosis and treatment. Possible surgical treatments are: 1) radical operation of primary tumor and diagnosed metastases (rare); 2) biopsy for histological confirmation; and 3) tracheotomy to ensure airway patency. Survival with anaplastic thyroid cancer is possible only with accidentally diagnosed anaplastic cancer, usually within papillary or follicular cancer which is well defined and radically treated by surgery.

Thyroid gland lymphoma is not treated surgically but it is necessary to confirm the diagnosis with biopsy before treatment. After immunohistochemical analysis and disease staging, thyroid gland lymphomas are treated with primary radiotherapy, chemotherapy or chemoradiotherapy.

In this presentation we discuss guidelines for surgical treatment of medullary, poorly differentiated and anaplastic thyroid cancer based on available literature

karcinomi s dijelovima tumora koji pokazuju slabiju diferencijaciju (karcinom visokih stanica, karcinom kolumnarnih stanica – bez značajka inzularnog karcinoma), mucinozni i mucoepidermoidni karcinom. Prognoza bolesnika sa slabo diferenciranim karcinomom štitnjače lošija je od prognoze bolesnika s dobro diferenciranim karcinomima, ali bolja od prognoze bolesnika s anaplastičnim karcinomom. Kirurško liječenje uključuje totalnu tiroidektomiju i disekciju limfnih čvorova skupine VI., te modificiranu radikalnu disekciju vrata ako postoje metastaze. Poslijeoperacijski se primjenjuje radiojodna terapija, a kemoterapija i radioterapija imaju paliјativnu ulogu.

Anaplastični karcinom štitnjače rijetko je moguće kirurški liječiti, jer se u trenutku prezentacije najčešće radi o uznapredovalom, inoperabilnom tumoru. Sličnu kliničku prezentaciju, ali različitu prognozu i liječenje imaju limfomi štitne žlijezde i de Quervainov tireoiditis, te ih je potrebno prepoznati prije konačne odluke o liječenju. Moguće operacije kod anaplastičnog karcinoma štitnjače su: 1. radikalna operacija primarnog tumora i dijagnosticiranih metastaza (rijetko); 2. biopsija radi postavljanja točne dijagnoze; 3. traheotomija radi osiguravanja dišnog puta. O preživljenju kod anaplastičnog karcinoma štitnjače možemo govoriti samo kod slučajno otkrivenih anaplastičnih karcinoma, najčešće unutar papilarnog ili folikularnog karcinoma koji su dobro ograničeni i kirurški radikalno liječeni.

Limfom štitne žlijezde ne liječi se kirurški, ali je postavljanje točne dijagnoze biopsijom tumora neophodno prije početka liječenja. Nakon određivanja imunohistokemijskih značajka i stadija bolesti limfomi štitne žlijezde liječe se primarnom radioterapijom, kemoterapijom ili kombinirano kemoradioterapijom.

U ovom radu prikazane su smjernice za kirurško liječenje medularnog, slabo diferenciranog i anaplastičnog karcinoma štitnjače temeljene na dostupnoj literaturi i iskustvu u kirurškom liječenju bolesti štitnjače tijekom 39 godina postojanja Službe za tumore glave i vrata Klinike za tumore.



## HISTOPATHOLOGY OF MEDULLARY, POORLY DIFFERENTIATED AND ANAPLASTIC THYROID CARCINOMA

### HISTOPATOLOGIJA MEDULARNOG, SLABO DIFERENCIRANOG I ANAPLASTIČNOG KARCINOMA ŠTITNJAČE

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#### Medullary thyroid carcinoma

Medullary thyroid carcinoma accounts for 5%-10% of all thyroid malignancies and up to 25% of these tumors are heritable (MEN and familial). In patients with MEN syndrome it occurs in infancy, early childhood and early adulthood, whereas familial and sporadic tumors manifest at a mean age of 50 years.

The etiology of sporadic cases is unknown while hereditary cases harbor RET germline mutation. C-cell hyperplasia is a precursor of heritable medullary carcinoma. It is typically located in the middle third of the lobe. The tumor presents as a painless nodule cold on scintigraphic scan. Up to 50% of patients present with nodal metastasis and up to 15% may have distant metastases. The tumor produces calcitonin and many other products that result in different paraneoplastic syndromes. The tumor is white-gray to tan, gritty and well circumscribed, but not encapsulated. The characteristic histopathology includes sheets, nests or trabeculae of polygonal, round to spindle cells, separated by fibrovascular stroma. Nuclei are round to oval with coarse chromatin and nucleoli are not prominent. The cytoplasm is granular and eosinophilic, and has ill-defined margins. Necrosis and hemorrhage are infrequent. Congo red positive stromal deposits of amyloid can be identified in 80% of cases. The problem is that the histopathologic appearance is quite variable; 12 variants of medullary carcinoma showing unusual features have been described. It is the reason that makes the differential diagnosis so wide and difficult. Carcinoma is usually positive for calcitonin, CEA and neuroendocrine markers. According to histopathological criteria it has been suggested that necrosis, squamous metaplasia, less than 50% of calcitonin positive cells and CEA positive/calcitonin negative immunoprofile represent poor prognostic fea-

#### Medularni karcinom štitnjače

Medularni karcinom štitnjače ima učestalost od 5%-10% svih malignoma štitnjače, a 25% ovih tumora su nasljedni (MEN i obiteljski). Tumori koji se javljaju u sklopu sindroma MEN pojavljuju se u djetinjstvu i ranoj mladosti, dok se obiteljski i sporadični javljaju u dobi od oko 50 godina. Etiologija sporadičnih slučajeva je nepoznata, dok nasljedni posjeduju znakovitu RET mutaciju. C-stanična hiperplazija je preteča nasljednog medularnog karcinoma. Tipično je lokaliziran u srednjoj trećini režnja. Tumor se prezentira kao bezbolni čvor, "hladan" na scintigrafiji. Čak do 50% bolesnika dolazi s metastazama u limfnim čvorovima, a 15% ih već ima udaljene metastaze. Tumor stvara kalcitonin i mnoge druge proizvode koji daju sliku različitih paraneoplastičnih sindroma. Tumor je bjelkasto-sivkast do smeđkast, hrapave površine i oštro ograničen, ali ne i očahuren. Znakovita histopatologija su plaže, gnijezda i tračci poligonalnih, okruglastih do vretenastih stanica odijeljenih fibrovaskularnom stromom. Jezgre su okrugle do ovalne s raspršenim kromatinom, a jezgrice nisu uočljive. Citoplazma je granulirana, ružičasta s nejasnim rubovima. Nekroze i krvarenja su rijetki. Stromalni depoziti amiloida koji se boje Congo crvenilom mogu se naći u 80% slučajeva. Problem je u tome što je histopatologija medularnog karcinoma izrazito varijabilna, pa se danas raspoznaje 12 varijanata koje pokazuju vrlo neobične mikroskopske slike. To je i razlog što je diferencijalna dijagnostika izrazito opsežna i teška. Karcinom je uglavnom pozitivan na kalcitonin, CEA i neuroendokrine biljege. Shodno histopatološkim kriterijima smatra se da nekroza, pločasta metaplasija, manje od 50% na kalcitonin pozitivnih stanica i na CEA pozitivni/kalcitonin negativni imunološki profil stanica predstavljaju loše prognostičke značajke. Klinička obilježja sa skraćenim



tures. Clinical features with reduced survival are older age, male sex, local invasion and distant metastases.

