POSTERS

POSTERI

1

THE INFLUENCE OF RADIOIODINE DOSE ON PREGNANCY OUTCOME IN PATIENTS TREATED FOR DIFFERENTIATED THYROID CARCINOMA

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The aim of the study was to investigate the influence of radioiodine therapy (RAI) on pregnancies and the health status of children born to mothers who had received therapeutic doses of I-131 for differentiated thyroid carcinoma (DTC). Gestational history of 76 women aged less than 35 years at the time when they were treated for DTC were evaluated. They were referred to University Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital during the 1971-2005 period. According to histologic type of cancer, 71 (93%) patients had papillary and 5 (7%) patients follicular carcinoma, and all were treated according to the standard protocol and regularly followed-up. During routine check-ups between January 2003 and April 2005, pregnancy history, outcome and physical and intellectual condition of their children were assessed. The outcome of 49 pregnancies after RAI was as follows: 35 (72%) live births, 5 (10%) miscarriages and 9 (18%) induced abortions. RAI had no adverse effect on the rate of successful delivery and live birth demographics. Pregnancies after RAI therapy were classified according to I-131 dose received before pregnancy into two groups: group A £100 mCi and group B >100 mCi. The higher therapeutic dose (>100 mCi) did not significantly alter pregnancy outcome. Congenital malformations and first year mortality were not observed. The children's age ranged from 1 month to 29 years (mean 8.0 years; SD 8.4). Accordingly, there is no reason to discourage females treated with I-131 from becoming pregnant. Patients should avoid pregnancy after RAI administration for at least 6 months.

1.

UČINAK DOZE RADIOJODA NA ISHOD TRUDNOĆE U ŽENA LIJEČENIH ZBOG DIFERENCIRANOG KARCINOMA ŠTITNJAČE

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Cilj studije bio je istražiti učinak terapijske doze radioaktivnog joda (RI) na ishod trudnoće i zdravlje djece žena liječenih zbog diferenciranog karcinoma štitnjače (DTC). Analizirane su trudnoće 76 žena mlađih od 35 godina koje su od 1971. do 2005. g. liječene na Klinici za onkologiju i nuklearnu medicinu Kliničke bolnice "Sestre milosrdnice". Prema histološkom tipu 71 (93%) bolesnica je imala papilarni karcinom, dok je 5 (7%) bolesnica imalo folikularni tip karcinoma, a sve su liječene prema standardnom protokolu i redovito praćene. Podaci o ishodu trudnoća, te o fizičkom i intelektualnom stanju djece prikupljani su za vrijeme redovitih kontrolnih pregleda od siječnja 2003. g. do travnja 2005. g. Ishod 49 trudnoća koje su nastupile nakon davanja radiojoda radi ablacije ili u terapijske svrhe bio je: 35 (72%) djece, 5 (10%) spontanih i 9 (18%) umjetno izazvanih pobačaja. Terapija radiojodom nije imala negativan učinak na stopu živorođenih, kao niti na ostale parametre u djece. Nisu zabilježene prirođene malformacije niti smrtnost u prvoj godini. Trudnoće su s obzirom na ukupnu terapijsku dozu koju su bolesnice primile razvrstane u skupinu A (£100 mCi) i skupinu B (>100 mCi). Kod skupine s većom primljenom terapijskom dozom (>100 mCi) nije zabilježen lošiji ishod. Srednja dob djece bila je 8,0 godina (SD 8,4), raspon od 1 mjeseca do 29 godina. Dakle, ženama liječenim radioaktivnim jodom zbog karcinoma štitnjače nije potrebno preporučavati izbjegavanje trudnoće. Bolesnice bi trebalo savjetovati da odgode trudnoću najmanje 6 mjeseci nakon provedene terapije radiojodom.

2

AGGRESSIVE FORM OF PAPILLARY THYROID CARCINOMA – A CASE REPORT

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Papillary carcinoma is the most common thyroid carcinoma, accounting for more than 70% of all cases. Ten-year survival is higher than 90%, while mortality rate is 1.5% and 1.4% in women and men, respectively. Tumor cells usually take up radioactive iodine, but when they do not, therapeutic possibilities are very narrow. We present a patient with 18-year history of treatment for papillary thyroid carcinoma with metastases. T. J., a 70-year-old female from Lovran (near Rijeka), first presented in 1989, when total thyroidectomy was performed due to papillary carcinoma, followed by three radioiodine therapeutic doses to a total of 12.3 GBq because of neck metastases, however, without response. In 1995, partial resection of the larynx, trachea and cervical part of the esophagus with placement of temporary laryngotracheostoma and pharyngostoma was performed at University Hospital for Tumors in Zagreb. In 1998, radical left sided neck dissection was done at the same institution. Although whole body iodine 131 scans were negative at the time, recurrences were present again on ultrasonography of the neck, both supraclavicular regions and axillae, with elevated thyroglobulin concentration. Computerized tomography of the neck, mediastinum, thorax and abdomen was done on several occasions. Whole body scintigraphy with 99mTc MIBI was performed in 2004, also yielding negative finding. From the onset of the disease, the patient was hospitalized 38 times. She was operated on 24 times (15 times at University Hospital for Tumors in Zagreb, 7 times at Rijeka University Hospital Center, and once at Jordanovac University Hospital for Lung Diseases in Zagreb). In 2002, chemotherapy and radiotherapy was applied. In June 2004, she suffered a fracture of the left clavicle due to a metastasis in the middle third of the bone. Local finding aggravated in spite of radiotherapy. Surgical operations were performed on both sides of the neck, left supraclavicular region and axilla, where 15 lymph nodes were extracted, nine of which were positive for metastases. In spite of all therapeutic attempts, the disease was in progress and the majority of metastatic lymph

2.

AGRESIVNI OBLIK PAPILARNOG KARCINOMA ŠTITNJAČE – PRIKAZ BOLESNIKA

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Papilarni karcinom je najčešći rak štitnjače (>70%). Desetogodišnje preživljenje je više od 90%. Smrtnost je 1,5% kod žena i 1,4% kod muškaraca. Rijetko tumorske stanice ne nakupljaju ili prestanu nakupljati radioaktivni jod, čime dijagnostički i terapijski postupci postanu vrlo ograničeni. Prikazujemo bolesnicu koja se 18 godina neprekidno liječi zbog metastazirajućeg papilarnog karcinoma štitnjače. U bolesnice T. J. rođene 1937. g. iz Lovrana pokraj Rijeke učinjena je u 5. mj. 1989. g. totalna kirurška tireoidektomija zbog papilarnog karcinoma štitnjače. U 3 navrata dobila je radioaktivni 131 J u ukupnoj količini od 12,3 GBq. Terapije radioaktivnim jodom nisu dale željeni učinak te je u 3. mj. 1995. g. u Institutu za tumore u Zagrebu učinjena djelomična resekcija larinksa, traheje i cervikalnog ezofagusa uz formiranje privremene laringotraheostome i faringoezofageostome. U istoj ustanovi je 1998. g . učinjena radikalna disekcija vrata s lijeve strane. Nakon toga javljaju se stalni recidivi. Na kontrolnim scintigramima čitavog tijela pomoću 131 J ne vidi se nakupljanje aktivnosti u metastazama. Metastaze se pronalaze učestalim ultrazvučnim pregledima vrata, supraklavikularnih regija i aksila te redovitim praćenjem koncentracije tireoglobulina u serumu. Povremeno se izvodi CT opisanih regija uz medijastinum, pluća i abdomen. U 2004. g. učinjen scintigram čitavoga tijela pomoću 99mTc MIBI, a nalaz je bio negativan. Od dijagnosticiranja bolesti do 2006. g. bolesnica je hospitalizirana 38 puta. U 24 navrata je operirana, od toga 15 puta u Klinici za tumore, Zagreb, 7 puta u KBC Rijeka te jednom u Klinici za plućne bolesti Jordanovac. Primila je kemoterapiju i radioterapiju 2002. godine. U 6. mj. 2004. g. dolazi do patološke frakture lijeve ključne kosti zbog metastaze u medijalnoj trećini kosti. Lokalni je nalaz usprkos zračenju u pogoršanju. Operacije su izvedene u području vrata obostrano, supraklavikularno lijevo, kao i u lijevoj aksili gdje je odstranjeno 15 limfnih čvorova, od kojih je u 9 nalaz bio pozitivan. Usprkos svim operacijama bolest je u daljnjoj progresiji te je sada veći dio čvorova inoperabilan. Bolesnica je tražila pomoć u dvjema zdravstvenim ustanovama u Italiji, gdje joj je

nodes were inoperable. At the time, the patient was seeking advice at two medical centers in Italy, where she was told that there were no other therapeutic options; therefore she eventually turned to alternative medicine. Although papillary carcinomas generally have good prognosis, low mortality and rare recurrences, treatment options are quite meager when there is no therapeutic response. The only way is surgical resection. The long survival of this patient is the result of her extraordinary desire for life and dedication, together with strict follow up.

rečeno kako pomoći nema. Sada se liječi bioenergijom i alternativnom medicinom. Premda je prognoza bolesti kod papilarnog karcinoma dobra, smrtnost niska, pojava recidiva rijetka, liječenje bolesti je teško kada tumor recidivira i ne reagira na preostale oblike liječenja. Jedini način je kirurško liječenje. Smatramo da je bolesnica upornošću i željom za životom uz redovite kontrole uspjela dugo preživjeti i podnijeti tolike operacijske zahvate.

3

ONE-YEAR EXPERIENCE WITH MIVAT

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We report our one-year experience in the treatment of thyroid disease with Minimally Invasive Videoassisted Thyroidectomy (MIVAT) introduced by Miccoli. From June 2006 to June 2007, we treated 24 patients with MIVAT. The procedure is carried out through an incision of 18-22 mm and thyroidectomy is performed by dedicated instruments. We analyzed and compared the operation time, volume of intraoperative hemorrhage and postoperative course between thyroid surgery using MIVAT and conventional open surgery methods. Postoperative hypocalcemia and nerve palsy were comparable with conventional methods. Cosmetic results were excellent and postoperative pain level low. It is concluded that MIVAT is a safe and reproducible technique with an indication in a minority of patients candidates for thyroidectomy, and is characterized by less postoperative discomfort and scar.

3.

JEDNOGODIŠNJE ISKUSTVO S TEHNOLOGIJOM MIVAT

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Prikazuje se naše jednohodišnje iskustvo u liječenju bolesti štitnjače pomoću minimalno invazivne videoasistirane tiroidektomije (MIVAT) koju je uveo prof. Miccoli. Od lipnja 2006. do lipnja 2007. smo 24 bolesnika operirali tehnologijom MIVAT. Postupak započinje rezom kože duljine od 18-22 mm, a tiroidektomija se radi namjenskim instrumentima. Analizirali smo i usporedili trajanje operacije, intraoperacijsko krvarenje i poslijeoperacijski tijek uz primjenu tehnologije MIVAT i klasičnog operacijskog zahvata. Posslijoperacijska hipokalcemija i pareza živca je usporediva s rezultatima klasične operacije. Kozmetički rezultati su bili izvrsni, kao i poslijeoperacijska bol. MIVAT je sigurna tehnika, može se provoditi kod manjine bolesnika koji imaju indikaciju za tiroidektomiju. Značajke su bolji poslijeoperacijski oporavak i manji ožiljak.

4

IDENTIFICATION OF RECURRENT LARYNGEAL NERVE – MAIN POINTS

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The fundamental surgical principle to avoid damage to any vital structure during operation is that the structure be clearly identified by the surgeon. It is of special importance in case of recurrent laryngeal nerve (RLN).

4.

IDENTIFIKACIJA POVRATNOG LARINGEALNOG ŽIVCA

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Osnovni kirurški zakon je prikazati sve vitalne strukture tako da se ne oštete tijekom operacije. To je vrlo važno kod operacija u blizini povratnog laringealnog živca. Tri najvažnija čimbenika koji dovode do oštećenja

The three most significant factors leading to nerve damage are inadequate surgeon's experience, second operation (the extent and difficulty of the procedure) and failure to identify the nerve. A meaningful and successful identification of the nerve requires thorough knowledge of the normal anatomy and awereness of the common variations in the nerve location. Only rarely is the nerve actually in the tracheoesophageal groove, and furthermore, the right nerve has a more oblique course in the lower third and is at a greater distance from the trachea than it is on the contralateral side. Identification may also be assisted by palpation, the nerve feels like a cord that can be rolled against the trachea. Its visualization throughout the remainder of its course requires careful dissection, particularly in the region of inferior artery. It is very important to know where the nerve is and to follow that structure up to the larynx. After that, the structures around the nerve can be dissected. There are numerous descriptions of how to locate the RLN. We suggest wide exposure of the nerve after both superior and inferior pole dissection and lobe medialization. The inferior thyroid artery (ITA) has been described as an important landmark to identify RLN. However, there is much variation in its relationship to the nerve. Berry's ligament is the most common site of injury to the nerve. The nerve may run deep to the ligament, pass through it, or even penetrate the gland at a short distance at this level. The use electrophysiologic monitoring of the RLN during thyroid surgery is helpful in inexperienced hands and revision thyroid surgery. With special care we prepare the nerve in the region of thyroid tissue known as tubercles of Zuckerkandl and before entering the larynx where small branches of ITA must be ligated or carefully coagulated with bipolar coagulation. It is very important when we use new devices like harmonic scalpel or bipolar divices (BiClamp). Our one-year experience with these devices in minimally invasive thyroid surgery will be discussed.

živca su neiskusni kirurg, druga operacija i neprikazivanje živca. Uspješno prikazivanje živca zahtijeva dobro poznavanje anatomije i svjesnost o čestim varijacijama lokacije živca. Živac se rijetko može naći u traheo-ezofagusnom žlijebu. Bitna činjenica je da desni živac ima zavijeniju putanju u donjoj trećini i udaljeniji je od dušnika u odnosu na lijevi živac. Pri identifikaciji živac se palpira kao žica koja se pomiče po dušniku. Za prikazivanje živca potreban je oprez pri disekciji, naročito u području donje arterije. Važno je znati gdje se nalazi živac i slijediti strukturu do larinksa. Tek nakon toga možemo prerezati strukture oko živca. Postoji mnogo opisa za prikazivanje živca. Naš prijedlog je prikazivanje na širokom području, nakon rezanja gornjeg i donjeg pola te nakon medijalizacije režnja. Donja tiroidna arterija je opisana kao važan pokazatelj za identifikaciju povratnog živca. No, treba paziti na razne varijacije u odnosu prema živcu. Najčešće mjesto ozljede živca je Berryev ligament. Živac može prolaziti duboko kroz ligamet ili čak prodirati u žlijezdu. Tijekom operacije se može primijeniti i elektrofiziološko motrenje živca, što je vrlo korisno u iskusnim rukama i prilikom ponovnih operacija. Živac se vrlo pažljivo preparira u području tuberkula Zuckerkandel i prije ulaska u larinks gdje se moraju pažljivo koagulirati bipolarnom koagulacijom i podvezati male grane donje tiroidne arterije. To je vrlo važno prilikom uporabe novih uređaja, na primjer harmonic skalpela ili bipolarnih uređaja (BiClamp). U ovom prikazu opisuju se naša iskustva u jednogodišnjem radu s tim uređajima u minimalno invazivnoj kirurgiji štitnjače.