### Poorly Differentiated Carcinoma

By definition, poorly differentiated carcinoma is a follicular cell neoplasm that shows limited evidence of structural follicular cell differentiation and occupies both morphologically and behaviorally an intermediate position between differentiated and anaplastic carcinomas. It remains a controversial entity with different geographic distribution and diagnostic criteria. In Italy and some Latin American countries, it has been reported to account for 4%-7% of all thyroid carcinomas. The tumor is more common in women older than 50 years. It usually appears as a solitary, large, "cold" mass. Most of them present as a recent growth of long standing nodular thyroid. Nodal, lung and bone metastases are frequent at the time of diagnosis. It typically appears as a tumor over 3 cm in diameter, solid and gray with necrosis, pushing borders and invasive peritumoral growth. There are three histologic patterns recognized: insular, trabecular and solid. The insular pattern is characterized by nests of tumor cells, trabecular by cells arranged in ribbons, and solid exhibits large sheets. Tumor cells are immunoreactive to thyroglobulin and TTF-1, focally to p53, Ki-67 and nuclear beta-catenin. The outcome is poor, with a 50% 5-year survival rate. It depends on TNM staging, completeness of surgery and responsiveness to radioactive iodine therapy.

### Undifferentiated (Anaplastic) Carcinoma

Undifferentiated (anaplastic) carcinoma is a highly malignant tumor that histologically appears wholly or partially composed of undifferentiated cells that exhibit immunohistochemical or ultrastructural features indicative of epithelial differentiation. It presents as a rapidly expanding neck mass with hoarseness, dysphagia, vocal cord paralysis and dyspnea. The tumor is large, fixed and hard, single or multiple. At the time of diagnosis more than 40% of patients have lung, bone or brain metastases. The tumor is fleshy and white-tan with necrosis and hemorrhage. Infiltrative growth can replace most of the thyroid and invade surrounding structures. On histology, there is admixture of spindle cells, pleomorphic giant cells and epithelioid cells. Mitotic figures are frequent and necrosis with vascular wall invasion is common. Tumor cells are immunoreactive for cytokeratin. Thyroglobulin is almost invariably negative,

razdobljem preživljenja su starija dob, muški spol, lokalna invazija i udaljene metastaze.

### Slabo diferencirani karcinom

Slabo diferencirani karcinom je po definiciji neoplazma koja nastaje iz folikularnih stanica, ali koja histološki pokazuje ograničenu diferencijaciju folikularnih stanica te zauzima i morfološki i po ponašanju položaj između dobro diferenciranih karcinoma podrijetlom iz folikularnog epitela i anaplastičnog karcinoma. Postoje kontroverze koje uključuju različitu zemljopisnu rasprostranjenost ili pak dijagnostičke kriterije. Shodno tome se u Italiji i nekim zemljama Južne Amerike navodi učestalost od 4%-7% svih karcinoma štitnjače. Tumor je češći kod žena starijih od 50 godina. Uglavnom se pojavljuje kao solitarna, velika "hladna" masa. Mnogi od njih predstavljaju se kao nagli rast dugotrajne čvoraste štitnjače. Metastaze u limfnim čvorovima, plućima i kostima često su prisutne već u vrijeme dijagnoze. Tipično se pojavljuje kao tumor veći od 3 cm, solidan, siv, s nekrozama, gurajućim rubovima i invazivnim rastom. Tri su opisana histološka tipa: inzularni, trabekularni i solidni. Inzularni tip čine gnijezda ili otočići, trabekularni tračci, a solidni plaže tumorskih stanica. Stanice su pozitivne na tireoglobulin i TTF-1, žarišno na p53, Ki-67 i beta katenin. Prognoza je loša, petogodišnje preživljenje je 50% i ovisi o TNM stadiju, potpunom kirurškom odstranjenju i odgovoru na terapiju radioaktivnim jodom.

### Nediferencirani (anaplastični) karcinom

Nediferencirani (anaplastični) karcinom je izrazito maligni tumor u potpunosti ili djelomice histološki građen od nediferenciranih stanica koje pokazuju imunohistokemijske i ultrastrukturne značajke epitelne diferencijacije. Javlja se kao brzo rastuća ekspanzivna masa na vratu sa simptomima promuklosti, otežanog gutanja, paralize glasnica i otežanog disanja. Karcinom je velik, fiksiran i čvrst, može biti solitarni ili višestruk. U vrijeme dijagnoze više od 40% bolesnika ima metastaze u plućima, kosti i mozgu. Tumor izgleda mesnat, bijelo-siv, s nekrozama i krvarenjem. Invazivni rast može prožeti čitavu štitnjaču i invadirati okolne strukture. U histologiji se nalazi mješavina vretenastih, pleomorfnih orijaških i epiteloidnih stanica. Mitoze su učestale, a vide se i nekroze stijenka krvnih žila s tumorskom invazijom. Tumorske stanice su pozitivne na citokeratin. Tireoglobulin je gotovo u pravilu negativan, TTF-1 je rijetko pozitivan, a p53 je izrazito pozitivan. Postoji neko-

TTF-1 is rarely expressed but p53 is strongly positive. There are several variants: osteoclast-like, carcinosarcoma, lymphoepithelioma, paucicellular. Differential diagnosis includes most sarcomas (rhabdo, leio, angio) and melanoma, lymphoma and medullary carcinoma. It is a highly aggressive neoplasm with overall 5-year survival of 0%-14%, median 2.5-6 months.

liko histoloških varijanata: nalik osteoklastima, karcinosarkom, limfoepiteliom, oskudno stanični. Diferencijalna dijagnoza obuhvaća većinu sarkoma (rhabdo, leio, angio) te melanom, limfom i medularni karcinom. To je izrazito agresivan karcinom čije se petogodišnje preživljenje kreće od 0% do 4%, a srednje iznosi 2,5-6 mjeseci.

## ONCOLOGICAL TREATMENT OF THYROID CANCER ONKOLOŠKO LIJEČENJE RAKA ŠTITNJAČE

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### Introduction

Usually, thyroid cancer (TC) is well treatable disease with excellent prognosis. The vast majority of differentiated thyroid cancers (DTC) can be successfully treated with surgery, followed by radioiodine and L-thyroxine therapy. By this strategy, permanent remission is obtained in most patients with limited disease and in nearly 50% of those with distant metastases, which are rare in DTC patients.

Only several percent of patients present with poorly differentiated and anaplastic tumors which do not take up radioiodine, but dedifferentiation (loss of thyroid-specific functions) can also occur in DTCs during the course of tumor progression. When these lesions are surgically unresectable, standard therapeutic options include chemotherapy and external radiotherapy (ERT).

Medullary thyroid cancer (MTC) represents a distinct pathological entity, descending from parafollicular cells which do not take up radioiodine. Primary treatment of MTC is surgical removal of all neoplastic tissue with very limited therapeutic options for residual, recurrent or metastatic disease due to modest response to radiotherapy and/or chemotherapy.

The lack of an effective therapy for tumors that do not respond to radioiodine and TSH-suppressive therapy led to intensive investigations of the pathways in-

### Uvod

Rak štitnjače (RŠ) je bolest koja se uglavnom uspješno liječi i ima odličnu prognozu. Velika većina diferenciranih karcinoma štitnjače (DKŠ) uspješno se liječi operacijom, praćenom terapijom radioaktivnim jodom i L-tiroksinom. Ovim se pristupom postiže trajna remisija u većine bolesnika s ograničenom bolešću i u gotovo 50% bolesnika s udaljenim metastazama, koje su rijetke u bolesnika s DKŠ.

U svega nekoliko postotaka bolesnika nalazimo slabo diferencirane i anaplastične karcinome koji ne nakupljaju radiojod, no dediferencijacija (gubitak funkcija specifičnih za štitnjaču) može se javiti u bolesnika s DKŠ tijekom napredovanja bolesti. Kada ove tumore nije moguće kirurški odstraniti, standardni postupci liječenja uključuju kemoterapiju i izvanjsku radioterapiju (ERT).

Medularni karcinom štitnjače (MKŠ) zaseban je patološki entitet, jer potječe od parafolikularnih stanica koje ne nakupljaju radioaktivni jod. Primarna terapija MKŠ je kirurško odstranjenje cjelokupnog tumora, dok su terapijske mogućnosti kod ostatne, recidivirajuće ili metastatske bolesti vrlo ograničene zbog njegove male osjetljivosti na radioterapiju i/ili kemoterapiju.

Nedostatak učinkovite terapije za tumore koji ne odgovaraju na terapiju radioaktivnim jodom i terapiju supresijom TSH potaknuo je intenzivna istraživanja bi-

volved in TC genesis and progression. These investigations have resulted in the development of novel treatment strategies, especially molecularly targeted therapies, which will, hopefully, help overcome the resistance to standard treatment modalities.

### Overview of standard treatment options

In DTC, ERT is commonly used in the following settings: primary therapy if the tumor is locally unresectable, particularly if it does not accumulate  $^{131}\text{I}$ ; residual bulky tumor in neck region after surgery, not controlled by  $^{131}\text{I}$  alone; continually recurring TC regardless of  $^{131}\text{I}$  accumulation; and recurrent or metastatic TC occurring after maximal  $^{131}\text{I}$  therapy. The role of adjuvant ERT for patients with high risk features (e.g., extracapsular lymph node spread or involvement of adjacent neck tissues) is controversial, but may be considered. ERT portals for inoperable disease should encompass the entire thyroid tumor, neck, and superior mediastinum if indicated; tumor dose of 65 to 70 Gy in 7 to 8 weeks (1.8 to 2 Gy *per* fraction) is recommended.

The effectiveness of ERT for MTC is still controversial, but recent data indicate that it can be used with curative intent for microscopic or gross residual disease. Because of high incidence of cervical and mediastinal nodal involvement, treatment portals should be quite large, encompassing the whole neck, supraclavicular regions and superior mediastinum. These regions are irradiated to 60 Gy in 6-7 weeks (for residual disease), or 65-70 Gy in 7-8 weeks (for inoperable tumors). Tumor regression after radiotherapy is quite slow, necessitating a longer follow up to assess therapeutic effects. There is no solid evidence that adjuvant ERT in MTC prolongs overall survival, although it may be considered in high-risk patients.  $^{131}\text{I}$  adjuvant therapy in MTC, on the basis of so-called “bystander effect”, is controversial, without proven effect on overall survival.

In the treatment of metastatic MTC, internal RT with radionuclides bound to specific tracers, if tumor accumulated ( $^{131}\text{I}$ -MIBG therapy), or its “cold” analogues (somatostatine analogue, based on the tumor accumulation of  $^{111}\text{In}$ -octreotide), is sometimes applicable.

In patients with anaplastic thyroid cancer (ATC), ERT should be administered after maximal debulking surgery. Because of its radioresistance, higher doses (up to 60 Gy in 6 weeks) must be delivered to achieve therapeutic effect, but the disease is seldom controlled with radiotherapy alone. In conjunction with chemotherapy

okemijskih mehanizama uključenih u nastanak i napredovanje RŠ. Rezultati tih istraživanja temelj su za razvoj novih terapijskih pristupa, poglavito onih usmjerenih na specifične molekule. Nadamo se da će se ovim pristupom prevladati otpornosti na standardne načine liječenja.

### Pregled standardnih terapijskih postupaka

U DKŠ, ERT se obično rabi u slijedećim slučajevima: kao primarna terapija kod lokalno neresektibilnog tumora, osobito ako ne nakuplja  $^{131}\text{I}$ ; opsežan ostatni tumor na vratu nakon operacije, koji se ne može kontrolirati isključivo terapijom  $^{131}\text{I}$ ; stalno recidivirajući RŠ neovisno o tome nakuplja li  $^{131}\text{I}$ ; te recidivirajući ili metastatski RŠ koji se javlja nakon maksimalne doze terapije  $^{131}\text{I}$ . Uloga adjuvantne ERT u visokorizičnih bolesnika (npr. proboj kapsule limfnog čvora ili zahvaćenost susjednih tkiva na vratu) je kontroverzna, no može ju se razmotriti. Polja zračenja ERT kod inoperabilne bolesti trebaju obuhvatiti cjelokupni tumor štitnjače, vrat i, ako je indicirano, gornji medijastinum; preporuča se tumorska doza od 65 do 70 Gy kroz 7 do 8 tjedana (doza po frakciji 1,8 do 2 Gy).

Učinkovitost ERT u MKŠ još je uvijek proturječna, no nedavni podaci ukazuju na to da se može rabiti s namjerom izliječenja kod mikroskopske ili makroskopske ostatne bolesti. Zbog česte zahvaćenosti cervikalnih ili medijastinalnih limfnih čvorova potrebna su velika polja zračenja koja obuhvaćaju cijeli vrat, supraklavikularne regije i gornji medijastinum. Ova polja zrače se do 60 Gy tijekom 6-7 tjedana (kod ostatne bolesti), odnosno 65-70 Gy tijekom 7-8 tjedana (kod inoperabilnih tumora). Regresija tumora nakon radioterapije je dosta spora, što zahtijeva dulje praćenje za uočavanje terapijskog učinka. Nema čvrstih dokaza da adjuvantna ERT u MKŠ produljuje ukupno preživljenje, premda ju se može razmotriti u visokorizičnih bolesnika. Adjuvantna primjena  $^{131}\text{I}$  u MKŠ, zasnovana na takozvanom “učinku promatrača”, proturječna je, bez dokazanog učinka na ukupno preživljenje.

U liječenju metastatskog MKŠ ponekad se može primijeniti i unutarnja RT uz uporabu radionuklida vezanih za specifične spojeve, ako ih tumor akumulira (terapija pomoću  $^{131}\text{I}$ -MIBG) ili njihovih “hladnih” analoga (analog somatostatina, temeljeno na tumorskoj akumulaciji  $^{111}\text{In}$ -oktreotida).

U bolesnika s anaplastičnim karcinomom štitnjače (AKŠ) ERT treba primjenjivati nakon maksimalnog operacijskog smanjenja tumorske mase. Zbog njegove radi-

(the most commonly used regimen is weekly low-dose doxorubicin), ERT administered once or twice daily, to a total dose of 56- 57.6 Gy, may result in a 5-year survival rate of about 10%.

ERT is also indicated for treatment of skeletal metastases, especially in danger of pathologic fracture, or to relieve pressure symptoms occurring in vital areas caused by soft-tissue masses, brain metastases, superior vena cava syndrome, etc.

In patients with TC, chemotherapy is commonly used only in cases of progressive metastatic disease refractory to radioiodine treatment and not manageable by surgery and/or ERT. Among various cytotoxic agents, anthracyclines appear to be most effective, either as monotherapy, or in conjunction with e.g., platinum compounds, with an average 30% response rate. Other chemotherapeutics showing certain efficacy in TC are: bleomycin, vincristin, taxanes, etoposide, cyclophosphamide, 5-fluorouracil, streptozotocin, etc.

Pulmonary metastases are most responsive to chemotherapy, followed by skeletal and regional neck metastases. The most significant responses to doxorubicin monotherapy were seen in patients with DTC and MTC. Unfortunately, responses are mostly partial and short lasting.