5

CYTOLOGY OF LYMPHOMA IN THE THYROID

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We present our cases of lymphoma in the thyroid. According to the literature, thyroid is affected in 20% of generalized lymphoma cases. A lymphoma can be con-

5.

CITOLOGIJA LIMFOMA U ŠTITNJAČI

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U radu opisujemo naše slučajeve limfoma u štitnjači. Prema literaturi, štitnjača je zahvaćena u 20% slučajeva generaliziranog limfoma. Primarni limfomi štitnjače su vrlo

sidered as primary in the thyroid when it is localized only in the thyroid or when it has MALT morphology. During the 17-year period (1990-2007), fine-needle aspiration (FNA) of the thyroid was performed in 7012 patients; 198 primary tumors of the thyroid, 7 metastatic carcinomas and 13 lymphomas were found. Initially lymphoma was found only in the thyroid in four, in the lymph nodes of the neck in six, in the anterior mediastinum in two patients, and in the adrenal gland in one patient. There were nine female and four male patients aged 21-86 (mean 57) years. Signs of chronic lymphocytic thyroiditis in cytologic smears were found in only three cases. Histopathology was performed in eight cases, and it matched cytology in six cases. In two cases cytology assumed MALT lymphoma but histopathological diagnosis was large B cell lymphoma. Atypical lymphatic cells were found in four cases of chronic lymphocytic thyroiditis. In one of them a lymphoma was found in FNA of another thyroid lobe. In another three flow cytometry and PCR demonstrated lymphocyte polyclonality of the lymphocytes. Cytological diagnosis of lymphoma in the thyroid is reliable and disagreement may occur on determination of the type of lymphoma. Cytomorphology is insufficient when atypical lymphatic cells are found in chronic lymphocytic thyroiditis.

rijetki; to su MALT limfomi ili drugi tipovi limfoma u slučajevima kada je štitnjača jedino sijelo bolesti. U razdoblju od sedamnaest godina (1990.-2007.) učinjeno je 7012 punkcija štitnjače. Nađeno je 198 primarnih tumora štitnjače, sedam metastatskih karcinoma i trinaest limfoma. Pri inicijalnoj obradi bolesnika limfom je dokazan samo u štitnjači u četvoro bolesnika, u štitnjači i u limfnim čvorovima vrata u šestoro bolesnika, u prednjem medijastinumu u dvoje bolesnika, a u jednog istodobno u štitnjači i u nadbubrežnoj žlijezdi. Bilo je devet ženskih i četiri muška bolesnika starih 21-86 godina s prosjekom 57 godina. Samo u tri slučaja u citološkom materijalu su bili prisutni znaci kroničnog limfocitnog tireoididtisa. U osam slučajeva je učinjena patohistološka pretraga i nalaz se podudarao s citološkim u šest slučajeva. U dva slučaja citološki se pretpostavilo da se radi o MALT limfomu, a histološki je nađen velikostanični B limfom. U četiri slučaja kroničnog limfocitnog tireoiditisa nađene su atipične limfatične stanice. Kod jednog od njih je u drugom režnju štitnjače nađen limfom, a kod ostalih je protočnom citometrijom i pretragom PCR nađena poliklonska populacija limfocita. Citološka dijagnoza limfoma u štitnjači je pouzdana, a neslaganje s histološkom dijagnozom tipa limfoma imali smo u dva od osam nalaza. Problematično područje predstavlja nalaz atipičnih limfatičnih stanica u kroničnom limfocitnom tireoiditisu te ga treba razjasniti dopunskim pretragama.

6

OCCURENCE AND EPIDEMIOLOGIC FEATURES OF DIFFERENT HISTOLOGIC TYPES OF THYROID CANCER IN THE 1980-2006 PERIOD

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Thyroid cancer (TC) is the most common endocrine malignancy. Histologic type is an important factor of prognosis in TC. There are four main varieties of TC: papillary, follicular, medullary and anaplastic. The aim of our retrospective study was to evaluate distribution of histologic variants, age of patients at the time of diagnosis, sex distribution and trends in cancer size during a 17-year period. Data were obtained from the

6.

UČESTALOST I EPIDEMIOLOŠKE ZNAČAJKE RAZLIČITIH HISTOLOŠKIH TIPOVA KARCINOMA ŠTITNJAČE U RAZDOBLJU 1980.-2006.

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Karcinomi štitnjače (KŠ) su najčešći endokrini maligni tumori. Histološki tip KŠ važan je prognostički čimbenik. Glavna četiri tipa su papilarni, folikularni, medularni i anaplastični. Cilj ove retrospektivne studije bila je procjena histoloških tipova karcinoma, starosti bolesnika u trenutku postavljanja dijagnoze, raspodjele prema spolu te veličini tumora u razdoblju od 17 godina. Obrađeni podaci dobiveni su iz kompjutorske baze po-

computer-based Thyroid Cancer Registry at Ljudevit Jurak Department of Pathology. We analyzed data of all patients with TC who underwent surgery in our Hospital during the 1980-2006 period. Total number of patients was 925 (210 (22.7%) male and 715 (77.3%) female). Papillary cancer was diagnosed in 74.9% (693), follicular in 9.5% (88), medullary in 7% (65), anaplastic in 4.1% (38) and other types in 4.5% (41) of patients. When we analyzed the distribution of histologic variants during the observed period, a trend of increase in papillary cancer and decrease in follicular and anaplastic cancer was found. The mean age (yrs) at presentation was 48.7 (male 48.2 and female 49.2) for papillary, 48.6 (male 47.9 and female 49.3) for follicular, 55.3 (male 54.6 and female 55.9) for medullary, 63.3 (male 60.5 and female 66.1) for anaplastic cancer, and 60.1 (male 61.6 and female 58.6) for other types. Analyzed data for papillary cancer showed a decrease in tumor size from a maen of 1.8 cm in the 1990-1998 period to 1.3 cm in the 1999-2006 period. During the study period, sex distribution revealed female predominance in all types of TC (3.4:1). The mean age at presentation for was higher for anaplastic cancer (63.3) than for papillary (48.7) and follicular (48.6) cancer. Tumor size decreased, especially in the last 8 years of the study period. The frequency of papillary cancer increased, and that of follicular and anaplastic cancer decreased during the period of observation.

7

SURGICAL MANAGEMENT OF RECURRENT THYROID CANCER

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Recurrent thyroid tumors are much less frequent but more aggressive than primary tumors. The aim of the study was to assess their characteristics, aggressiveness and the possibility of radical surgical excision as well as the frequency of complications. This retrospective study included 162 patients operated on for recurrent thyroid tumors at Center for Endocrine Surgery, Belgrade (January 1995 - June 2007). Recurrent tumors were found in 97 patients with papillary (27 smaller than 1 cm), 16 follicular (13 Hurthle), 16 medullary, 12 anaplastic, 1 lymphoma, 5 with metastatic thyroid tumors, and 14

dataka "Thanatos" Zavoda za patologiju Ljudevit Jurak. Obrađeni su podaci svih bolesnika koji su operirani na Klinici za otorinolaringologiju i cervikofacijalnu kirurgiju Kliničke bolnice "Sestre milosrdnice" u razdoblju od 1980. do 2006. godine. Ukupni broj bolesnika operiranih od tumora bio je 925 (M 210 (22,7%), F 715 (77,3%)). Papilarni karcinom dijagnosticiran je kod 74,9% (693), folikularni kod 9,5% (88), medularni kod 7% (65), anaplastični kod 4,1% (38) te ostali tipovi kod 4,5% (41) operiranih bolesnika. Histološka distribucija u promatranom razdoblju pokazuje trend porasta papilarnog, te trend pada folikularnog i anaplastičnog karcinoma. Prosječna dob u trenutku dijagnoze bila je 48,7 (M 48,2 i F 49,2) za papilarni, 48,6 (M 47,9 i F 49,3) za folikularni, 55,3 (M 54,6 i F 55,9) za medularni, 63.3 (M 60,5 i F 66,1) za anaplastični karcinom i 60,1 (M 61,6 i F 58,6) za ostale tipove. Prosječna veličina tumora za papilarni karcinom smanjila se s 1,8 cm u razdoblju 1990.-1998. na 1,3 cm u razdoblju 1999.-2006. Tijekom promatranog razdoblja raspodjela po spolu pokazuje veću učestalost svih tipova KŠ kod žena (3,4:1). Prosječna dob u trenutku postavljanja dijagnoze bila je veća za anaplastični (63,3) negoli za papilarni (48,7) i folikularni (48,6) karcinom. Prosječna veličina tumora se smanjila, osobito u posljednjih 8 godina promatranog razdoblja. Učestalost papilarnog karcinoma povećala se u promatranom razdoblju, dok se učestalost folikularnog i anaplastičnog karcinoma smanjila.

7.

KIRURŠKO LIJEČENJE RECIDIVIRAJUĆEG RAKA ŠTITNJAČE

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Recidivirajući tumori štitnjače su manje učestali, ali agresivniji od primarnih tumora štitnjače. Cilj ove studije bio je utvrditi značajke, agresivnost, mogućnost radikalnog kirurškog zahvata te učestalost komplikacija. Retrospektivna studija je uključivala 162 bolesnika operiranih u Centru za endokrinološku kirurgiju u Beogradu zbog recidivirajućeg tumora štitnjače u razdoblju od siječnja 1995. do lipnja 2007. Recidivirajući tumor otkriven je u 97 bolesnika s papilarnim karcinomom (u 27 njih manji od 1 cm), 16 s folikularnim (u njih 13 s karcinomom Hürthleovih stanica), 12 s anaplastičnim, jed-

without malignancy on second operation. Relapse in thyroid bed on the dominant side was found in 85 (52.5%), on the opposite side in 54 (33.3%) and in lymph nodes outside thyroid bed in 57 (35.2%) patients. In 102/162 patients, the first procedure was incomplete (reduction in 8, partial resection in 62, and hemithyroidectomy in 32). The second procedure was incomplete in 54, near total and total thyroidectomy in 94, and dissection of lymph nodes in 57 patients, in 43 of them with operation in thyroid bed. Preoperative recurrent nerve palsy was recorded in ten patients, and transient recurrent nerve palsy after second procedure developed in six patients. Out of 94 patients undergoing thyroidectomiy for recurrent tumor, postoperative lymphoparathyroidism occurred in 20 (21.3%) patients, permanent in five (5.3%) of them. The main causes of thyroid cancer relapse are incomplete first procedure and cancer aggressiveness; it is not always possible to excise the complete recurrent tumor.

8

SOME CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF PAPILLARY THYROID CARCINOMA

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Papillary thyroid cancer accounts for the vast majority (80%-90%) of patients with well differentiated thyroid malignancies, and most patients typically show excellent specific prognosis and overall survival. In scientific literature, there are many studies based on clinical and pathological characteristics as well as patient risk stratification (AMES, AGES, MACIS, etc.) but many controversial issues are still present (influence of tumor size, grade, multicentricity, and metastasizing potential specifically in focus). In our retrospective study we reviewed the clinical and pathological records of 572 patients with papillary thyroid cancer operated on between 1980 and 2006 at University Department of ENT, Head and Neck Surgery, Sestre milosrdnice University Hospital, Zagreb, Croatia. We investigated some pathological characteristics and their relevance to clinical behavior according to the previously chosen parameters of interest (primary tumor, multicentricity, and locoregional

nog s limfomom, 5 s metastatskim tumorom štitnjače te 14 bolesnika bez maligne bolesti kod ponovljenog zahvata. Recidiv u ležištu štitnjače pojavio se na dominantnoj strani u 85 (52,5%), na suprotnoj strani u 54 (33,3%) te u limfnim čvorovima izvan ležišta štitnjače u 57 (35,2%) bolesnika. U 102 od 162 bolesnika primarni zahvat nije bio totalna tireoidektomija (smanjenje tumora u 8, djelomična resekcija u 62 i hemitireoidektomija u 32 bolesnika). Ponovljeni zahvat bio je djelomičan u 54 bolesnika, skoro totalna i totalna tireoidektomija učinjena je u 94 bolesnika, a disekcija limfnih čvorova u 57 bolesnika, 43 s operacijom ležišta štitnjače. Prijeoperacijska lezija povratnog živca postojala je u 10 bolesnika, a poslijeoperacijska prolazna slabost pojavila se u njih 6. Među 94 bolesnika kojima je učinjena tireoidektomija zbog recidivirajućeg tumora, poslijeoperacijski hipoparatireoidizam se pojavio u njih 20 (21,3%), a kod 5 bolesnika (5,3%) bio je ireverzibilan. Glavni razlozi recidiva karcinoma štitnjače su nedostatnost primarnog zahvata i agresivnost samog malignog procesa, a recidiv nije uvijek moguće odstraniti u potpunosti.

8.

NEKE KLINIČKOPATOLOŠKE OSOBITOSTI PAPILARNOG KARCINOMA ŠTITNJAČE

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Papilarni karcinom najčešći je maligni tumor štitne žlijezde i spada u skupinu dobro diferenciranih tumora štitnjače. Prisutan je u 80%-90% novootkrivenih karcinoma štitnjače, a prognoza mu je najbolja od svih malignih tumora u štitnjači. U znanstvenostručnoj literaturi opisani su mnogi klasifikacijski kriteriji zasnovani na kliničkopatološkim značajkama bolesti (AMES, AGES, MACIS itd.). Međutim, još prisutne brojne kontroverze o pitanju značajnosti pojedinih varijabla uključenih u postojeće klasifikacijske sustave, poput veličine, gradusa tumora, pojave multicentričnosti te metastaza, ostavljaju brojna neriješena pitanja. U našoj retrospektivnoj studiji rađenoj na materijalu od 569 bolesnika s papilarnim karcinomom prezentiranih i liječenih na Klinici za ORL i kirurgiju glave i vrata KB "Sestre milosrdnice", Zagreb, Hrvatska, tijekom razdoblja 1980.-2006. godine, prikazane su neke kliničkopatološke značajke papilarnog karcinoma štitnjače od osobitog značenja (značajke primarnog tumora, pojava multicentričnosti bolesti te

spread). The results showed close relationship of some important study variables, especially size and pathological features of the tumor, with its clinical behavior, and patient age and sex.

9

THE PREVALENCE OF THYROID NODULES IN WORKING POPULATION OF ZAGREB

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It is known that thyroid nodules are a frequent finding, their incidence being on an increase since the 1980s, most probably due to the introduction of ultrasonography (US) as a routine method in thyroid diagnosis. The aim of the study was to establish the prevalence of thyroid nodules in an unselected adult population. Thyroid US scans performed in 995 subjects during the 2004-2006 period were analyzed. The scans were performed at Nemetova Clinic as part of the routine check-up of employees of various Zagreb companies and institutions. The group consisted of unselected individuals aged 20-65, median 44 years. All nodules visualized on US were taken in consideration irrespective of their size. Total prevalence of thyroid nodules was 28.3% (18% in males and 32% in females). Solitary nodules were detected in 11.6% and multiple nodules in 16.7% of cases. The prevalence was 25% in subjects below 50 and 36% in those older than 50. In the subgroup of subjects older than 50, nodules were recorded in 41% of female and 26% of male subjects. This study showed a relatively high prevalence (28%) of thyroid nodules in the Zagreb working-age population (aged 18-65), higher in female than male subjects (32% *vs*. 18%) and rising with age.

lokoregionalnog ponašanja tumora) i analiza njihove međusobne povezanosti. Rezultati upućuju na značajnu povezanost nekih parametara od interesa, prije svega veličine i patoloških značajka tumora s njegovim kliničkim ponašanjem, te s dobi i spolom bolesnika.