### Review of potential new therapeutic approaches

The knowledge of TC biochemistry has enormously improved over the past two decades. Overexpression and/or uncontrolled activation of tyrosine kinase receptors and downstream signaling molecules, as well as inhibition of apoptosis have all been demonstrated to occur in TC. Several novel therapeutic approaches already showed results *in vitro* and in animal models. These approaches target molecular pathways responsible for the pathogenesis of TC, especially tyrosine kinase receptors and Ras-pathway as well as other pathways involved in angiogenesis and proliferation. They are utilizing antisense technology or agents that act as antibodies, receptor antagonists, multikinase inhibitors or apoptotic agents. Many of these agents are currently tested in phase II clinical trials.

Other novel approaches for the treatment of TC include gene therapy, radioimmunotherapy and redifferentiation therapy. Mutations of the *ret* oncogene play a prominent role in the pathogenesis of MTC, but genetic alterations have also been identified in DTC. Gene therapy techniques use viral or non-viral vectors for the

orezistentnosti potrebne su više doze (do 60 Gy tijekom 6 tjedana) za postizanje terapijskog učinka, no bolest se rijetko može kontrolirati primjenom isključivo radioterapije. U kombinaciji s kemoterapijom (najčešće se primjenjuje tjedni niskodozni doksorubicin) ERT se provodi jednom ili dvaput na dan do ukupne doze od 56 do 57,6 Gy, što može rezultirati 5-godišnjim preživljenjem od oko 10%.

ERT je indicirana i u liječenju koštanih metastaza, osobito kod opasnosti od patološke frakture, ili za smanjenje simptoma kompresije u vitalnim područjima uslijed pritiska mekotkivnih masa, moždanih metastaza, sindroma gornje šuplje vene itd. U bolesnika s RŠ kemoterapija se obično rabi samo u slučajevima progresivne metastatske bolesti koja je refraktorna na radiojodnu terapiju ili ju se ne može liječiti operacijom i/ili ERT. Među različitim citotoksičnim agensima vjerojatno su najučinkovitiji antraciklini, bilo kao monoterapija ili u kombinaciji s npr. spojevima platine, s prosječnom stopom odgovora od 30%. Ostali kemoterapeutici koji pokazuju određenu učinkovitost u RŠ su: bleomicin, vinkristin, taksani, etopozid, ciklofosfamid, 5-fluorouracil, streptozotocin itd.

Plućne metastaze najbolje odgovaraju na kemoterapiju, a nakon njih koštane i lokalne metastaze na vratu. Najbolji odgovori na monoterapiju doksorubicinom zamijećeni su u bolesnika s DKŠ i MKŠ. Nažalost, odgovor na terapiju je uglavnom djelomičan i kratkotrajan.

### Pregled potencijalnih novih terapijskih pristupa

Razumijevanje biokemije RŠ neizmjenjivo se poboljšalo tijekom posljednja dva desetljeća.

Utvrđeno je da kod RŠ dolazi do prekomjerne ekspresije i/ili nekontrolirane aktivacije tirozin-kinaznih receptora, kao i molekula koje se nalaze niže u signalnom putu, te inhibicije apoptoze. Nekoliko je novih terapijskih pristupa već pokazalo učinke *in vitro* i u životinjskim modelima. Ti su pristupi usmjereni na molekularno-biokemijske mehanizme odgovorne za patogenezu RŠ (u koje ubrajamo receptorske tirozin-kinaze i signalni put Ras, kao i druge signalne puteve uključene u angiogenezu i proliferaciju), te primjenjuju *antisense* tehnologiju ili spojeve koji djeluju poput protutijela, receptorskih antagonista, multikinaznih inhibitora ili potiču apoptozu. Mnogi se od njih trenutno istražuju u kliničkim studijama II. faze.

Ostali novi pristupi liječenju RŠ uključuju gensku terapiju, radioimunoterapiju i rediferencijacijsku terapiju. Mutacije onkogenog *ret* imaju istaknutu ulogu u pa-

introduction of “therapeutic” DNA into target cells. Strategies of gene therapy for TC are directed to replacement of mutated tumor suppressor gene *p53*, activation of enzymes that potentiate cell sensitivity to chemotherapy, reexpression of sodium iodide symporter (NIS; responsible for iodide accumulation in follicular thyroid cells), etc. Despite theoretical advantages, there are still many limitations for the clinical use of gene therapy.

Radioimmunotherapy is the therapeutic option for MTC, associated with expression of tumor-associated carcinoembryonic antigen (CEA). Mouse monoclonal anti-CEA antibodies labeled with <sup>131</sup>I were evaluated in phase I and II clinical trials in patients with metastatic MTC. This therapy showed evidence of biochemical and antitumor activity. The use of humanized antibodies helps overcome the host immune reaction to mouse antibodies.

Redifferentiation therapy, mostly with retinoic acid, is aimed to restoration of thyroid-specific functions (expression of NIS) in cells of dedifferentiated tumors, so radioiodine therapy may be applicable again.

All these treatment approaches still need further investigation, so patient enrolment in clinical studies must be strongly encouraged.

togenezi MKŠ, no genske promjene otkrivene su i u DKŠ. Tehnike genske terapije rabe virusne ili nevirusne vektore za uvođenje “terapijske” DNA u ciljne stanice. Genskom je terapijom moguće zamijeniti mutirani tumor-supresorski gen *p53*, aktivirati enzime koji povećavaju osjetljivost stanica na kemoterapiju, reeksprimirati simporter za natrij-jodid (NIS; odgovoran za akumulaciju jodida u folikularnim stanicama štitnjače) itd. Unatoč teorijskim prednostima, još je mnogo ograničenja za kliničku primjenu genske terapije.

Radioimunoterapija je terapijska opcija kod MKŠ, ovisna o ekspresiji karcinoembrijskog antigena (CEA) povezanog s tumorom. Mišja monoklonska anti-CEA protutijela obilježena <sup>131</sup>I istraživana su u kliničkim studijama I. i II. faze u bolesnika s metastatskim MKŠ. Terapija je pokazala biokemijsku i antitumorsku učinkovitost. Primjena humaniziranih protutijela olakšava prevladavanje imune reakcije domaćina na mišja protutijela.

Rediferencijacijska terapija, uglavnom retioničnom kiselinom, usmjerena je ka obnavljanju funkcija specifičnih za štitnjaču (ekspresija NIS) u stanicama dediferenciranih tumora, kako bi se ponovno mogla primijeniti radiojodna terapija.

Svi ovi terapijski pristupi zahtijevaju daljnja istraživanja, te se snažno potiče uključivanje bolesnika u kliničke studije.

## MULTIMODALITY APPROACH IN THYROID CANCER IMAGING

### RAZLIČITE METODE SLIKOVNOG PRIKAZA RAKA ŠTITNJAČE

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For a long time, classic radioiodine whole-body scintigraphy was the mainstay in thyroid cancer imaging. Currently, in addition to serum thyroglobulin (Tg) as a very sensitive and specific tumor marker for residual or recurrent disease, and ultrasonography that can be combined with fine needle aspiration biopsy as a major tool in the detection of locoregional disease, radioiodine imaging still plays an important role in the follow up of

Radiojodna scintigrafija cijelog tijela je dugo vremena bila slikovna metoda izbora u bolesnika s karcinomom štitnjače. Posljednjih godina je uz ultrasonografiju i po potrebi punkciju pod kontrolom ultrazvuka i određivanje osjetljivog i specifičnog tumorskog biljega tireoglobulina u serumu radiojodna scintigrafija i dalje važna metoda u praćenju bolesnika s diferenciranim karcinomom štitnjače nakon tiroidektomije i radiojodne ablacije os-





patients with differentiated thyroid cancer after surgery and radioiodine ablation. A whole-body scan (WBS) using I-123 or I-131 may detect iodine avid local recurrences or distant metastases and direct radioiodine treatment.

Although radioiodine uptake in recurrent thyroid cancer is a highly specific finding, the sensitivity of radioiodine imaging is rather low. Various other imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI), and bone scintigraphy have been used in order to localize tumor sites and aid in the decision on appropriate treatment such as surgery or external-beam radiotherapy. Also, several other radiopharmaceuticals including Tl-201, Tc-99m sestamibi, Tc-99m tetrofosmin, and In-111 octreotide have been evaluated in the detection of a recurrent tumor or metastatic disease.

Cross-sectional imaging, including both CT and MRI, has a limited role in thyroid cancer imaging, mostly in invasive neoplasms to assess the local extent of the disease and to detect the involvement of adjacent structures such as the larynx, trachea and vessels. An MRI evaluation is essential for suspected central nervous system involvement and possible spinal cord compression in case of large vertebral lesions.

During recent years, significant developments in cancer imaging have also changed imaging approaches in thyroid cancer patients. Molecular imaging, positron emission tomography (PET) imaging with F-18 fluorodeoxyglucose (FDG) in particular, has become the most powerful tool for staging and restaging of cancers. In respect of well-differentiated thyroid cancers, FDG-PET is commonly utilized when there is discordance between elevated Tg and negative radioiodine WBS.

Also, there is discordance between radioiodine and FDG-PET imaging. Radioiodine uptake in metastatic lesions usually indicates more differentiated cancers. Recurrent cancers that do not concentrate radioiodine are generally associated with more aggressive clinical behavior. These tumors are usually rapidly growing, demonstrate high metabolic rates and increased FDG uptake on PET scan. The lack of the ability to concentrate iodine in Tg positive patients appears to be due to the lower expression of the sodium-iodine symporter.

The utility of FDG-PET scan for the detection of thyroid cancer lesions in patients with a negative radioiodine scan and increased Tg levels has already been well documented. It has been shown that FDG-PET is the most accurate method in this situation with sensi-

tatka štitnjače. Scintigrafijom cijelog tijela pomoću I-123 ili I-131 mogu se otkriti lokalni recidivi i udaljene metastaze koje nakupljaju jod i pratiti rezultate liječenja pomoću J-131.

Iako je nakupljanje radioaktivnog joda u recidivu i metastazama karcinoma štitnjače izrazito specifičan nalaz, osjetljivost slikovne metode je niska. Razne druge dijagnostičke metode uključujući CT, MR i scintigrafiju kostiju rabe se u cilju lokaliziranja tumora za određivanje optimalne terapije kao što su operacijski zahvat i zračenje vanjskim izvorima. Također je pokušana upotreba nekoliko drugih radiofarmaka uključujući Tl-201, Tc-99m sestamibi, Tc-99m tetrofosmin i In-111 oktreotid u otkrivanju recidiva i metastaza. CT i MR najčešće se rabe kod invazivnih tumora kako bi se procijenila zahvaćenost okolnih organa kao što je larinks, traheja i krvne žile. MR ima značajnu ulogu u otkrivanju metastaza u središnjem živčanom sustavu, kao i u dijagnostici moguće kompresije leđne moždine u slučaju zahvaćenosti kralježnice.

U posljednje vrijeme značajan razvoj slikovnih metoda za prikazivanje tumora doveo je do promjena i u dijagnostici i terapiji bolesnika s karcinomom štitnjače. Molekularne slikovne metode, osobito pozitronska emisijska tomografija (PET) s fluor-18 deoksiglukozom (FDG) postale su važno sredstvo u određivanju stadija bolesti u bolesnika s raznim malignim bolestima. U bolesnika s diferenciranim karcinomom štitnjače FDG-PET se rabi kada postoji neslaganje među drugim dijagnostičkim metodama, najčešće u slučaju povišenih vrijednosti Tg i negativne radiojodne scintigrafije cijelog tijela. S obzirom na nakupljanje radiofarmaka u metastazama često je neslaganje između radiojodne scintigrafije i PET. Nakupljanje radiojoda u metastazama najčešće se nalazi u dobro diferenciranim tumorima, dok se u slučaju lezija koje ne akumuliraju radiojod najčešće radi o agresivnijim tumorima. Ovakvi tumori obično brzo rastu, imaju jaku metaboličnu aktivnost i pojačano nakupljaju FDG na PET. Nemogućnost akumulacije radiojoda kod bolesnika s povišenim vrijednostima Tg najvjerojatnije je posljedica slabo izražene ekspresije natrij-jodne kotransportne molekule.

Mnoge studije pokazale su značenje FDG PET u otkrivanju metastaza u bolesnika s karcinomom štitnjače s negativnom radiojodnom scintigrafijom i povišenim vrijednostima Tg. Smatra se da je u ovakvih bolesnika osjetljivost i specifičnost nalaza FDG-PET između 85% i 95%. U usporedbi sa scintigrafskim metodama s drugim radiofarmacima FDG-PET ima najveću osjetljivost

tivity and specificity ranging between 85% and 95%. In comparison to other noniodine radionuclide imaging agents, FDG-PET provides highest resolution for detecting aggressive metastatic thyroid cancer lesions. Also, several studies indicate its potential as a prognostic marker. In addition to the reduced survival of patients with FDG avid disease, a significant correlation was found with the highest metabolic activity measured as maximum SUV, and with the volume of FDG-avid tumor. FDG-PET has been suggested as a monitoring procedure in high-risk patients, patients with adverse histology (tall cell, columnar cell and insular variants), elevated Tg with no known source and Hürthle cell carcinoma.

Another important recent development in cancer imaging was the integration of two basic aspects of imaging, function and structure. This concept of fusion, merging anatomic with molecular image information, provides precise localization of metabolic findings and more accurately characterizes structural alterations. The concept has been materialized with the development of dual-modality hybrid scanners including PET/CT and SPECT/CT, providing near-simultaneous imaging of molecular and anatomic information.

Early reports on integrated FDG PET/CT imaging indicated an improved diagnostic accuracy and higher diagnostic confidence in comparison to either imaging modality alone. The most important advantage of combined PET/CT was the precise localization of local recurrences and distant metastatic disease, which improved surgery and external-beam radiation planning and changed management in up to 50% of patients. An additional important benefit of fused anatomic and functional information is that the pitfalls of PET could be reduced by increasing the specificity of FDG-PET.

There is also an important role for FDG PET/CT in other thyroid cancers that do not concentrate iodine, including anaplastic cancer, medullary cancer, and lymphoma. It is superior to anatomic imaging in defining the local extent of the disease, the presence of distant metastases and monitoring the response to therapy.

Another PET tracer that has a potential to improve treatment planning in thyroid cancer as an ideal tracer for dosimetry is iodine radionuclide, I-124. It appears that I-124 PET/CT may have an important role for individualized dosimetry in patients with metastatic thyroid cancer.

In summary, PET/CT plays an important role in the management of well-differentiated thyroid cancers de-

u otkrivanju metastaza agresivnih tumora štitnjače. Neke studije su pokazale i moguće prognostičko značenje ove metode. Nađena je korelacija metabolične aktivnosti metastaza određena pomoću standardiziranog indeksa akumulacije radiofarmaka i volumena tumora. Također je uočeno smanjeno preživljenje u bolesnika čije metastaze pojačano nakupljaju FDG. FDG PET je predložen za praćenje bolesnika koji imaju lošiju prognozu. To su bolesnici s tumorima visokih stanica, tumorima cilindričnih stanica i inzularnim tumorima, bolesnici s Hürthleovim tumorima, kao i bolesnici s visokim vrijednostima Tg nepoznatog ishodišta.