9.

UČESTALOST ČVOROVA ŠTITNJAČE U RADNOJ POPULACIJI U ZAGREBU

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Poznato je da su čvorovi u štitnjači česta pojava. Njihova incidencija je u porastu od 80-ih godina prošloga stoljeća, što je najvjerojatnije posljedica uvođenja ultrazvuka kao jedne od rutinskih metoda za dijagnostiku bolesti štitnjače. Cilj ovoga rada bio je otkriti učestalost čvorova u štitnjači u neselekcioniranoj populaciji. Analizirani su nalazi ultrazvuka štitnjače u 995 ispitanika u razdoblju od 2004. do 2006. godine. Ultrazvuk štitnjače učinjen je kao dio sistematskog pregleda zaposlenika zagrebačkih tvrtka u Poliklinici "Nemetova". Ispitivanu skupinu je činila radna populacija od 280 muških i 715 ženskih ispitanika u dobi od 20 do 65 godina, medijan dobi 44 godine. U obzir su uzeti svi ultrazvukom jasno vidljivi čvorovi bez obzira na veličinu. Ukupna učestalost čvorova je iznosila 28,3% (muškarci 18%, žene 32%). Solitarni nodusi su nađeni u 11,6%, a višestruki u 16,7% ispitanika. Učestalost čvorova je iznosila 25% u ispitanika mlađih od 50 godina, odnosno 36% u starijih od 50 godina. U populaciji starijoj od 50 godina čvorovi su zabilježeni u 41% ženskih i 26% muških ispitanika. U istraživanju smo otkrili da su čvorovi u štitnjači u radnoj populaciji (od 18 do 60 godina) u Zagrebu relativno česta pojava (28%), da su češći u žena (32% naprama 18%) te da njihova učestalost raste s dobi.

10

ULTRASONOGRAPHY OF THE NECK IN PATIENTS OPERATED FOR DIFFERENTIATED THYROID CARCINOMA AND VALUE OF THYROGLOBULIN DETERMINATION IN NODE ASPIRATE

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Ultrasonography (US) of the neck is routinely obtained in patients with differentiated thyroid carcinoma (DTC). US-guided fine needle aspiration biopsy (FNAB) with cytology is performed when suspect masses are detected. The aim of the study was to estimate the value of thyroglobulin (Tg) measurement in needle washouts in detection of lymph node metastases and/or recurrences. Neck US was obtained in 423 patients with operated differentiated thyroid carcinoma. US-guided FNAB and cytology were performed in 167 suspect masses sized 5-31 mm in 113 patients. Immediately after obtaining smear for cytology, the needle was rinsed with 0.5 mL of saline solution and Tg was determined in these washouts or in cystic aspirates. Elevated Tg values ranging from 149 ng/mL to >600 ng/mL indicating metastases were measured in 40 nodes of 25 patients. Cytology revealed cystic nodes and was nondiagnostic in 17 neck masses in 10 patients with increased Tg levels. In four patients cytology findings were negative for DTC metastases. In the rest of patients cytology findings were positive for DTC metastases and/or recurrences. Tg levels were undetectable in 125 node aspirates from 86 patients and reactive lymph nodes were found by cytology. In two patients with undetectable Tg values cytology revealed metastases from other carcinoma (planocellular and adenocarcinoma). Our study indicates that cytology is not sensitive enough to detect all DTC cervical lymph node metastases and/or recurrences. Tg measurement in fine needle washouts of neck masses is useful, especially when cytology is nondiagnostic due to cystic aspirates. Thus, the combined use of US and US-guided FNAB with cytology and Tg measurement in aspirate is suggested for neck evaluation in patients with DTC.

10.

ULTRAZVUČNA PRETRAGA VRATA U BOLESNIKA S OPERIRANIM DIFERENCIRANIM KARCINOMOM ŠTITNJAČE I ZNAČENJE ODREĐIVANJA TIREOGLOBULINA U PUNKTATU

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Ultrazvučna pretraga (UZV) vrata rabi se redovito u praćenju bolesnika s diferenciranim karcinomom štitnjače. U bolesnika u kojih se nađu povećani limfni čvorovi ili žarišne tvorbe u ležištu štitnjače s ultrazvučnim značajkama koje ukazuju na mogućnost malignosti izvodi se aspiracijska punkcija pod kontrolom UZV i citološka analiza punktata. Cilj ove studije bio je utvrditi značenje mjerenja tireoglobulina (Tg) u punktatu tvorba na vratu. UZV pretraga je učinjena u 423 bolesnika s operiranim diferenciranim karcinomom štitnjače. Punkcija pod kontrolom UZV učinjena je u 113 bolesnika. Punktirano je 167 čvorova veličine od 5 do 31 mm. Nakon punkcije učinjen je razmaz za citološku analizu, a zatim je igla isprana s 0,5 mL fiziološke otopine i određen je Tg. Tumorski biljeg određen je i u aspiratu dobivenom nakon punkcije cističnih tvorba. Tumorski biljeg bio je povišen (149 ng/mL do >600 ng/mL) ukazujući na sekundarizam u 40 tumorskih tvorba u 25 bolesnika. Citološka analiza odgovarala je pseudocističnim promjenama u 17 čvorova u 10 bolesnika. U četiri bolesnika s povišenim vrijednostima Tg citološki nalaz nije ukazivao na metastaze. Citološki nalaz bio je pozitivan na recidiv i metastaze u preostalih 11 bolesnika. U 125 čvorova u 86 bolesnika vrijednosti Tg u punktatu su bile nemjerljive, a citološkom analizom punktata nisu nađene tumorske stanice. U dvije bolesnice u punktatu čvorova određena je nemjerljiva razina Tg, a citološki nalaz je odgovarao metastazama planocelularnog karcinoma i adenocarcinoma. Naša studija ukazuje na to da je određivanje Tg u punktatu sumnjivih tvorba na vratu korisna metoda u otkrivanju recidiva i metastaza karcinoma štitnjače osobito u slučaju dobivanja neadekvatnog materijala kod cističnog aspirata, kao i kada je citološka analiza lažno negativna. Zato se u praćenju bolesnika s diferenciranim karcinomom štitnjače uz punkciju pod kontrolom UZV i citološku analizu preporuča i određivanje Tg u punktatu.

11

THE ROLE OF 18-FDG-PET IN POST-TREATMENT RESTAGING OF RECURRENT DIFFERENTIATED/MEDULLARY THYROID CARCINOMA (DTC/MTC)

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The aim of the study was to assess the utility of 18-FDG-PET in DTC/MTC patients with increased serum levels of thyroglobulin (Tg)/calcitonin, but negative morphological and scintigraphic imaging. Between 2005-2007, 13 patients [age 52±16 yrs, 9F/4M, histotype: papillary carcinoma (n=6), Hûrthle cell/follicular (n=2), MTC (n=5)] with biochemically suspect recurrence, previously treated by total thyroidectomy and 131I ablation, underwent PET scan (Siemens ECAT-EXACT 47/GE Advance NXi, 3D-mode/30-35 min) 45 min following iv. administration of 296-444 MBq 18-FDG under TSH suppression; all lesions were evaluated by SUVmax. Two TgAb-positive patients showed undetectable serum Tg levels off LT4; one developed recurrence during follow up. PET showed hypermetabolic lesions in 8/13 patients (5/8 DTC, 3/5 MTC; 3 pT2-4N1-1b, 2 pT3N0, 3 pT1-1bN0-1b) and changed intended management in 37% of them, while it was presumably false-negative in 4 patients (2 DTC/2 MTC; 3 pT1-2bN0, 1 pT2N1; non-progressive disease) and true negative in 1 DTC patient (TgAb-positive, pT1N1); the involved regions were: head-neck (5/8), mediastinum (7/8), lungs (2/8), liver (2/8) and spleen (1/8). In all patients, 131I-WB-scan, CT-MRI, 111In-octreotide, 99mTc-DMSA(V), SESTAMIBI and ultrasound were initially negative or showed a lower number of lesions. Two patients with lymph node involvement underwent extensive surgery with histologically confirmed metastases. PET is an efficient tool to locate recurrent/metastatic disease in high-risk, I-131 non-avid DTC with increased Tg and MTC with elevated calcitonin. Superior sensitivity, provision of anatomic guidance for biopsy/surgical procedures and impact on management/prognostication are major advantages in carefully selected patients; however, different pre-test probabilities, acquisition protocols and TSH-stimulation may yield different diagnostic efficiency.

11.

ULOGA 18-FDG POZITRONSKE EMISIJSKE TOMOGRAFIJE (PET) U POSTTERAPIJSKOJ REEVALUACIJI REKURENTNOG DIFERENCIRANOG/MEDULARNOG KARCINOMA ŠTITNJAČE (DTC/MTC)

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Cilj rada bio je procijeniti dijagnostičku učinkovitost 18-FDG pozitronske emisijske tomografije (PET) u bolesnika s rekurentnim diferenciranim/medularnim karcinomom štitnjače (DTC/MTC), rastućim serumskim tireoglobulinom (Tg)/kalcitoninom i negativnim morfološkim i scintigrafskim nalazima. Između 2005. i 2007. godine PET je učinjen u 13 bolesnika prethodno podvrgnutih totalnoj tiroidektomiji i 131-I ablaciji s biokemijski sumnjivim recidivom [dob 52±16 god., 9Ž/4M, patohistološki: papilarni karcinom (n=6), karcinom Hûrthleovih stanica/folikularni (n=2), medularni (n=5); Siemens ECAT-EXACT 47/GE Advance NXi, 3D-mod/30-35 min] 45 min nakon iv. injiciranja 296-444 MBq 18-FDG u uvjetima supresije TSH. Sve lezije procijenjene su primjenom SUVmax. Tijekom razdoblja praćenja recidiv bolesti utvrđen je u jednog od 2 TgAb-pozitivna bolesnika s nedetektabilnim Tg bez LT4. Hipermetabolične lezije otkrivene su u 8/13 bolesnika [5/8 DTC, 3/5 MTC; 3 pT2-4N1-1b, 2 pT3N0, 3 pT1-1bN0-1b; zahvaćene regije: glava-vrat (5/8), medijastinum (7/8), pluća (2/8), jetra (2/8) i slezena (1/8)], uz promjenu predviđenog terapijskog plana u 37% njih, vjerojatno lažno negativan nalaz u 4 (2 DTC/2 MTC; 3 pT1-2bN0, 1 pT2N1; neprogresivna bolest) i točno negativni nalaz u jednog bolesnika (DTC, pozitivna TgAb, pT1N1). Dva bolesnika s metastatskom limfadenopatijom podvrgnuta su kirurškom liječenju, uz histološku verifikaciju metastaza. U svih bolesnika su nalazi 131I-WB-scintigrafije, CT-MRI, 111In-oktreotida, 99mTc-DMSA(V), SESTAMIBI i ultrazvuka bili na početku negativni. Zaključuje se kako je PET učinkovita tehnika u lokalizacijskoj dijagnostici rekurentne/metastaske bolesti kod visokorizičnih, I-131 neavidnih DTC s rastućim Tg i bolesnika s MTC i porastom kalcitonina. Superiorna senzitivnost, osiguranje anatomskih smjernica za kirurške/biopsijske postupke i utjecaj na planiranje liječenja-prognostikaciju vodeće su prednosti PET dijagnostike u pažljivo odabranih bolesnika. Različite a priori vjerojatnosti, akvizicijski protokoli i TSH-stimulacija mogu rezultirati razlikama u dijagnostičkoj učinkovitosti.

12

IMPACT OF UROKINASE-TYPE PLASMINOGEN ACTIVATOR (uPA) AND ITS INHIBITOR (PAI-1) ON PROGRESSION-FREE SURVIVAL IN THYROID CANCER

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Elevated levels of urokinase-type plasminogen activator (uPA) and its inhibitor (PAI-1) are linked to the poor prognosis in a variety of malignances. uPA and PAI-1 were expressed in most thyroid carcinomas, as measured immunohistochemically. However, no relationship between their expression and clinicopathological parameters has yet been described. The aim of the present study was to investigate the expression and clinical relevance of uPA and PAI-1 in thyroid cancer. uPA and PAI-1 in paired cytosol samples of thyroid tumor and normal tissue were determined in 23 patients using enzyme-linked immunosorbent assay (ELISA) and correlated to the known prognostic features. Both uPA and PAI-1 concentrations were significantly higher in malignant thyroid tumors (uPA=1.342±2.944 and PAI-1=17.615±31.933 ng/mg protein) than in normal tissue (uPA =0.002±0.009; p=0.011 and PAI-1=2.333±0.338 ng/mg protein; p=0.001) with positive correlation of the two proteins in tumors. uPA and PAI-1 were significantly higher in anaplastic vs. well-differentiated cancers (uPA p=0.014 and PAI-1 p=0.026), if extrathyroid invasion (uPA p=0.019 and PAI-1 p=0.009) or distant metastases (uPA p=0.006 and PAI-1 p=0.003) were present, and in tumors of more than 1 cm in diameter (uPA p=0.009 and PAI-1 p=0.035). Only PAI-1 but not uPA was significantly higher in multicentric vs. solitary tumors (p=0.012) and lymph node positive compared to lymph node negative patients (p=0.042). The differences of uPA and PAI-1 did not reach significance when patients with well-differentiated tumors below and above 40 years of age were compared. Survival analysis revealed a significant impact of both uPA and PAI-1 on the Progression-Free Survival (PFS) (38.84 vs. 3.67 months for patients with low and high uPA, respectively; p<0.001; 38.2 vs. 12 months for patients with low and high PAI-1, respectively; p=0.016). The correlation of high uPA and PAI-1 with the known prognostic fac-

12.