Nedavno je došlo do još jednog važnog napretka u slikovnom prikazu tumora: učinjena je integracija funkcionalnih i morfoloških metoda. Spoj molekularnog i anatomske slikovnog prikaza daje preciznu lokalizaciju metaboličnog nalaza i točniju karakterizaciju strukturnih promjena. Ovaj koncept omogućen je razvojem hibridnih skenera PET-CT i SPECT-CT, kojima se dobiju gotovo simultani prikazi molekularnih i anatomske informacije.

Prve studije FDG PET-CT pokazale su veću dijagnostičku vrijednost ovih hibridnih nalaza u usporedbi sa svakom metodom pojedinačno. Najznačajniji napredak PET-CT je točnija lokalizacija recidiva i udaljenih metastaza, što omogućuje planiranje operacija i zračenja vanjskim izvorima i mijenja pristup u oko 50% bolesnika. Još jedna dobra značajka hibridnih metoda je i povećana specifičnost u odnosu na nehibridne slikovne metode.

FDG PET-CT ima važnu ulogu u bolesnika s rakom štitnjače koji ne akumuliraju jod (bolesnici s anaplastičnim karcinomom, medularnim karcinomom i limfomom). Ova metoda superiornija je u odnosu na anatomske slikovne metode u određivanju lokalne proširenosti bolesti, otkrivanja udaljenih metastaza i praćenja odgovora na terapiju.

Smatra se da novi PET radiofarmak I-124 ima velik potencijal u poboljšanju terapije i dozimetrije u bolesnika karcinomom štitnjače. Nedavne studije pokazale su da I-124 PET-CT može imati važnu ulogu u individualizaciji dozimetrije u bolesnika s metastazama karcinoma štitnjače.

U zaključku, PET-CT je nova slikovna metoda koja omogućuje otkrivanje recidiva i metastaza u bolesnika s diferenciranim karcinomom štitnjače koji ne nakupljaju radiojod, a koje su klinički značajne, što može rezultirati odstranjenjem sekundarizma. PET-CT ima sličnu ulogu kod bolesnika s medularnim karcinomom štitnjače



detecting sites of metastatic disease and recurrence that are occult on radioiodine imaging, which is clinically relevant and can result in a curative removal of metastatic lesions. PET/CT plays a similar role for medullary thyroid cancers with a persistent elevated calcitonin level of unknown source. In anaplastic thyroid cancer and thyroid lymphoma, PET/CT is used at initial staging to determine the local extent of the disease, detect distant metastases and evaluate the response to therapy.

The concept of fusion, combining anatomic and functional information using hybrid systems, has been further extended to include SPECT tracers such as I-131. It has been shown that integrated I-131 SPECT/CT has an additional value over conventional planar radioiodine imaging in patients with differentiated thyroid cancer providing correct characterization of equivocal tracer uptake on planar imaging and precise localization of iodine avid lesions in the neck, chest and skeleton. SPECT/CT optimized the localization of radioiodine uptake to lymph node metastases *versus* remnant thyroid tissue, to lung *versus* mediastinal metastases, and to the skeleton. It also had a clinical impact on patient management influencing referral for radioiodine treatment, tailoring the administered radioiodine dose and/or the addition of surgery or external radiation therapy when indicated.

In conclusion, rapid and widespread clinical acceptance of hybrid PET/CT and SPECT/CT systems in clinical oncology has helped change diagnostic algorithms in the management of thyroid cancer in recent years.

koji imaju povišene vrijednosti kalcitonina. U bolesnika s anaplastičnim karcinomom i limfomom u štitnjači PET-CT se rabi za određivanje stadija bolesti. Ova metoda omogućuje otkrivanje lokalne proširenosti bolesti, udaljenih metastaza i evaluaciju terapijskog učinka.

Koncept fuzije anatomskih i funkcionalnih informacija upotrebom hibridnog sustava je proširen dalje uključivanjem SPECT radiofarmaka kao što je J-131. Pokazano je da integrirani J 131 SPECT-CT ima dodatnu vrijednost u odnosu na uobičajene planarne radiojodne slikovne metode u bolesnika s diferenciranim karcinomom štitnjače omogućujući točniju karakterizaciju lezija za koje nije sigurno da akumuliraju radiojod i točniju lokalizaciju lezija koje akumuliraju J-131 na vratu, prsnom košu i skeletu. SPECT-CT poboljšava razlučivanje metastaza na vratu u regionalnim limfnim čvorovima u odnosu na ostatno tkivo štitnjače, u plućima u odnosu na metastaze u medijastinumu i otkrivanje metastaza u kostima. Ova metoda ima značenje u i liječenju bolesnika zbog pouzdanijeg utvrđivanja bolesnika u kojih je indicirana radiojodna terapija, kirurško odstranjenje lezija ili zračenje vanjskim izvorima.

U novije vrijeme brzo prihvaćena i raširena upotreba hibridnog PET-CT i SPECT-CT u kliničkoj onkologiji uzrokovala je promjene u dijagnostičkim algoritmima za praćenje bolesnika s rakom štitnjače.

## PREGNANCY AND THYROID CANCER

### TRUDNOĆA I RAK ŠTITNJAČE

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Thyroid gland is an uncommon site of cancer, accounting for 0.6% and 1.6% of cancers among men and women, respectively. However, age distribution analysis reveals a considerable number of patients affected at a younger age. The peak age is 30 years for develop-

Rak štitnjače spada u rjede tumore, a javlja se u oko 0,6% muškaraca i 1,6% žena. Dobro diferencirani karcinomi štitnjače (DKŠ), koji su i najčešći oblik raka štitnjače, vrlo često se pojavljuju u mlađih bolesnika, papilarni karcinom najčešće oko 30., a folikularni oko 45. go-



ing papillary carcinoma and 45 years for follicular carcinoma, and both types are about three times more frequent in women. Thyroid cancer is among the five most common cancers that occur during reproductive life. Approximately 1 *per* 10,000 pregnancies is complicated by a malignant tumor of the thyroid in mother. In contrast, thyroid nodules are relatively common; therefore differentiation between benign and malignant nodules is particularly important. The incidence of thyroid carcinoma among thyroid nodules discovered during pregnancy is similar to the malignancy rate observed in the general population, and the natural history of cancer during pregnancy does not differ from that observed in non-pregnant women. There is no report of fetal metastases from maternal thyroid carcinoma. However, pregnancy imposes several limitations on thyroid cancer management as certain diagnostic and therapeutic options are contraindicated. How and when to treat thyroid cancer discovered during pregnancy remains controversial, but its management will also depend on the following: when the cancer is discovered during pregnancy, the extent of disease, the patient's willingness, and the clinician's opinion. Since outcomes in pregnant women were similar whether neck surgery was performed during or after pregnancy, there is no compelling reason to routinely perform thyroidectomy during pregnancy and most pregnant women with a newly discovered thyroid nodule can safely undergo diagnostic studies and therapy after delivery. Treatment should not be delayed for more than a year. When the nodule is found early during pregnancy (particularly if greater than 1.5 cm), surgery during the mid-trimester is recommended, followed by thyroid suppression therapy for the rest of gestation, but radioiodine therapy is delayed until after delivery and breast-feeding have been completed.