UTJECAJ UROKINAZNOG TIPA AKTIVATORA PLAZMINOGENA (uPA) I NJEGOVOG INHIBITORA (PAI-1) NA PREŽIVLJENJE BEZ PROGRESIJE BOLESTI U BOLESNIKA S KARCINOMOM ŠTITNJAČE

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Visoke vrijednosti urokinaznog tipa aktivatora plazminogena (uPA) i njegovog inhibitora (PAI-1) povezane su s lošom prognozom u različitim malignim tumorima. U dosadašnjim radovima uPA I PAI-1 su bili imunohistokemijski izraženi u većini tipova karcinoma štitnjače. Međutim, odnos njihovih vrijednosti i kliničko-patoloških parametara dosada nije opisan. Cilj rada bio je istražiti kliničko značenje uPA i PAI-1 u karcinomima štitnjače. uPA i PAI-1 određenis su u citosolu tumora štitnjače i normalnom tkivu u 23 bolesnika testom ELISA i potom korelirani s poznatim prognostičkim parametrima karcinoma štitnjače. Koncentracije uPA i PAI-1 bile su značajno više u malignim tumorima štitnjače (uPA=1,342±2,944 i PAI-1=17,615±31,933 ng/mg proteina) nego u normalnom tkivu štitnjače (uPA=0,002±0,009; p=0,011 i PAI-1=2,333±0,338 ng/mg proteina; p=0,001). Između oba proteina (uPA i PAI-1) nađena je pozitivna korelacija. uPA i PAI-1 bili su značajno viši u anaplastičnim u odnosu na dobro diferencirane karcinome (uPA p=0,014 i PAI-1 p=0,026), također ako je prisutna ekstratiroidna invazija (uPA p=0,019 i PAI-1 p=0,009) ili udaljene metastaze (uPA p=0,006 i PAI-1 p=0,003). Kad su tumori bili veći od 1 cm vrijednosti uPA i PAI-1 bile su značajno više (uPA p=0,009 i PAI-1 p=0,035). PAI-1 je bio značajno viši u multicentričnim u odnosu na solitarne tumore (p=0,012), te u citosolu karcinoma štitnjače u bolesnika s pozitivnim limfnim čvorovima u usporedbi s onima s negativnim limfnim čvorovima (p=0,042). Nije nađena statistički značajna razlika uPA i PAI-1 između uzoraka bolesnika starijih i mlađih od 40 godina. Analize preživljenja su otkrile značajan utjecaj uPA i PAI-1 na preživljenje bez progresije bolesti (38,84 prema 3,67 mjeseci za bolesnike s niskim odnosno visokim uPA, p<0,001; 38,2 prema 12 mjeseci za bolesnike s niskim odnosno visokim PAI-1, p=0,016). Povezanost povišenih vrijednosti uPA i PAI-1 u boles-

tors of poorer outcome and with lower PFS rate in patients with thyroid cancers proved that these proteins could be used as an additional prognostic parameter.

13

INCIDENCE AND MORTALITY OF THYROID CANCER IN CROATIA FROM 1968 TO 2004

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During the past decades, a significant increase in the incidence of thyroid cancer (TC) has been recorded worldwide. However, the mortality from TC has remained stable at low levels or even declined. Evolution in clinical practice is one of the proposed explanations for this increase, especially the introduction of ultrasound and fine needle aspiration biopsy at the beginning of the 1980s. The great majority of this increase is considered to be the result of improved diagnosis of small thyroid tumors, especially papillary thyroid microcarcinomas because the prevalence of these tumors at autopsy findings is 5%-35%. The aim of the study was to present the epidemiology of TC in Croatia 1968-2004 and to investigate the possible influence of improved diagnosis on TC incidence. New cases of and deaths from TC in Croatia 1968-2004 with census data were obtained from the National Cancer Registry. Data on the size of differentiated thyroid cancer (DTC) were obtained from hospital records of new patients with DTC treated at University Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital during the 1988-1992 (n=84) and 2000-2004 (n=287) periods. The incidence and mortality of TC in Croatia are presented as crude and world-age standardized rates (wasr) per 100,000 population, with trend analysis. Histopathologic findings were the source of data on the size of DTC. Mann-Whitney test was used on statistical analysis. The proportion of thyroid microcarcinomas (<1 cm) was presented for each study period. During the 1968-2004 period, the incidence (wasr) of TC increased in Croatia 8.6 times in women (1.1:9.4) and 3.6 times in men (0.8:2.9), while the mortality (wasr) remained stable at low levels in both sexes with a mild descending trend in women (y=-0.01x+0.61) and men (y=-0.002x

nika s karcinomom štitnjače i standardnih prognostičkih čimbenika lošeg ishoda bolesti, te povezanost uPA i PAI-1 s kraćim preživljenjem bez progresije ukazuju na prognostičko značenje uPA i PAI-1.

13.

INCIDENCIJA I SMRTNOST OD KARCINOMA ŠTITNJAČE U HRVATSKOJ 1968.-2004.

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Tijekom posljednjih desetljeća zabilježen je višestruk porast incidencije karcinoma štitnjače u svijetu, dok je smrtnost ostala na niskim razinama. Glavni pretpostavljeni uzrok je evolucija u kliničkoj praksi, a osobito uvođenje ultrazvuka i citološke punkcije početkom osamdesetih godina prošloga stoljeća. Otkrivaju se sve manji tumori pa je osobito porasla incidencija papilarnih mikrokarcinoma štitnjače, učestalost kojih je u populaciji temeljem nalaza autopsije 5%-35%. Cilj studije bio je prikazati epidemiologiju karcinoma štitnjače u Hrvatskoj u razdoblju 1968.-2004. i utvrditi mogući utjecaj poboljšane dijagnostike putem otkrivanja sve manjih karcinoma. Broj novooboljelih i umrlih od karcinomom štitnjače u razdoblju 1968.-2004. i podaci o broju stanovnika prikupljeni su iz Hrvatskoga registra za rak. Za usporedbu veličine diferenciranog karcinoma štitnjače upotrebljeni su podaci Klinike za onkologiju i nuklearnu medicinu KB "Sestre milosrdnice", novooboljeli bolesnici liječeni u razdoblju 1988.-1992. (n=84) i 2000.-2004. (n=287). Incidencija i smrtnost od karcinoma štitnjače u Hrvatskoj prikazani su kao grube i dobno standardizirane stope (wasr) na 100.000 stanovnika uz analizu trenda. Patohistološki nalazi upotrebljeni su kao izvor podataka o veličini tumora, a u statističkoj obradi rabio se Mann-Whitneyev test. Prikazan je udio mikrokarcinoma (<1 cm) u oba razdoblja. Dobno standardizirana stopa incidencije karcinoma štitnjače porasla je u Hrvatskoj u razdoblju 1968.-2004. 8,6 puta u žena (1,1:9,4) i 3,6 puta u muškaraca (0,8:2,9), dok je stopa smrtnosti ostala niska u oba spola uz blagi silazni trend u posljednjih 20 godina u žena (y=-0.01x+0,61) i tek naznačen silazni trend u muškaraca (y=-0,002x+0,43), a u 2004. je iznosila 0,4 u oba spola. Medijan veličine novootkrivenog diferenciranog karcinoma štitnjače sma-

+0.43) in the last 20 years. In 2004, the TC mortality rate was 0.4 in both sexes. The median size of newly diagnosed DTC decreased from 20 mm in the 1988-1992 period to 12 mm in the 2000-2004 period, which was statistically highly significant ($p<0.001$). The proportion of microcarcinomas increased from 14.3% in the first to 28.4% in the second study period. Croatia is among countries with a high incidence and low mortality rate of TC, e.g., Italy, France, Finland, USA and Australia. While the incidence of TC in Croatia has been constantly increasing, the mortality remained low or even mildly declined. A significant decrease in the size of newly diagnosed DTC with an increase in the proportion of microcarcinomas was recorded. The data presented suggest that the improved diagnosis is one of the important reasons for the increase in the incidence of TC in Croatia.

14

PAPILLARY THYROID MICROCARCINOMA – CLINICAL PRESENTATION AND PROGNOSIS

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Papillary thyroid microcarcinoma (mPTC) is papillary thyroid carcinoma of less than 10 mm in size. Nowadays, they are frequently detected due to the wide use of ultrasound and fine-needle aspiration biopsy (FNAB) of small impalpable thyroid nodules. The prevalence of mPTC at autopsy is 5%-35%, suggesting indolent clinical behavior. According to the recently published American and European guidelines, mPTC does not require postoperative treatment with iodine-131. The aim of the study was to evaluate clinical presentation, treatment, follow up and prognosis of patients with mPTC. We studied 258 patients (226 women and 32 men, median age 50 years) with mPTC treated at University Department of Oncology and Nuclear medicine, Sestre milosrdnice University Hospital, Zagreb. After initial treatment patients were followed with serum thyroglobulin (Tg) measurement, whole body scan with iodine-131, neck ultrasound and FNAB with Tg measurement. In 150 patients follow up was longer than 2 years (median 4.5, range 2-18 years). Total thyroidectomy was

njio se s 20 mm u razdoblju 1988.-1992. na 12 mm u 2000.-2004., što je statistički značajno ($p<0,001$). Udio mikrokarcinoma se povećao s 14,3% u prvom na 28,4% u drugom razdoblju. Hrvatska se svrstava među zemlje s visokom incidencijom i niskom smrtnošću od karcinoma štitnjače poput Italije, Francuske, Finske, SAD i Australije. Dok je incidencija karcinoma štitnjače u Hrvatskoj u stalnom porastu, smrtnost je ostala niska i čak blago pada. Utvrđeno je značajno smanjenje veličine novootkrivenog diferenciranog karcinoma štitnjače uz porast udjela mikrokarcinoma, a sve navedeno upućuje na poboljšanu dijagnostiku kao jedan od razloga za porast incidencije karcinoma štitnjače u Hrvatskoj.

14.

PAPILARNI MIKROKARCINOM ŠTITNJAČE – KLINIČKA OBILJEŽJA I PROGNOZA

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Papilarni mikrokarcinom štitnjače (PMŠ) je papilarni karcinom promjera do 10 mm. Incidencija PMŠ je u posljednje vrijeme u porastu zbog česte upotrebe ultrazvuka i citološke punkcije malih nepalpabilnih čvorova. Prema nalazima autopsije prevalencija papilarnih mikrokarcinoma štitnjače u populaciji je 5%-35%, što sve upućuje na nizak stupanj malignosti i dobru prognozu. Prema najnovijim smjernicama Američkog i Europskog udruženja za štitnjaču PMŠ ne zahtijeva poslijeoperacijsko liječenje radioaktivnim jodom niti hormonsko supresijsko liječenje. Cilj istraživanja bio je prikazati klinička obilježja, postupak liječenja i praćenja, te prognozu bolesnika s PMŠ liječenih u Klinici za onkologiju i nuklearnu medicinu, KB "Sestre milosrdnice". U istraživanje je bilo uključeno 258 bolesnika (226 žena i 32 muškarca, medijan dobi 50 godina) s PMŠ. Nakon provedenog liječenja bolesnici su praćeni mjerenjem serumskog biljega tireoglobulina (Tg), scintigrafijom cijelog tijela jodom-131, ultrazvukom vrata i citološkom punkcijom uz anal-

performed in 98% of patients, with neck dissection in 13%, lobectomy in 1.6%, and operation for a thyroglossal duct cyst in one patient. The diagnosis of mPTC was made preoperatively by FNAB in 225 (87%) patients, while mPTC was an incidental finding at histological examination of thyroid treated by surgery for benign diseases in 33 (13%) patients. Multifocal mPTC was present in 21.7% and bilateral mPTC in 14.3% of patients. Patients were categorized according to clinical stage into four groups: I, with intrathyroid disease (n=202, 78.3%); II, cervical node metastases (n=39, 15.1%); III, with extrathyroid invasion (n=15, 5.8%); and IV, distant metastases (n=2, 0.8%). Postoperative treatment with iodine-131 was performed in 88% of patients. At the end of follow up, 141 (94%) patients were free of the disease, cervical node metastases were present in 5 (3.3%), recurrences in the thyroid bed in 2 (1.7%) and persistent biochemical disease in 2 (1.7%) patients. Both patients with distant metastases were successfully treated and are free of the disease. None of the patients died from mPTC. After initial treatment papillary thyroid microcarcinoma has a benign clinical course and good prognosis. Recurrence or persistent disease was recorded in only 6% of patients at the end of follow up. Distant metastases are rare and successfully treated. None of the patients died from mPTC during the period of observation.

15

NO INCREASE IN CHILDHOOD THYROID CANCER IN CROATIA DUE TO CHERNOBYL ACCIDENT

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The nuclear power plant accident in Chernobyl took place on April 26, 1986, and led to the release of vast amounts of radioactivity from the reactor with contamination of the adjacent areas of Belarus, Ukraine and western part of the former Soviet Union, but also contamination of other European countries and other parts of the world. After Chernobyl accident, a dramatic increase in the incidence of thyroid cancer was recorded in most contaminated regions with about 4000 cases, mainly papillary thyroid cancer in children and adolesizu Tg u punktatu. U 150 bolesnika razdoblje praćenja je bilo dulje od 2 godine (medijan 4,5 godine, raspon praćenja 2-18 godina). Totalna tireoidektomija je učinjena u 98% bolesnika, s disekcijom vrata u 13% bolesnika, lobektomija u 1,6% bolesnika, a u jednog bolesnika odstranjenje ciste duktusa tireoglosusa. Prijeoperacijska dijagnoza PMŠ postavljena je citološkom punkcijom u 225 (87%) bolesnika, dok je slučajno otkriven tijekom operacije štitnjače zbog benignih bolesti u 33 (13%) bolesnika. Višežarišni PMŠ utvrđen je u 21,7% bolesnika, u 14,3% bolesnika u oba lobusa. Prema stupnju proširenosti bolesnici su podijeljeni u skupine I., karcinom ograničen na štitnjaču (n=202, 78,3%); II., sekundarizmi na vratu (n=39, 15,1%); III., prodor kapsule uz invaziju tkiva izvan štitnjače (n=15, 5,8%); IV., udaljene metastaze (n=2, 0,8%). Poslijeoperacijsko liječenje jodom-131 provedeno je u 88% bolesnika. Na kraju praćenja u 141 (94%) bolesnika nisu utvrđeni znakovi bolesti, u 5 (3,3%) bolesnika utvrđeni su sekundarizmi na vratu, u 2 (1,7%) bolesnika recidiv u ležištu štitnjače, a u 2/150 (1,7%) bolesnika stalno prisutna bolest. Oba bolesnika s udaljenim metastazama su uspješno liječena i nemaju znakove bolesti. Nije zabilježen smrtni ishod. Papilarni mikrokarcinom štitnjače nakon provedenog liječenja ima dobroćudan klinički tijek i dobru prognozu. Recidiv ili ustrajna bolest utvrđena je u samo 6% bolesnika. Udaljene metastaze su izrazito rijetke i uspješno se liječe pa nije zabilježen smrtni ishod.

15.