Radioactive iodine I-131 (RAI) has been used for decades in the diagnosis of patients with well differentiated thyroid carcinoma (DTC) and as an effective therapeutic option in both preventing relapses and treating metastases. A large number of young female patients may be considered cured after thyroidectomy and RAI, and their desire to have child is therefore normal. However, it is well known that radiation exposure induces genetic mutation. Therefore, besides the positive effects of such therapy, great interest has been shown in the research of the possible mutagenic effect on germ cells, which could result in adverse outcome of pregnancy (spontaneous abortion, congenital abnormalities and malignancies in the offspring). Knowledge that ra-

dine života, i oba karcinoma su tri puta češći u žena. Karcinom štitnjače spada među pet najčešćih karcinoma koji se javljaju u reproduktivnom razdoblju života, a oko 1 na 10.000 trudnoća zakomplicira se pojavom ovoga tumora. Za razliku od raka štitnjače, pojava čvora u štitnjači je relativno česta u trudnica, stoga je važno razlikovati dobroćudne čvorove od onih zloćudnih. Incidencija karcinoma štitnjače u čvorovima dijagnosticiranim za vrijeme trudnoće slična je incidenciji u općoj populaciji, a tijek bolesti se u trudnica također ne razlikuje od onoga u žena koje nisu trudne. Nije zabilježena pojava metastatske bolesti kod fetusa majke s karcinomom štitnjače. Međutim, trudnoća nameće određena ograničenja u postupku kod bolesnica s karcinomom štitnjače s obzirom na to da su neki dijagnostički i terapijski postupci kontraindicirani za vrijeme trudnoće.

Kada i kako liječiti oboljele trudnice s karcinomom štitnjače još uvijek nije usuglašeno, a to ovisi i o različitim čimbenicima kao što su razdoblje trudnoće u kojem je karcinom dijagnosticiran, stupnju proširenosti bolesti, odluci bolesnice i mišljenju kliničara. S obzirom na to da je utvrđeno kako se ishodi bolesti ne razlikuju ako je operacijski zahvat izvršen za vrijeme ili nakon završene trudnoće, u većine bolesnica nema potrebe za rutinskim izvođenjem tireoidektomije za vrijeme trudnoće. U bolesnica s novootkrivenim čvorom u štitnjači dijagnostički i terapijski postupci mogu se izvesti i nakon poroda, ipak terapijski postupci se ne bi smjeli odlagati dulje od godinu dana. Ako se maligni čvor u štitnjači utvrdi u ranoj fazi trudnoće (prvi trimestar), a osobito ako je veći od 1,5 cm, preporuča se izvršiti operacijski zahvat za vrijeme drugog trimestra, nakon čega slijedi supresijska terapija, dok se terapija radioaktivnim jodom-131 odlaže nakon poroda, odnosno nakon razdoblja dojenja.

Radioaktivni jod-131 se desetljećima upotrebljava u dijagnostici, te kao uspješan terapijski postupak za prevenciju metastatske bolesti i liječenje metastaza u bolesnika s DKŠ. Kako je prognoza bolesti u ovih bolesnika dobra, većina mladih žena se nakon tireoidektomije i terapije radiojodom može smatrati izliječenima, te je stoga njihova želja da imaju djecu prirodna. Međutim, dobro je poznato kako liječenje radioaktivnim tvarima dovodi do genetskih mutacija, zbog čega se uz pozitivne učinke terapije istražuje i potencijalni mutageni učinak na zametne stanice, koji može dovesti do neželjenih ishoda trudnoća kao što su spontani pobačaj, kongenitalne anomalije i maligne bolesti u djece majki liječenih radiojodom. Spoznaja da radijacija ima mutageni učinak i može djelovati na zametne stanice dovela je do opreza

diation is mutagenic and may affect gonads has raised concern particularly regarding the use of RAI in young patients during their reproductive years. Virtually every patient treated with any dose of I-131 is exposed to some potential risk. The potential hazards that have greatest impact on the decision to utilize this modality are the induction of second tumors and genetic and chromosomal damage. It has been estimated that the radiation dose delivered to the ovary is approximately 0.14 cGy after administration of 37 MBq (1 mCi) of RAI and correlates well with *in vivo* measured doses. Several studies addressing this problem found no statistically significant associations between previous RAI exposure and unfavorable pregnancy outcome except for miscarriages. In our previously published study a slight increase in the rate of miscarriages was also observed. More miscarriages (up to 40%) but no other unfavorable pregnancy outcomes were observed among women treated with RAI in the year immediately preceding conception. However, it is hard to clinically estimate the real risk associated with radiation exposure because it is relatively low with the use of I-131, while clinical data determining the contribution of this risk factor against all other factors with a considerably greater impact on pregnancy outcome are quite scanty. During pregnancy, well-defined changes in thyroid hormone physiology reflect an increased demand for thyroid hormone production (in one-third of patients on L-thyroxine therapy a dosage increase is required), which can also affect pregnancy outcome.

In the general population, the incidence of miscarriages in clinically recognized pregnancies is about 10%, but in prospective studies, when healthy women attempting to conceive were under medical supervision, the incidence of miscarriages was significantly higher (the incidence ranged from 18% to up to 63%). In the general population, a great deal of early pregnancy loss remains clinically unrecognized. Patients with a diagnosis of DTC are because of their primary disease under medical control and their pregnancies are usually planned and more carefully supervised. The data published so far indicate a low level of RAI therapy associated risk and point to individual differences due to non-uniform distribution of internally deposited radionuclides and different level of gene activity and chromosome repair in each patient. However, some recently published studies established a connection between the dose and chromosomal damage. Acute and late chromosomal damage was evaluated in peripheral lymphocytes

u primjeni ove terapije, osobito u mladih bolesnica u reproduktivnoj dobi. Svaki bolesnik koji je liječen bilo kojom dozom I-131 izložen je nekom potencijalnom riziku, a rizici koji imaju najveći utjecaj na odluku da se primjenjuje ova terapija su pojava sekundarnih tumora te genetska i kromosomska oštećenja.

Procjenjuje se kako nakon primjene 37 MBq (1 mCi) I-131 radijacijska doza na ovarije iznosi oko 0,14 cGy i korelira s mjerenjima *in vivo*. Istraživanja koja su se bavila ovom problematikom nisu pokazala statistički značajnu povezanost između terapije radiojodom i neželjenih ishoda trudnoća, osim za pojavu spontanog pobačaja. Naši objavljeni rezultati također su potvrdili blago povišenu stopu spontanih pobačaja u odnosu na stopu u općoj populaciji. Viša stopa pobačaja (do 40%), ali ne i drugi neželjeni ishodi, utvrđena je među ženama koje su liječene u godini neposredno prije pojave trudnoće. Sam rizik izlaganja radijaciji vrlo je teško klinički utvrditi, jer je taj rizik kod primjene I-131 relativno mali i nema dovoljno kliničkih podataka koji bi utvrdili doprinos ovoga rizičnog čimbenika u odnosu na ostale koji imaju puno veći utjecaj na trudnoću. Kako se za vrijeme trudnoće javljaju promjene u razini hormona štitnjače zbog povećanih potreba organizma (u oko trećine trudnica na supresivnoj terapiji treba povisiti dozu L-tiroxina), ove promjene također mogu utjecati na ishod trudnoće.