ČERNOBIL NIJE UZROKOVAO PORAST KARCINOMA ŠTITNJAČE U DJECE U HRVATSKOJ

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Černobilska nesreća koja se dogodila 26. travnja 1986. uzrokovala je oslobađanje velikih količina radioaktivnosti i kontaminaciju okolnih područja Ukrajine, Bjelorusije i zapadnog dijela SSSR, ali i većeg područja Europe i ostalih dijelova svijeta. Višestruki porast incidencije karcinoma štitnjače zabilježen je u najizloženijim područjima pa je do danas utvrđeno oko 4000 oboljelih, uglavnom djece i adolescenata s papilarnim karcinomom štitnjače, od kojih je najmanje devetero umrlo. Pretpostavlja se da razdoblje latencije od izlaganja radioaktivnom zračenju

cents, and at least nine children died of thyroid cancer. It is assumed that the latency period between exposure to ionizing radiation and development of thyroid cancer in children is about 8-10 years. The aim of the study was to investigate the exposure of Croatian population to ionizing radiation from the damaged reactor and to evaluate the possible influence of radiation dose on the incidence of childhood thyroid cancer in Croatia. New cases of thyroid cancer in Croatia in the 0-14 age group and the incidence of thyroid cancer before and after Chernobyl accident are presented *per* 10-year periods: 1976-1985, 1986-1995 and 1996-2004. Data were collected from the National Cancer Register. Exposure data were taken from UNSCEAR reports on Croatia and measurements of the radioactive fallout activity that contaminated Croatian territory in 1986. According to the UNSCEAR reports, Croatia was significantly affected by ionizing radiation only in the north-west region. However, measurement of radioactive fallout activity demonstrated relatively homogeneous contamination of the Croatian territory that was estimated to be approximately $5.2x10^{15}$ Bq or 0.28% of the released radioactivity from the damaged reactor. During the 1976-1985 period, seven cases of childhood thyroid cancer were recorded in Croatia, and after Chernobyl nine cases in the 1986-1995 period and twelve cases in the 1996-2004 period. The average incidence of thyroid cancer increased from 2.5 in the 1976-1995 period to 3.5 and 6.9 *per* 100,000 in the 1986-1995 and 1996-2004 period, respectively. The number of thyroid cancer cases in adolescents has also increased, especially in the 1996-2004 period, with 35 new cases. According to the data presented, there was no increase in childhood thyroid cancer in Croatia due to Chernobyl accident. The number of children with thyroid cancer remained very low after the accident and referred to sporadic cases. Levels of ionizing radiation in Croatia due to Chernobyl accident were low, and iodine prophylaxis that was introduced in Croatia in 1953 additionally decreased radiation dose to the thyroid. The significant increase in the overall incidence of thyroid cancer recorded in Croatia should probably be ascribed to diagnostic improvements.

do razvoja karcinoma štitnjače u djece iznosi oko 8-10 godina. Cilj istraživanja bio je procijeniti izloženost populacije Hrvatske radioaktivnom zračenju iz oštećenog reaktora i je li ta doza radioaktivnog zračenja utjecala na pojavnost karcinoma štitnjače u djece u Hrvatskoj. Prikazani su novooboljeli u Hrvatskoj u dobi od 0-14 godina i ukupna incidencija karcinoma štitnjače prije i nakon Černobila u 10-godišnjim razdobljima 1976.-1985., 1986.-1995. i 1996.-2004. Podaci o novooboljelima od karcinoma štitnjače prikupljeni su iz Hrvatskoga registra za rak. Podaci o izloženosti populacije Hrvatske radioaktivnom zračenju prikupljeni su iz izvješća UNSCEAR i procjene kontaminacije područja Hrvatske putem radioaktivnih oborina iz 1986. godine. Prema izvještajima UNSCEAR sjeverozapadni dio Hrvatske je bio zahvaćen značajnom dozom radioaktivnosti, ali procjena kontaminacije područja Hrvatske putem radioaktivnih oborina utvrdila je relativno homogenu kontaminaciju čitavog teritorija koja je ukupno iznosila približno $5,2x10^{15}$ Bq ili 0,28% oslobođene radioaktivnosti iz oštećenog reaktora. U razdoblju 1976.-1985. zabilježeno je 7 novooboljele djece u Hrvatskoj, a nakon Černobila 9 u razdoblju 1986.-1995. i 12 u razdoblju 1996.-2004. Prosječna incidencija karcinoma štitnjače porasla je s 2,5 u razdoblju 1976.-1995. na 3,5 u razdoblju 1986.-1995. i potom na 6,9 u razdoblju 1996.-2004. na 100.000. Porastao je i broj karcinoma štitnjače u adolescenata, osobito u razdoblju 1996.-2004., kada je utvrđeno 35 novooboljelih. Prema navedenim podacima u Hrvatskoj nije došlo do porasta karcinoma štitnjače u djece nakon nuklearne nesreće u Černobilu. Broj novooboljele djece je ostao izrazito nizak nakon incidenta i odnosi se na sporadične slučajeve.

Razina ionizirajućeg zračenja u Hrvatskoj kao posljedica černobilske nesreće bila je niska, a jodna profilaksa koja je uvedena u Hrvatskoj 1953. godine dodatno je smanjila dozu radioaktivnog zračenja na štitnjače. Utvrđen je značajan porast ukupne incidencije karcinoma štitnjače u Hrvatskoj, što se uglavnom pripisuje poboljšanoj dijagnostici.

16

RET PROTOONCOGENE MUTATION IN A PATIENT WITH MULTIPLE ENDOCRINE NEOPLASIA SYNDROME TYPE 2B (MEN 2B)

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The RET protooncogene is constitutively mutated by point mutations in hereditary medullary thyroid carcinoma but somatic RET point mutations have also been recorded in 40%-50% of sporadic medullary thyroid carcinoma. In the future of medicine, molecular diagnosis of malignant neoplasm is going to be a basic diagnostic method for aerly diagnosis of thyroid cancer. We report a case of a patient with multiple endocrine neoplasia syndrome type 2B (MEN 2B), which was diagnosed after standard diagnostic procedure. In therapy, thyroid medullary carcinoma was surgically removed and bilateral pheochromocytoma treated with octreotide. Blood samples were obtained genetic analysis. Genomic DNA was isolated from white blood cells and the sample was analyzed for exons 10, 11, 13 and 16 of RET protooncogene with polymerase chain reaction (PCR) and electrophoresis.

PCR results:

- exone 11: a point mutation for restriction fragment Cfo I on codone 634 (TGC in CGC)
- exone 10: no mutation
- exone 13: no mutation
- exone 16: no mutation

Our results as well as recent litarature data confirm strong relationship between mutation of codone 634 of the RET protooncogene and development of medullary thyroid cancer. The presence of this mutation in a patient with MEN 2B syndrome is clinicaly interesting because there are little literature data on this phenomenon.

In accordance with genetic results, further testing is needed to evaluate the presence of this mutation in the patient's family members.

16.

MUTACIJA PROTOONKOGENA RET U BOLESNICE SA SINDROMOM MULTIPLE ENDOKRINE NEOPLAZIJE TIP 2B (MEN 2B)

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Protoonkogen RET je podložan konstitucijskoj točkastoj mutaciji kod nasljednog medularnog karcinoma štitnjače, dok se somatske točkaste mutacije RET također mogu naći u 40%-50% slučajeva sporadičnog medularnog karcinoma štitnjače. U novije vrijeme sve se veća pozornost obraća molekularnoj dijagnostici malignih neoplazma, koja bi u budućnosti trebala postati jedna od temeljnih dijagnostičkih metoda za otkrivanje raka štitnjače. U bolesnice kojoj je nakon standardnog dijagnostičkog postupka kojim se otkrilo postojanje sindroma multiple endokrine neoplazije tip 2B operacijski odstranjen medularni karcinom štitnjače, a bilateralni feokromocitomi se uspješno liječe primjenom oktreotida, uzeta je krv za naknadnu gensku analizu. Izdvajanjem genomske DNA iz leukocita periferne krvi pristupilo se umnažanju eksona 10, 11, 13 i 16 protoonkogena RET polimeraznom lančanom reakcijom (PCR). Ispitano je postojanje točkastih mutacija u "vrućim regijama" analiziranih eksona putem djelovanja restrikcijskih endonukleaza. Odsječci su nakon toga analizirani elektroforezom u poliakrilamidnom gelu i dobiveni su slijedeći rezultati:

- ekson 11: postoji točkasta mutacija koja je promijenila restrikcijsko mjesto za Cfo I endonukleazu na 634. kodonu (TGC u CGC)
- ekson 10: bez mutacije
- ekson 13: bez mutacije
- ekson 16: bez mutacije

Rezultatima naših ispitivanja dodatno smo potvrdili novije literaturne podatke koji potvrđuju mutaciju kodona 634 kao visoko rizičnu mutaciju za nastanak medularnog karcinoma štitne žlijezde. Postojanje ove mutacije i u sindromu MEN 2B klinički je zanimljivo budući da su podaci o mutacijama protoonkogena RET u sindromu MEN 2B relativno skromni. U skladu s rezultatom genske analize i trenutnih spoznaja, a radi utvrđivanja postojanja mutacija u obitelji bolesnice, potrebno je učiniti i dodatno genetsko testiranje srodnika.

17

THYROID MICROCARCINOMAS

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Thyroid microcarcinomas are tumors of less than 1 cm in diameter that usually present as an incidental finding on definitive histopathologic analysis. The aim of the study was to establish the incidence of microcarcinomas in patients operated on for benign thyroid disease and to analyze the operation performed. This retrospective study included patients operated on at Center for Endocrine Surgery, Belgrade, from January 1 to December 31, 2004. Out of 719 patients operated on for thyroid disease, there were 578 patients with benign thyroid deseases, i.e. multinodular goiter in 201, thyroiditis in 31, thyroid adenoma in 178, Graves' disease in 89 and Plummer's disease in 79 patients. The presence of microcarcinoma was noticed on definitive histopathologic examination in 13.4% of patients operated for goiter, 6.4% for thyroiditis, 5.6% for thyroid adenomas, 9.0% for Graves' disease and 7.0% for Plummer's disease. Thyroid operation was performed in 578 patients with benign thyroid disease, microcarcinoma was confirmed by definitive histopathologic analysis in 51 (9%) patients, 31 female and 20 male aged 19-79 (average 49) years. Tumor size was 2-9 (average 5) mm. Total thyroidectomy was performed in 93% of patients with goiter, 84% with thyroiditis, 97% with Graves' disease and 92% with Plummer's disease. Hemithyroidectomy was performed in 97% of patients with benign tumors. Microcarcinomas are frequent in all benign thyroid diseases, so total thyroidectomy is the treatment of choice in such benign thyroid disease.

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HYPERTHYROIDISM AND THYROID CANCER

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The association of hyperthyroidism and thyroid cancer (TC) is considered a rare event. Thyroid cancer is often diagnosed incidentally by fine-needle aspiration or on postoperative histopathology. The aim of this study

17.

MIKROKARCINOMI ŠTITNJAČE

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Mikrokarcinomi štitnjače su tumori promjera manjeg od 1 cm i u većini su slučajeva slučajan nalaz pri histopatološkoj analizi. Cilj ove studije bio je utvrditi incidenciju mikrokarcinoma među bolesnicima koji su operirani zbog benignih bolesti štitnjače te analizirati vrstu operativnog zahvata. Retrospektivna studija provedena je među bolesnicima operiranim u Centru za endokrinološku kirurgiju u Beogradu u razdoblju od 1. siječnja do 31. prosinca 2004. godine. Od ukupno 719 bolesnika operiranih tijekom te godine, njih 578 operirano je zbog neke benigne bolesti štitnjače: 201 zbog multinodozne strume, 31 zbog tireoiditisa, 178 zbog adenoma štitnjače, 89 zbog Gravesove bolesti i 79 zbog Plummerove bolesti. Mikrokarcinom je potvrđen histopatološkom analizom u 13,4% bolesnika operiranih zbog strume, 6,4% operiranih zbog tireoiditisa, 5,6% operiranih zbog adenoma, 9% operiranih zbog Gravesove bolesti i 7% operiranih zbog Plummerove bolesti. Ukupno je zbog benignih bolesti štitnjače operirano 578 bolesnika, a mikrokarcinom je histopatološkom analizom otkriven kod 51 osobe (tj. njih 9%), 31 žene i 20 muškaraca, u dobi od 19-79 godina (prosječne dobi 49 godina). Veličina tumora iznosila je 2-9 mm (prosječna veličina 5 mm). Totalna tireoidektomija učinjena je u 93% bolesnika sa strumom, 84% s tireoiditisom, 97% s Gravesovom bolesti i 92% s Plummerovom bolesti. Parcijalna tireoidektomija (hemitireoidektomija) je učinjena u 97% bolesnika s benignim tumorima. Mikrokarcinomi su čest nalaz kod svih benignih bolesti štitnjače pa je totalna tireoidektomija zahvat izbora u tih bolesnika.

18.

HIPERTIREOZA I RAK ŠTITNJAČE

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Povezanost hipertireoze i raka štitnjače (RŠ) se smatra rijetkom pojavom. Rak štitnjače se često dijagnosticira slučajno citološkom punkcijom ili patohistološki nakon

was to establish the association between hyperthyroidism and thyroid cancer, and the percent of microcarcinoma in patients with coexistence of thyroid cancer and hyperthyroidism. We retrospectively reviewed 568 patients with TC treated at our department between January 2000 and July 2007. In 35 (6.3%) patients, the diagnosis of hyperthyroidism was established. Hyperthyroidism was diagnosed by assessing clinical symptoms, TSH and thyroid hormones, thyroid scintigraphy and neck ultrasonography. Thyroid cancer was confirmed by histopathology in all patients with hyperthyroidism and data on tumor size, local invasiveness, regional and distant metastases were analyzed. Out of 35 hyperthyroid patients (29 women and 6 men, median age at diagnosis 48.6, range 22-74 years), 27 patients had Graves' hyperthyroidism, 7 patients had multinodular toxic goiter, and one patient had toxic adenoma. In 11 patients TC was identified incidentally during surgery for benign thyroid disease (8 with microcarcinoma), while in 24 patients surgery was performed due to cytologically suspected TC. Papillary TC was diagnosed in 33 (94%) patients, one patient had follicular TC and one Hürthle cell cancer. All patients underwent total thyroidectomy with unilateral neck dissection in 3 and bilateral in one patient. The median tumor size was 16 mm (range 2 to 60 mm). Local disease was evidenced in 25 (71%) patients, 8 had regional lymph node metastases, and two had distant metastases at the time of diagnosis of thyroid cancer. Papillary microcarcinoma (≥10 mm in diameter) was detected in 19 (54 %) patients and four of them had regional lymph node metastases without distant metastases at the time of diagnosis. Although TC is a rare in patients with hyperthyroidism, there are cases with more advanced clinical presentation that require careful examination and awareness of the possible presence of associated malignancy in such patients.

operacije. Cilj studije bio je utvrditi povezanost hipertireoze i raka štitnjače te učestalost mikrokarcinoma u bolesnika s istodobnom pojavom hipertireoze i raka štitnjače. Provedena je retrospektivna analiza u 568 bolesnika s rakom štitnjače koji su liječeni u Klinici za onkologiju i nuklearnu medicinu u razdoblju od siječnja 2000. do lipnja 2007. godine. U 35 (6,3%) bolesnika postavljena je dijagnoza hipertireoze. Dijagnoza hipertireoze postavljena je na temelju kliničkih simptoma, mjerenjem TSH i hormona štitnjače, scintigrafijom štitnjače te ultrazvukom vrata. Rak štitnjače je potvrđen patohistološki u svih bolesnika, a analizirani su podaci o veličini tumora, lokalnoj proširenosti, zahvaćenosti limfnih čvorova te prisutnosti udaljenih metastaza. Od 35 bolesnika s hipertireozom (29 žena, 6 muškaraca, medijan dobi 48,6 god., raspon 22-74 godine), Gravesova bolest je utvrđena u 27, multinodozna toksična guša u 7, a toksični adenom u jednog bolesnika. U 11 bolesnika je RŠ otkriven slučajno nakon operacije zbog benigne bolesti štitnjače (od kojih 8 s papilarnim mikrokarcinomom), a u 24 je postavljena citološka sumnja na RŠ. U 33 (94%) bolesnika dijagnosticiran je papilarni, a u po jednog bolesnika folikularni karcinom i karcinom Hürthleovih stanica. U svih bolesnika je učinjena totalna tiroidektomija, u troje bolesnika i dodatna jednostrana, a u jednog bilateralna disekcija vrata. Medijan veličine tumora iznosio je 16 mm (raspon od 2 do 60 mm). Bolest je bila lokalizirana u 25 (71%) bolesnika, dok su u osam bolesnika zabilježene metastaze u limfne čvorove, a u dvoje bolesnika udaljene metastaze u vrijeme postavljanja dijagnoze raka. Papilarni mikrokarcinom (≥10 mm u promjeru) je pronađen u 19 (54%) bolesnika, od kojih su u četvoro utvrđene metastaze u regionalne limfne čvorove, ali bez udaljenih metastaza u trenutku postavljanja dijagnoze. Iako je rak štitnjače rijetka pojava u bolesnika s hipertireozom, postoje slučajevi s malignim kliničkim tijekom kada je neophodan pažljiv pregled i svijest o mogućoj prisutnosti udruženog maligniteta u takvih bolesnika.

19

COLOR DOPPLER IMAGING, US-FNAB AND THYROID BLOOD TESTS IN EVALUATION OF THYROID DISEASES

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Color Doppler imaging (CDI), ultrasonography (US) guided fine needle aspiration biopsy (US-FNAB) and thyroid blood tests were analyzed in 145 patients with different thyroid diseases. All patients underwent CDI, US-FNAB and standard thyroid blood tests. Out of 145 study patients, 99 (68%) had nodular thyroid disease. Out of 146 thyroid nodules evaluated, 118 (81%) were solid, 27 (18%) mixed, and one nodule was cystic. Nodule diameter ranged from 3 to 60 (median 14) mm. Most nodules were hypoechoic (44%), 31% were isoechoic, 3% were hyperechoic, and other nodules had mixed echostructure. Cytological evaluation revealed 6 (4%) neoplastic lesions and definitive histology confirmed 4 thyroid carcinomas. The carcinoma diameter was 6-to 39 mm, all were hypoechoic and showed increased vascularity on CDI and Power Doppler. On cytology, most of the nodules showed a goiter pattern (56%), 30% showed some level of cell proliferation, and Hashimoto's disease was found in 4 nodules. Twenty-four (17%) patients had Hashimoto's disease. TPO antibody level was increased in 20 (14%) patients. Positive correlation was found between TPO value and cytology (r=0.509), and negative correlation between TPO value and echostructure of the thyroid (r=-0.204). According to our experience, a diagnostic protocol that includes CDI, US-FNAB and thyroid blood tests can significantly upgrade thyroid disease evaluation on the outpatient basis.

19.

KOLOR DOPPLER, ULTRAZVUČNO VOĐENA CITOLOŠKA PUNKCIJA I LABORATORIJSKI TESTOVI U PROCJENI BOLESTI ŠTITNJAČE

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Kolor Doppler, ultrazvučno vođena citološka punkcija s naknadnom citološkom analizom uzoraka te rezultati laboratorijskih pretraga analizirani su u bolesnika s različitim bolestima štitnjače. U ovu studiju je bilo uključeno 145 bolesnika. Kod svih bolesnika je učinjen ultrazvuk štitnjače kolor Dopplerom, ciljana citološka punkcija pod kontrolom ultrazvuka s naknadnom citološkom analizom te standarndni laboratorijski testovi za štitnjaču. U većine ispitivanih bolesnika (n=99; 68%) nađen je čvor u štitnjači. Ukupno je obrađeno 146 čvorova, od kojih su 118 (81%) bili solidni, 27(18%) ih je imalo miješanu (solidnu i cističnu) strukturu, a samo jedna promjena je imala isključivo cistični sadržaj. Promjer čvorova se kretao od 3 do 60 (median 14) mm. Većina čvorova (44%) je imala hipoehogenu ultrazvučnu strukturu, nešto manje je bilo čvorova s izoehogenom strukturom (31%), a u samo 3% čvorova zamijećena je hiperehogena struktura odjeka. Preostali čvorovi su imali miješanu ehostrukturu. Citološka analiza ukazivala je na neoplastičnu narav procesa u 6 (4%) čvorova. Histološka analiza je potvrdila karcinomatozne promjene u 4 čvora. Promjer karcinoma je bio od 6 do 39 mm i svi su bili hipoehogene ultrazvučne strukture, pokazujući patološki pojačanu vaskularizaciju na kolor Doppleru. Većina čvorova (56%) je citološki imala sliku različitih oblika strume, a u značajnom dijelu čvorova (30%) citološki su nađene različite razine stanične proliferacije. U 4 čvora citološki su nađeni samo elementi kronične limfocitne upale (Hashimotov tireoiditis). U 24 (17%) bolesnika postavljena je dijagnoza kronične limfocitne upale (Hashimotov tireoiditis). Titar TPO protutijela bio je povišen u 20 (14%) bolesnika. Pozitivna korelacija je zamijećena između titra TPO protutijela i citološke slike (r=0,509), dok je između titra TPO protutijela i ultrazvučne strukture tkiva štitnjače zamijećena loša korelacija (r=-0,204). Sukladno našim iskustvima te rezultatima ove studije skloni smo preporučiti dijagnostički protok koji uključuje

ultrazvuk štitnjače nadopunjem kolor Dopplerom, ciljanu citološku punkciju te temeljne laboratorijske pretrage kako bi se unaprijedila rana dijagnostika kako karcinoma tako i drugih bolesti štitnjače.

20

CALCITONIN IN FOLLOW-UP OF PATIENTS WITH MEDULLARY THYROID CANCER

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Calcitonin (CT) is a polypeptide produced by parafollicular or C-cells of the thyroid. In patients with medullary thyroid cancer (MTC), due to malignant transformation of C-cells, blood CT concentration increases prior to the appearance of the clinical signs of the disease. In postoperative follow-up of MTC patients, CT is the main specific tumour marker tumor marker in establishing tumour recurrence or metastases. The level of CT relates to the amount of residual thyroid tissue. As an additional, nonspecific tumor marker, carcinoembryonic antigen (CEA) can be used. The aim of the study was to review all CT results determined over a period of 10 years and to evaluate the changes in CT concentrations during the monitoring period. CT concentration was determined by different quantitative assays using monoclonal antibodies: 1. IRMA-CT (CIS bio International, Gif-Sur-Yvette Cedex, France; cut-off <10 pg/mL), 2. EIA-CT (IASON Labormedizin GmbH, Graz-Seiersberg, Austria; cut-off <10 pg/mL), and 3. LIA-CT (Immulite, DPC Los Angeles, USA; cut-off <13 pg/mL). Results were expressed as positive when the value of CT was above the respective cut-off value. During the 1996-2007 period, there were 630 CT determinations in 57 patients with MTC (34 women and 23 men). A group of 54 patients were followed-up more than three times, and only three patients had less then two CT determinations. The highest number of visits was 38, recorded in only one patient. During the period of monitoring, 25 (46 %) patients had all negative results, and at least one positive CT value was detected in 29 (54 %) patients. Changes in CT level corresponded with clinical condition of the patient (positive response to therapy or progression). In tree patients (10%) an increased CT concentration was found without any pathological substrate. CT is a useful tumor marker in monitoring of patients with MTC to detect progression of the disease or therapy efficiency.

20.

KALCITONIN U PRAĆENJU BOLESNIKA S MEDULARNIM KARCINOMOM ŠTITNJAČE

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Kalcitonin (CT) je polipeptid koji izlučuju parafolikularne stanice ili C-stanice štitnjače. U bolesnika s medularnim karcinomom štitnjače (MKŠ), zbog maligne transformacije C stanica, CT se pojačano luči pa ga je moguće odrediti u serumu prije nego se pojave kliničke značajke bolesti. Nakon operacije bolesnika s MKŠ, CT se rabi kao specifični tumorski biljeg, a karcinoembrijski antigen (CEA) kao dodatni, nespecifični tumorski biljeg za otkrivanje recidiva ili metastaza. Cilj rada je prikazati rezultate koncentracije CT u serumu bolesnika s MKŠ određene u proteklih 10 godina i utvrditi promjene u razini CT nastale tijekom praćenja bolesnika. Razina CT određivala se je pomoću tri kvantitativne metode uz primjenu monoklonskih protutijela: 1. IRMA-CT (CIS bio International, Gif-Sur-Yvette Cedex, Francuska; granična vrijednost <10 pg/mL), 2. EIA-CT (IASON Labormedizin GmbH, Graz-Seiersberg, Austrija; granična vrijednost <10 pg/mL) i 3. LIA-CT (Immulite, DPC Los Angeles, SAD; granična vrijednost <13 pg/mL). Rezultati su izraženi kao pozitivni ako su bili viši od granične vrijednosti za dotičnu metodu. U razdoblju od 1996. do 2007. g. određeno je ukupno 630 CT pretraga za 57 bolesnika (34 žena, 23 muškaraca) s MKŠ. Skupina od 54 bolesnika praćena je više od tri puta dok je u troje bolesnika CT određen samo jednom ili dva puta. Najveći broj posjeta tijekom deset godina praćenja bio je 38. Sustavno negativan nalaz CT imalo je 25 (46 %) bolesnika dok je 29 (54%) bolesnika imalo barem jedan pozitivan nalaz. Promjena razine CT uglavnom je odgovarala kliničkom tijeku bolesti (pozitivan odgovor na terapiju ili progresija).U troje bolesnika nađene su povišene vrijednosti CT ali bez pratećeg patološkog supstrata na učinjenim pretragama. CT je koristan tumorski biljeg u praćenju bolesnika s MKŠ, kako progresije bolesti, tako i odgovora na liječenje.

21

TWENTY FIVE YEARS OF THYROGLOBULIN MEASUREMENT

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Thyroglobulin (Tg) is a glycoprotein containing iodine (660 000 D) and is the main component of the colloid cells of the thyroid. It is responsible for the production, storage and excretion of the thyroid hormone into circulation. Serum concentration of thyroglobulin is significantly raised in hyperthyroidism, inflammatory and other forms of thyroid damage, and especially in differentiated thyroid cancer (DTC).The level of Tg is related to the size of the thyroid remnant and can signal the existence of metastases and also their location. The interpretation of Tg results can be complicated because thyroglobulin antibodies (TgA) may interfere with the test and false negative/false positive results may be obtained.

Our laboratory first introduced Tg testing in 1982 and data input began in 1990 when the laboratory information system was established. The purpose of this article is to give an overview of the results obtained for the period of the last twenty-five years. In this period, six commercial diagnostic kits were used (RIA, IRMA, LIA, and EIA) for which the cut-off level of Tg was less than 2ng/mL. The concentration of TgA was determined using eight different commercial kits, initially using agglutination method (titration) and later using quantitative methods (RIA, EIA, LIA). During the period from 1990-2006, our laboratory carried out 8077 Tg assays in 1171 patients with DTC (943 female and 228 male patients). Patients were tested for Tg at least once to a maximum of 27 times (1-27 visits). The level of Tg higher than the cut-off value was observed in 14% of patients. The concentration of Tg was compared with the concentration of thyrotropin and with the results of whole body scintigraphy (^{131}I WBS).

Results obtained in these studies confirm that Tg can be considered a tumor marker of choice in the postoperative follow-up of patients with DTC.

21.

DVADESETPETOGODIŠNJE ISKUSTVO U ODREĐIVANJU TIREOGLOBULINA

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Tireoglobulin (Tg) je jodirani glikoprotein (660000 D) koji čini glavni sastojak koloida stanica štitnjače. Odgovoran je za stvaranje, skladištenje i izlučivanje hormona štitnjače u cirkulaciju. Serumska koncentracija se značajnije povećava u hipertireozi, pri upalnim i drugim oblicima oštećenja štitnjače te osobito u diferenciranom karcinomu štitnjače (DKŠ). Razina Tg odražava veličinu mase ostatnog tkiva štitnjače i ukazuje na pojavu metastaza, pa čak i na njihovu lokalizaciju. Problem u interpretaciji nalaza Tg javlja se zbog moguće interferencije tireoglobulinskih protutijela (TgA) u postupku mjerenja Tg, što može uzrokovati lažno negativne/pozitivne rezultate. Prvo određivanje Tg u našem laboratoriju izvršeno je 1982. g., a računalna obrada rezultata započeta je 1990. g. U ovom radu prikazujemo rezultate Tg određene u proteklih 25 godina. Tijekom godina rabili smo Tg komplete šest proizvođača (RIA, IRMA, LIA, EIA) za koje je granična vrijednost (cut-off) Tg iznosila < 2 ng/mL. Razina TgA određivana je s osam različitih kompleta, u početku aglutinacijskom tehnikom (titar), a kasnije kvantitativnim metodama (RIA, EIA, LIA). U razdoblju od 1990. do 2006. g. izvršeno je 8077 pretraga Tg za 1171 bolesnika s DKŠ od kojih je bilo 943 (81%) žene i 228 (19%) muškaraca. Bolesnicima je određena razina Tg barem jednom ili najviše 27 puta (1-27 posjeta). Razina Tg iznad cut-off vrijednosti zabilježena je u 14% bolesnika. Vrijednost koncentracije Tg uspoređena je s vrijednošću razine tireotropina i nalazom scintigrafije cijelog tijela (^{131}I WBS).

Rezultati potvrđuju da se Tg može smatrati, gotovo idealnim, tumorskim biljegom u poslijeoperacijskom praćenju bolesnika s DKŠ.

22

FOLLOW UP AND SURVIVAL OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

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Patients with histopathologically proved differentiated thyroid carcinoma (DTC) require a life long follow up in order to determine the remission rate and recurrence of the desease. These patients should have the survival rate (SR) determined. The aim of the study was to determine SR in patients with DTC, especially infiltrative, lymphonodal with distant metastases, and to detect the shortcomings of therapy. Patients with DTC were followed-up according to the protocol. SR was determined by Kaplan Meier method. SR was determined in DTC patients (n=296, follow up 20 years). We recorded SR 0.91 for both forms; FTC 0.85; PTC 0.93; st I 0.99; st II 0.91; st III 0.93 and st IV 0.33. SR was determined with infiltrative pT4DTC (n=71/321 (22.1%), follow up 23 years). In this group 5-year SR was 0.90, 10-year SR 0.84 and 15-year SR 0.76. Determination of SR in patients with DTC of lymphonodal type N1a/b (n=180/360 (49.4%), follow up 23 years) yielded the following results: 5-year SR 0.87, 10-year SR 0.71 and 20-year SR 0.56. SR was also determined in patients with distant metastases M1: (n=75/367 (20.6%), follow up 25 years): 5-year SR 0.60, 10-year SR 0.51 and 20-year SR 0.38. It is concluded that patients with DTC require lifelong follow up according to the protocol. SR of DTC patients depends on the early and rational diagnosis, initial surgery, prompt and ample first 131-I therapy, and long term hormone therapy with L-thyroxine.

22.