U općoj populaciji učestalost spontanih pobačaja u klinički prepoznatim trudnoćama je oko 10%, ali je u prospektivnim studijama u kojima su se pratile žene koje žele zanijeti ova stopa bila značajno viša (od 18% do 63%). Ova razlika se javlja zbog činjenice da u općoj populaciji u ranoj fazi trudnoće velik broj spontanih pobačaja ostaje klinički neprepoznat. Bolesnice s dijagnozom raka štitnjače su zbog svoje osnovne bolesti pod strožim nadzorom, a njihove trudnoće obično su planirane i pažljivo vođene. Dosad objavljeni podaci ukazuju na to da postoje i značajne individualne razlike koje su posljedica nejednakomjerne raspodjele radionuklida koji se nalaze u tijelu, kao i različite razine genske aktivnosti te mogućnosti oporavka kromosoma nakon oštećenja u svakog pojedinog bolesnika. Nadalje, u nedavno objavljenim studijama utvrđeno je kako postoji povezanost između doze I-131 i kromosomskog oštećenja. Analizirana su akutna i kronična kromosomska oštećenja perifernih limfocita bolesnika koji su primali različite doze I-131. Akutni učinak (koji se analizirao 3. dan nakon davanja I-131) definiran je kao tzv. "stupanj oštećenja", a kasni učinak (nakon 6 mjeseci) definiran je kao tzv. "stupanj oporavka" u bolesnika liječenih I-131 zbog hipertireoze ili DKŠ.



of patients who received various doses of I-131. Acute effects were defined using the “damage ratio” (effect on 3<sup>rd</sup> day) and late effects using the “recovery ratio” (effect after 6 months) in patients treated for thyrotoxicosis or DTC. Acute effect was not related to the dose administered, but a negative correlation was found between I-131 dose and “recovery ratio”, suggesting that a part of damaged lymphocytes disappeared from the circulation in a dose dependent manner following I-131 treatment. These results, together with some other studies, indicated a dose-effect relationship at chromosome level.

Although previous studies showed no increase in untoward pregnancy outcomes (stillbirth, congenital abnormalities or malignancies in the offspring) except for miscarriages and no correlation with the dose administered, there is the need for further studies to assess biological effects and clinical impact of RAI therapy in patients receiving different therapeutic doses of I-131. On the basis of the data published on this subject, there is no reason to discourage patients treated with RAI from becoming pregnant. However, patients should be advised to avoid pregnancy for at least 6 months after I-131 administration. Thyroid hormone status should be evaluated prior to pregnancy and during pregnancy thyroxine dose carefully adjusted.

Akutni učinci nisu bili povezani s primijenjenom dozom, međutim za kasne učinke utvrđena je povezanost s dozom. Utvrđena je negativna korelacija između doze RI i “stupnja oporavka”, a rezultat je ukazivao na to da dio oštećenih limfocita nestaje iz cirkulacije u ovisnosti o datoj radioaktivnoj dozi I-131, te također na povezanost primijenjene doze s oštećenjima na kromosomskoj razini.

Iako dosada objavljene studije nisu utvrdile značajne negativne posljedice nakon liječenja I-131 osim povišene stope spontanog pobačaja (učestalost mrtvorođenih, kongenitalnih anomalija ili malignih tumora u djece nije povišena), potrebno je dalje provoditi istraživanja o biološkim učincima i kliničkom značenju terapije radiojodom. Također više terapijske doze I-131 nisu rezultirale lošijim konačnim ishodom trudnoća u bolesnica liječenih zbog karcinoma štitnjače. Ipak, potrebno je savjetovati bolesnice da izbjegavaju trudnoću najmanje 6 mjeseci nakon primjene terapije RI, a hormonski status štitnjače treba utvrditi prije trudnoće i pažljivo pratiti za cijelo vrijeme trudnoće.

## INTEGRAL PSYCHOTHERAPEUTIC APPROACH TO PATIENTS WITH THYROID CANCER

### INTEGRALNI PSIHOTERAPIJSKI PRISTUP BOLESNICIMA OBOLJELIM OD RAKA ŠTITNJAČE

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Malignant diseases in general and those as specific as thyroid carcinoma in particular, require an integral and multidisciplinary approach. In our times, psychological and psychotherapeutic assistance has become a standard in the integral approach to oncologic patient. It does not mean that every patient will need psychotherapeutic

Maligna bolest općenito, a na osobit način ona specifična kao što je karcinom štitnjače, zahtijeva integralni i multidisciplinski pristup. U suvremeno vrijeme je psihološka i psihoterapijska pomoć postala standardom integralnoga pristupa onkološkom bolesniku. To ne znači da je svakom bolesniku neophodna psihoterapijska i psi-

tic and psychiatric aid. In most cases, the crucial psychological support, care and confidence as a central segment of anthropological-psychological assistance are provided by the treating physician and his team, with additional help offered by a psychotherapist in communication and integration of the complex relations among the patient, medical team and family. All this proceeds in a complex inter-relation of reactions, interactions, emotions, and information on and toward the disease that are differently perceived by the patient, the family and the physician. The variable perception of these facts may occasionally lead to misunderstanding, crisis, frustration, and eventually to mental problems in the patient.

Patient reactions may manifest in outward direction, in the form of perceivable behavior, or in the inner form, as facing the disease and taking attitude toward the disease and its treatment, toward family members and other persons from his daily environment, and toward medical personnel providing care for the patient. Proper communication has to be maintained, not only on the disease but also on other daily items because the patient will feel well at long term only if and while taking active part in daily activities.

Patient's emotions are characterized by uncertainty, fear and concern as well as hope, along with understanding and attention from the environment, which can stimulate or, if lacking, dampen the patient's hope. In this aspect, due attention should be paid to the specific hypersensitivity produced by life threat, as a "seismograph" activated by the malignant disease patient on his "new" encounter with the environment.

Besides its functional hormonal role, thyroid gland also influences the patient's mental state through its cosmetic dimension due to its anatomical location. As an enlarged or operated thyroid is "seen", the approach to patients with thyroid carcinoma has some specific in addition to general elements. Besides psychological impact, everything that is visible in the individual's outward appearance also bears the social implication of the others, i.e. looks, queries, subsequent comments, exposure to the others, provoking a negative feedback and disturbing the eroded psychological state of the patient.

hijatrijska pomoć. U većini slučajeva odlučujuću psihološku potporu, skrb i povjerenje kao središnji dio i antropološko-psihološke pomoći pruža ordinirajući liječnik i njegov tim, a psihoterapeut dodatno pomaže u komunikaciji i integraciji složenih odnosa između bolesnika, medicinskog tima i obitelji. To se događa u složenom suodnosu reakcija, interakcija, emocija, informacija o bolesti i na bolest, koje različito doživljava bolesnik, obitelj i liječnik. Ponekad različito shvaćanje tih činjenica može dovesti do zabune, krize, nezadovoljstva, te konačno i do psihičkih teškoća kod bolesnika.

Reakcije bolesnika se očituju prema van kao vidna ponašanja, a "prema unutra" kao susretanje s bolešću, zauzimanje stavova prema bolesti i liječenju, prema osobama iz okoline, te prema medicinskom osoblju koje skrbi za bolesnika. Nužno je i dalje nastaviti komunikaciju, i to ne samo o bolesti već i o drugim životnim sadržajima, jer se bolesnik može osjećati trajnije dobro samo ako i dok sudjeluje u životnim sadržajima.

Bolesnikove emocije su označene nesigurnošću, strahom, zabrinutošću, ali i nadom, razumijevanjem i pažnjom okoline koja može poticati ili, ako izostane, slabiti nadu. U tom smislu je važno obratiti pozornost i na posebnu preosjetljivost koju proizvodi životna ugroženost, svojevrsni "seizmograf" koji aktivira maligni bolesnik u "novom" susretanju s okolinom.

Štitnjača uz funkcionalnu hormonsku ulogu ima zbog svog anatomskeg položaja preko estetske dimenzije utjecaj i na psihu bolesnika. Kako se povećana ili operirana štitnjača "vidi", pristup bolesnicima oboljelim od karcinoma štitnjače uz opće ima i neke specifične elemente. Sve što je izvana vidno na osobi nosi uz psihološku i socijalnu implikaciju drugih – poglede, upite, naknadne komentare, izloženost drugima, što povratno negativno djeluje i uznemiruje već "načeto" psihološko stanje oboljele osobe.