PRAĆENJE I PREŽIVLJENJE BOLESNIKA S DIFERENCIRANIM KARCINOMOM ŠTITNJAČE

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Bolesnike s patohistološki dokazanim diferenciranim karcinomom štitnjače (DKŠ) potrebno je doživotno pratiti kako bi se odredila stopa remisije i recidiva bolesti. U ovih bolesnika potrebno je odrediti i stopu preživljenja (SP). Cilj ovog istraživanja bio je odrediti SP bolesnika s DKŠ, osobito infiltrajućim koji zahvaća limfne čvorove i stvara udaljene metastaze te otkriti nedostatke postojeće terapije. Bolesnici s DKŠ praćeni su prema protokolu. SP je određivana Kaplan Meierovom metodom. SP je određena u bolesnika s DKŠ (n=296, praćenje 20 godina). Za obje forme SP je iznosila 0,9; za FKŠ 0.85; za PKŠ 0,93; za st. I. 0,99; st. II. 0,91; st. III. 0,93 i st. IV. 0,33. SP je određena kod infiltrativnog pT4 DKŠ (n=71/321 (22,1%) praćenje 23 godine.) U ovoj je grupi 5-godišnja SP iznosila 0,90; 10-godišnja 0,84 i 15-godišnja 0,76. U bolesnika s DKŠ s limfonodalnim tipom N1a/b (n=180/360 (49,4%), praćenje 23 godine) određivana je SP. Dobiveni su rezultati: 5-godišnja SP 0,87; 10-godišnja 0,71 i 20-godišnja 0,56. SP je određivana i u bolesnika s udaljenim metastazama M1: (n=75/367 (20,6%), praćenje 25 godina); 5-godišnja SP iznosi 0,60; 10-godišnja 0,51 i 20-godišnja 0,38. Bolesnike s DKŠ potrebno je doživotno pratiti, prema protokolu. SP bolesnika s DKŠ ovisi o ranoj racionalnoj dijagnostici, inicijalnoj kirurgiji, pravovremenoj i dovoljnoj prvoj terapiji pomoću 131-I te dugotrajnoj hormonskoj terapiji L-tiroksinom.

23

COEXISTENCE OF PAPILLARY CARCINOMA AND HASHIMOTO THYROIDITIS: A STUDY OF CYTOLOGIC AND HISTOLOGIC MATERIAL

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The aim of the study was to determine the incidence of papillary carcinoma (PC) and Hashimoto thyroiditis

23.

ISTOVREMENA PRISUTNOST PAPILARNOG KARCINOMA I HASHIMOTOVOG TIREOIDITISA: ANALIZA CITOLOŠKOG I HISTOLOŠKOG MATERIJALA

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Cilj studije bio je analizirati istodobnu prisutnost papilarnog karcinoma (PK) i Hashimotovog tireoiditisa

(HT) coexistence in cytologic and histologic material. Cytologic and histologic data were collected from 11844 patients undergoing ultrasound-guided fine needle aspiration cytology (FNAC) of the thyroid; 891 of these patients underwent thyroid surgery. Of 11844 patients with FNAC diagnosis, 1841 (15.5%) had HT and 314 (2.6%) had PC, whereas 37 (0.3%) patients had both PC and HT. Among patients with FNAC diagnosis of HT, the prevalence of PC was 2.0%, and among patients with PC, the prevalence of HT was 11.8%. There was no statistically significant difference (p=0.1235) between the prevalence of PC in patients with HT and the prevalence of PC in total number of patients undergoing FNAC. Similarly, there was no statistically significant difference (p=0.0817) between the prevalence of HT in patients with PC and the prevalence of HT in total number of patients undergoing FNAC. Of 891 patients with thyroid surgery, 91 (10.2%) had histologic diagnosis of HT and 191 (21.4%) had PC, whereas 43 (4.8%) patients had both PC and HT. Among patients with histologic diagnosis of HT, the prevalence of PC was 47.2%, and among patients with PC, the prevalence of HT was 22.5%. The prevalence of HT was significantly higher in patients with PC (p<0.01) than the prevalence of HT in total number of patients undergoing thyroid surgery. Similarly, the prevalence of PC was significantly higher in patients with HT (p<0.01) than the prevalence of PC in total number of patients undergoing thyroid surgery. Results of the large study of patients with FNAC of the thyroid showed a low incidence (0.3%) of PC and HT coexistence. There was no statistically significant difference (p=0.1235) in the prevalence of PC in patients with HT as compared to the prevalence of PC in total number of patients undergoing FNAC. In histologic material, the association between PC and HT could be attributed to the selection of patients for surgery.

(HT) u citološkom i histološkom materijalu. Analizrani su citološki nalazi 11844 bolesnika kod kojih je učinjena citološka punkcija štitnjače pod kontrolom ultrazvuka. Kod 891 bolesnika je učinjen i kriruški zahvat na štitnjači te su analizirani i njihovi histološki nalazi. Od ukupnog broja bolesnika s učinjenom citološkom punkcijom štitnjače 1841 (15,5%) bolesnik je imao HT, a 314 (2,6%) ih je imalo PK, dok je 37 (0,3%) bolesnika imalo istodobno PK i HT. Među bolesnicima s citološkom dijagnozom HT učestalost PK je bila 2,0%, a među bolesnicima s citološkom dijagnozom PK je učestalost HT bila 11,8%. Nije nađena statistički značajna razlika (p=0,1235) u učestalosti PK kod bolesnika s HT prema učestalosti PK u ukupnom broju bolesnika. Također nije bilo statistički značajne razlike u učestalosti HT kod bolesnika s PK prema učestalosti HT u ukupnom broju bolesnika (p=0,0817). Kod 891 bolesnika je učinjen kriruški zahvat na štitnjači; 91 (10,2%) bolesnik je imao histološku dijagnozu HT, a 191 (21,4%) bolesnik je imao PK; 43 (4,8%) bolesnika su imali istodobno prisutan PK i HT. Među bolesnicima s histološkom dijagnozom HT je učestalost PK bila 47,2%, a među bolesnicima s histološkom dijagnozom PK je učestalost HT bila 22,5%. Učestalost HT je bila statistički značajno veća kod bolesnika s PK (p<0,01) nego u ukupnom broju bolesnika podvrgnutih operacijskom zahvatu. Slično tome, učestalost PK je bila statistički značajnija kod bolesnika s HT (p<0,01) nego u ukupnom broju bolesnika. Rezultati ove studije provedene na velikom broju bolesnika u kojih je učinjena citološka punkcija štitnjače pod kontrolom ultrazvuka pokazuju nisku incidenciju (0,3%) istodobno prisutnog PK i HT u citološkom materijalu. Nije nađena statistički značajna razlika (p=0,1235) u učestalosti PK kod bolesnika s HT u usporedbi s učestalosti PK u ukupnom broju bolesnika. Statistički značajna povezanost između PK i HT, koja je nađena u histološkom materijalu, može se objasniti odabirom bolesnika za kirurški zahvat.

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DETERMINATION OF URINARY EXCRETION OF 131-I FOLLOWING ITS THERAPEUTIC APPLICATION IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

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In a case of differentiated thyroid carcinoma (DTC) standard procedure is postoperative application of the ablative/therapeutic dose of 131I. However, there are just a small number of references on the exact mathematical evaluation of urinary excretion of 131I. The purpose of the study was to define mathematical function that exactly defines excretion process in order to evaluate optimal time for the administration of diuretic therapy. Twenty-five previously operated DTC patients (8 men and 17 women, mean age 43.2+/-82 years) were included in the study. In all of them, we first estimated fixation of 131I and laboratory data related to renal function. Five patients were treated with 1.85, 11 with 3.7 and 9 with 5.55 Gbq of 131I. After the application of 131I, all patients were ordered to urinate into a graded bottle to record urine volume and to obtain a specimen for further measurement. Total quantity of 131I excreted in urine was estimated for each urination. The measured value for each urination was expressed as percentage of the dose applied. We found the function y=76.2 *(1-e-x/13.7) to best fit our data. Based on this function, the optimal time for starting diuretic therapy is 2-3 hours after the application of 131I and it should be administered in the next 48 hours. Thus determined values of urinary excretion of 131I make it easier to evaluate the timing of diuretic therapy administration in patients treated with 131I.

24.

ODREĐIVANJE URINARNOG IZLUČIVANJA 131-I NAKON TERAPIJSKE PRIMJENE U BOLESNIKA S DIFERENCIRANIM KARCINOMOM ŠTITNJAČE

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Kod diferenciranog karcinoma štitnjače postoperacijska primjena ablativne/terapijske doze 131-I je dio standardne procedure. U literaturi postoji vrlo malo podataka o točnoj matematičkoj procjeni izlučivanja 131-I mokraćom. Cilj istraživanja bio je odrediti matematičku formulu koja bi točno prikazala proces izlučivanja 131-I radi procjene optimalnog vremena za primjenu diuretske terapije. Ispitivanje je obuhvatilo 25 prethodno operiranih bolesnika s diferenciranim karcinomom štitnjače (8 muškaraca i 17 žena prosječne starosti od 43.2 ±8.2 godina). Svima je prethodno učinjen test fiksacije 131-I, kao i laboratorijske analize za procjenu bubrežne funkcije. Pet bolesnika liječeno je s 1,85; 11 s 3,7; a 9 sa 5,55 GBq 131-I. Svim bolesnicima je objašnjeno da nakon aplikacije 131-I svaki put trebaju mokriti u menzuru kako bi mogli registrirati količinu izmokrenog urina i odvojiti uzorak za kasnije mjerenje. Izračunavali smo ukupnu količinu izmokrenog 131-I za svako mokrenje. Izmjerene vrijednosti za svako mokrenje izražene su kao postotak aplicirane doze. Dobiveni podaci usklađivani su pomoću funkcije y=76,2 *(1-e-x/13,7) koja je najbolje odgovarala našim podacima. Prema toj funkciji procijenili smo da je optimalno vrijeme za početak diuretske terapije oko 2-3 sata nakon aplikacije 131-I te da ju je nužno provesti u slijedećih 48 sati. Ovako određene vrijednosti ekskrecije 131-I mokraćom olakšavaju procjenu perioda optimalne primjene diuretske terapije u bolesnika liječenih pomoću131-I.

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INCREASED INCIDENCE OF THYROID CANCER IN THE SPLIT-DALMATIA COUNTY: EPIDEMIOLOGICAL CHARACTERISTICS

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The aim of this retrospective study was to investigate the incidence of thyroid cancer in the Split-Dalmatia County in the 1997-2006 period, and compare it with the incidence in the Republic of Croatia. Data were obtained from case records of all hospitals and Public Health Institute in the County and National Cancer Registry. Age-standardized incidence *per* 100,000 was calculated from the number of patients with thyroid cancer and number of inhabitants. During the 1997-2006 period, there were 503 new cases of thyroid cancer (401 women and 102 men) in the Split-Dalmatia County. Papillary carcinoma was diagnosed in 86.1%, follicular adenocarcinoma in 9.5%, medullar carcinoma in 4.2%, and anaplastic carcinoma in 0.2% of cases. In 2003, the age-standardized incidence rate for thyroid cancer *per* 100,000 population in Croatia was 8.5 (women 13.3 and men 3.5). The thyroid cancer incidence rate in the Split-Dalmatia County increased from 8.2 (women 13.5 and men 2.7) in 1997 to 11.5 in 2006 (women 15.6 and men 7.1). There was an increase in the reported incidence of thyroid cancer in the Split-Dalmatia County and in Croatia as a whole during the 1997-2006 period. Thyroid cancer was more common in female than in male patients.

25.

POVEĆANA UČESTALOST KARCINOMA ŠTITNJAČE U SPLITSKO-DALMATINSKOJ ŽUPANIJI: EPIDEMIOLOŠKE ZNAČAJKE

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Cilj studije bio je istražiti učestalost karcinoma štitnjače u Splitsko-dalmatinskoj županiji u razdoblju 1997.-2006. i usporediti ju s učestalošću u Republici Hrvatskoj. Retrospektivnim istraživanjem prikupljeni su podaci iz arhiva bolnica i Zavoda za javno zdravstvo županije Splitsko-dalmatinske i Hrvatskog registra za rak. Dobno standardizirana stopa učestalosti na 100.000 izračunata je iz broja bolesnika s karcinomom štitne žlijezde i broja stanovnika. U razdoblju 1997.-2006. na području Splitsko-dalmatinske županije je bilo 503 bolesnika s novodijagnosticiranim karcinomom štitnjače (401 žena i 102 muškarca). Papilarni karcinom dijagnosticiran je u 86,1%, folikularni u 9,5%, medularni u 4,2% i anaplastični u 0,2% slučajeva. Dobno standardizirana stopa učestalosti za karcinom štitnjače na 100.000 stanovnika u Hrvatskoj bila je 8,5 (žene 13,3, muškarci 3,5) u 2003. Stopa učestalosti karcinoma štitnjače u Splitsko-dalmatinskoj županiji porasla je s 8,2 (žene 13,5, muškarci 2,7) u 1997. na 11,5 u 2006. godini (žene 15,6, muškarci 7,1). U razdoblju 1997.-2006. godine u Splitsko-dalmatinskoj županiji i cijeloj Hrvatskoj uočava se povećana učestalost karcinoma štitnjače. Karcinom štitnjače češći je u žena nego u muškaraca.

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ANXIETY IN THYROID CANCER PATIENTS

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Anxiety in thyroid cancer (TC) patients can be present although differentiated TC is a disease with a generally very good prognosis. Therapy for TC is associated with multimodal interventions and lifelong thyroid hormone replacement therapy. The aim of the study was

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ANKSIOZNOST U BOLESNIKA S RAKOM ŠTITNJAČE

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Anksioznost u bolesnika s rakom štitnjače može biti prisutna iako je diferencirani rak štitnjače bolest s dobrom prognozom. Terapija raka štitnjače je povezana s multimodalnim intervencijama i doživotnim uzimanjem

to assess anxiety level in different groups of TC patients. The study included 100 patients with TC (83 female and 17 male; 90 patients on regular follow up visits and 10 recently diagnosed with TC who were recieving ablative therapy with radioactive iodine (RI); 95% of patients had papillary histologic subtype of TC). Anxiety level was assessed using Beck anxiety inventory. Pearson multiple comparison testing, binar logistic regression and t-test were used in statistical analysis. Histologic subtype of cancer, type and date of surgery, primary tumor extent, lymph node involvement, distant metastases, number and total dose of RI therapy were evaluated. Investigated sociodemographic factors were marital status, parenthood, education and employment status. Minimal anxiety level was present in 35, mild in 30, moderate in 25 and severe in 10 patients. The mean anxiety level of all patients was 14.65 (range of mild anxiety). A higher level of anxiety was recorded in patients on control visits than in those receiving ablative therapy with RI, both in the range of mild anxiety. Male patients had a significantly lower mean anxiety level than female patients ($p=0.007$). There was no statistically significant correlation between anxiety level and disease characteristics, received treatment and sociodemographic factors. Accordingly, the diagnosis, surgery and RI treatment of differentiated TC have minor impact on anxiety level in these patients. Very favorable prognosis of TC has a major influence on the patient anxiety status.

hormonske nadomjesne terapije. Cilj rada bio je odrediti razinu anksioznosti u različitih skupina bolesnika s diferenciranim rakom štitnjače. U istraživanje je uključeno 100 bolesnika s diferenciranim rakom štitnjače (83 žena i 17 muškaraca; 90 bolesnika na redovnim kontrolnim pregledima i 10 novodijagnosticiranih bolesnika koji su primili ablativnu terapiju radioaktivnim jodom; 95% bolesnika je imalo papilarni tip raka štitnjače). Razina anksioznosti je određena pomoću Beckove ljestvice anksioznosti. U statističkoj analizi primijenjeni su Pearsonov test višestruke usporedbe, binarna logistička regresija i t-test. Procjena je obuhvatila histološki tip raka, vrstu i vrijeme operacije, veličinu tumora, zahvaćenost limfnih čvorova, prisutnost udaljenih metastaza, broj i ukupnu dozu primljene terapije radioaktivnim jodom. Istraživani sociodemografski čimbenici bili su bračno stanje, roditeljstvo, stupanj školovanosti te zaposlenost. Najniža razina anksioznosti utvrđena je u 35, blaga u 30, umjerena u 25, a visoka u 10 bolesnika. Srednja razina anksioznosti iznosila je 14,65 (razina blage anksioznosti). Bolesnici na kontrolnim pregledima imali su višu razinu anksioznosti od bolesnika koji su primali ablativnu terapiju radioaktivnim jodom (obje razine bile su u području blage anksioznosti). Muški bolesnici su imali značajno nižu razinu anksioznosti od žena ($p=0,007$). Nije nađena statistički značajna korelacija između razine anksioznosti i osobina bolesti, primljene terapije i sociodemografskih čimbenika. U zaključku, dijagnoza, kirurški zahvat i liječenje radioaktivnim jodom imaju mali utjecaj na razinu anksioznosti u bolesnika s diferenciranim rakom štitnjače. Vrlo povoljna prognoza diferenciranog raka štitnjače ima najznačajniji utjecaj na razinu anksioznosti.

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MEDULLARY THYROID CARCINOMA – SURGICAL TREATMENT

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Medullary thyroid carcinoma (MTC) is a tumor of specific characteristics that undoubtely differentiate this tumor from other thyroid malignancies. Patients with sporadic or hereditary form of MTC differ in clinical presentation, recurrence of the disease and outcome. The aim of the study was to establish surgical charac-

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MEDULARNI KARCINOM ŠTITNJAČE – KIRURŠKO LIJEČENJE

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Medularni karcinom štitnjače (MKŠ) je tumor specifičnih karakteristika kojima se nedvojbeno razlikuje od ostalih malignih tumora štitnjače. Bolesnici sa sporadičnim ili nasljednim oblikom MKŠ razlikuju se u kliničkoj prezentaciji, recidiviranju te ishodu bolesti. Cilj studije bio je utvrditi kirurške karakteristike MKŠ, kao i kliničke

teristics of MTC as well as clinical factors that infulence surgical treatment. The study group consisted of patients with MTC managed at the Center of Endocrine Surgery between 1987 and 1999. During this period operation was performed in 68 patients with MTC (47 female and 21 male), including 58 patients with sporadic and 10 patients with hereditary form of MTC, mean age 47 years. The mean size of tumors was 80.5 cm3; 72% of patients had tumors greater than 4 cm in diameter or with extrathyroid spread. The majority of patients were in stage II and III of the disease. Primary operation (at least total thyroidectomy) was performed in 84% of patients; 3% had temporary postoperative nerve palsy and 10% had temporary hypoparathyroidism. The overall survival was 46.8+/-9.9% at 9 years and 63.6+/-7.2% at 5 years. Spearman's coefficient (R 0.7048) of vital status and postoperative calcitonin values showed high correlation. The treatment of choice is at least total thyroidectomy and central lymph node dissection if enlarged lymph nodes are found, with precise operative technique. Worse prognosis is in correlation with high postoperative calcitonin values.

čimbenike koji utječu na kirurško liječenje. Skupinu ispitanika činili su bolesnici oboljeli od MKŠ liječeni u Centru za endokrinu kirurgiju između 1987. i 1999. Tijekom navedenog razdoblja operirano je 68 bolesnika s MKŠ (47 žena i 21 muškaraca), tj. 58 bolesnika sa sporadičnim i 10 s nasljednim oblikom MKŠ. Srednja dob bila je 47 godina. Srednja veličina tumora bila je 80,5 cm^3, u 72% bolesnika promjer tumora bio je veći od 4 cm ili je nađeno ekstratiroidno širenje. Većina bolesnika bila je u II. i III. stadiju bolesti. Primarna operacija (najmanje totalna tireoidektomija) učinjena je u 84% bolesnika, 3% imalo je prolaznu postoperativnu paralizu živca, a 10% prolazni hipoparatireoidizam. Sveukupno preživljenje bilo je 46,8±9,9% nakon 9 godina i 63,6±7,2% nakon 5 godina. Spearmanov koeficijent (R 0,7048) vitalnog statusa i vrijednosti postoperativnog kalcitonina bili su u visokoj korelaciji. Terapija izbora je najmanje totalna tireoidektomija i, u slučaju njihovog povećanja, centralna disekcija limfnih čvorova, uz preciznu operativnu tehniku. Loša prognoza je u korelaciji s visokim postoperativnim vrijednostima kalcitonina.

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RET MUTATION, CYCLIN D1 AND P27 IN PAPILLARY MICROCARCINOMA OF THE THYROID

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The term microcarcinoma should be used for a papillary carcinoma which measures 1 cm or less in diameter and which is usually found incidentally. According to some authors it has been reported in up to 24% of surgical thyroidectomies performed for disorders unrelated to papillary carcinoma. In children these tumors behave more aggressively, and most of them are associated with external or therapeutic irradiation and presence of RET mutation. Located near the thyroid capsule, the tumor is often sclerosing. The smaller ones frequently show follicular pattern and the bigger ones papillary pattern. The prognosis is excellent but sometimes these tumors present with large cervical lymph node metastasis suggesting that these rare lesions have distinct immunohistochemical features including cyclin D1 and p27. The

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RET MUTACIJA, CIKLIN D1 I P27 U PAPILARNOM MIKROKARCINOMU ŠTITNJAČE

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Termin mikrokarcinom bi se trebao rabiti za one papilarne karcinome koji imaju u promjeru 1 cm ili manje, a uglavnom se nađu slučajno. Prema nekim autorima u 24% tireidektomija učinjenih iz nekog drugog razloga nađe se i ovaj karcinom. Kod djece se ovi karcinomi ponašaju agresivnije, mnogi su povezani s vanjskim ili terapijskim zračenjem te iskazuju prisutnost RET mutacije. Smješteni su u blizini čahure štitnjače, često sklerozirani. Manji uglavnom pokazuju folikularni tip rasta, dok su oni veći više papilarni. Prognoza je odlična, no ponekad se javljaju s opsežnim metastazama u limfnim čvorovima vrata, sugerirajući da ove rijetke lezije posjeduju znakovit imunološki profil koji uključije izražajnost ciklina D1 i p27. Ciklin D1 gen je pozitivni regulator staničnog ciklusa smješten na kromosomu 11q23 koji inaktivira Rb protein i tako dozvoljava stanici da prijeđe iz faze G1 u fazu S. Tumor supresorski gen p27

cyclin D1 gene is a positive regulator of cell cycle located on chromosome 11q23 that inactivates Rb protein and allows for cell cycle progression from G1 to S phase. Tumor suppressor gene p27 located on chromosome 12p13 inhibits Rb protein inactivation and prevents G1 to S phase transition. We analyzed papillary thyroid microcarcinomas in order to determine prognostic implications of RET mutation and cell cycle regulators cyclin D1 and p27 investigating their relation to metastatic spread. Tissues were retrieved from surgical pathology files of the Split University Hospital. Immunohistochemical staining was performed on formalin-fixed paraffin-embedded sections using monoclonal antibody against RET, cyclin D1 and p27 purchased from Novocastra, Vision Bio System, Newcastle, UK. We used immunohistochemical analysis to investigate their expression in 70 papillary microcarcinomas. Results of the univariate analysis showed the overexpression of cyclin D1 (p=0.014) and underexpression of p27 (p=0.093) to predict lymph node metastases in papillary microcarcinomas demonstrating their expression in inverse proportion. High risk microcarcinomas were cyclin D1 expressors and p27 nonexpressors, while low risk carcinomas were cyclin D1 nonexpressors and p27 expressors. RET expression (p=0.459) was not proven to have any statistically significant predictive value. Immunohistochemical analysis of cyclin D1 and p27 expression proved to be a valuable test to identify papillary microcarcinomas with metastatic potential. These data might contribute new treatment protocols and facilitate patient follow up.

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MEN 2B SYNDROME IN THREE GENERATIONS OF ONE FAMILY – FROM PALLIATION TO PREVENTION

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In 20%-25% of patients, medullary thyroid carcinoma (MTC) is part of the inherited syndromes. Hereditary forms of MTC are associated with the germline mutations in the ret protooncogene, and in 1993, genetic testing for inherited MTC was introduced. MEN 2B patients often have mutations connected with poor clinical outcome. The individuals from three generations of a MEN 2B family were followed-up for a total of 27 years.

smješten na kromosomu 12p13 spriječava inaktivaciju Rb proteina i tako spriječava prijelaz iz faze G1 u fazu S staničnog ciklusa. Analizirali smo papilarne mikrokarcinome štitnjače želeći utvrditi prognostički utjecaj RET mutacije i regulatora staničnog ciklusa ciklina D1 i p27 istražujući njihov odnos prema metastaziranju. Tumorsko tkivo smo uzeli iz arhive patologije Kliničke bolnice Split. Imunohistokemijska bojanja smo napravili na tkivu izrezanom iz parafinskih kocaka, koje je prethodno fiksirano u formalinu, a rabili smo antitijela za RET, ciklin D1 i p27 proizvođača Novokastra, Vision Bio System, Newcastle, UK. Njihovu smo imunohistokemijsku izražajnost analizirali na 70 mikrokarcinoma. Rezultati univarijantne analize pokazuju da povećana izražajnost ciklina D1 (p=0,014) i smanjena izražajnost p27 (p=0,093) predviđaju metastaze u limfnim čvorovima i to po tipu obrnute proporcije. Visokorizični karcinomi su izražavali ciklin D1, a nisu izražavali p27. Niskorizični karcinomi nisu izražavali ciklin D1, ali su izražavali p27. Za izražajnost RET mutacije (p=0,459) nismo dokazali da ima prediktivnu vrijednost. Imunohistokemijska analiza ciklina D1 i p27 je vrijedan test za otkrivanje papilarnih mikrokarcinoma s metastatskim potencijalom. Ovi podatci mogu značajno doprinijeti novim terapijskim protokolima i olakšati praćenje bolesnika.

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SINDROM MEN 2B U TRI GENERACIJE JEDNE OBITELJI – OD PALIJACIJE DO PREVENCIJE

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Medularni karcinom štitnjače (MKŠ) se u oko 20%-25% bolesnika pojavljuje nasljedno u obliku različitih sindroma. U nasljednih oblika MKŠ utvrđene su različite nasljedne genetske mutacije protoonkogena *ret*, te se od 1993. uvode metode njihove molekularne analize. U bolesnika sa sindromom MEN 2B često se pojavljuju mutacije povezane s najlošijim ishodom bolesti. Osobe s navedenim sindromom praćene su tijekom 27 godina kroz tri generacije jedne obitelji. Kad je djed imao 32

At the age of 32 (1980), grandfather was diagnosed with palpable thyroid nodules and underwent surgery. Thyroid cancer with regional lymph node metastases was diagnosed by histopathology. Postoperative irradiation of the neck and then ^{131}I ablation of remnant thyroid tissue were performed. Multiple operations were performed due to recurrent lymph node metastases. Hematogenous dissemination to the lungs and bones was detected, and the patient received monochemotherapy with doxorubicin in 1984. He died of the advanced disease in 1985. When father was 13 years old (1992), he was operated for a palpable nodule in the neck. MTC with multiple regional lymph node metastases was diagnosed on histopathology. Genetic testing of the ret protooncogene (performed for the first time in Croatia in 1993) revealed MEN 2B syndrome with mutation in codon 918. During the follow up period, new, previously unavailable diagnostic methods were used: ^{111}In-octreotide, ^{131}I-MIBG, and ^{99m}Tc-anti-CEA-antibodies scintigraphies, CT, MRI, tumor markers calcitonin and CEA, and VMA in urine. Over years, recurrent neck metastases, mediastinal lymph node metastases, and unresectable liver metastases were diagnosed, and the patient was treated by surgery, radiotherapy, chemotherapy, long lasting analogue of octreotide, and ^{131}I-MIBG. In 2006, pheochromocytoma of the suprarenal gland was diagnosed, and the patient underwent surgery. At subsequent follow up visits, there was no sign of progression of metastatic lesions in the neck and liver. In son, born in 2006, genetic testing revealed mutation in codon 918, identical with that found in his father. Due to the high risk of developing early and aggressive form of the disease, he has been scheduled for prophylactic thyroidectomy. Nowadays, thanks to the progress of molecular biology, prevention of MTC is possible in gene carriers of specific hereditary mutations, with timely prophylactic thyroidectomy. The three generations of this family have passed a long way from palliative treatment of advanced disease to the prevention of cancer.

godine (1980.) operiran je zbog palpabilnih masa u štitnjači. Dobiven je patohistološki nalaz raka štitnjače s metastazama u regionalnim limfnim čvorovima. Provedeno je poslijeoperacijsko zračenje vrata, a potom je primio terapijsku dozu ^{131}I. Zbog recidivirajućih metastaza u limfnim čvorovima vrata operiran je u više navrata. Zbog hematogene diseminacije bolesti u pluća i kosti bolesnik je 1984. primao kemoterapiju doksorubicinom. Godine 1985. preminuo je od posljedica osnovne bolesti. Otac je u svojoj 13. godini (1992.) operiran zbog palpabilnog čvora na vratu. Patohistološki je utvrđen MKŠ s multiplim metastazama u regionalnim limfnim čvorovima. Molekularnom analizom protoonkogena ret, koja se u Hrvatskoj provodi od 1993., dijagnosticiran je sindrom MEN 2B s mutacijom na kodonu 918. Kod praćenja bolesnika rabile su se ranije nedostupne dijagnostičke metode: scintigrafije ^{111}In-oktreotidom, ^{131}I-MIBG-om, ^{99m}Tc-anti-CEA-protutijelima, CT, MR, tumorski biljezi kalcitonin i CEA, VMA u mokraći. Tijekom godina utvrđene su recidivirajuće metastaze na vratu, metastaze u limfnim čvorovima medijastinuma, neresektabilne metastaze u jetri, te je zbog navedenog liječen operacijski, radioterapijom, polikemoterapijom, dugodjelujućim „hladnim“ analogom somatostatina, te ^{131}I-MIBG-om. Godine 2006. dijagnosticiran mu je feokromocitom nadbubrežne žlijezde, zbog čega je operiran. Naknadnim praćenjima bilježi se stacionarno stanje metastatskih promjena u limfnim čvorovima vrata i jetri. U sina rođenog 2006. godine provedena genetska analiza pokazuje mutaciju istovrsnu mutaciji dokazanoj u dječakova oca. S obzirom na to da je riječ o mutaciji s visokim rizikom razvoja agresivnog tipa MKŠ, u sina se planira učiniti profilaktičnu tireoidektomiju. Danas je, zahvaljujući napretku molekularne biologije, moguće prevenirati razvoj MKŠ u nosilaca mutacije pravodobnom profilaktičnom tireoidektomijom, te je kroz tri generacije ove obitelji prijeđen složen put od palijacije diseminirane bolesti do prevencije razvoja raka.

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CLINICAL FEATURES OF PAPILLARY THYROID CANCER IN PATIENTS WITH FAMILIAL OCCURRENCE OF THYROID CANCER

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Familial form of medullary thyroid cancer is a well known clinical entity. However, a familial occurrence of papillary thyroid cancer (PTC) has also been noticed and seems to have more aggressive behavior than the sporadic form. To establish whether the presence of thyroid cancer (TC) in patient's relatives has an impact on clinical features of PTC. From 1962 to 2007 ; 330 patients with PTC, all confirmed by pathohistology, were identified in the registry of Department of oncology and nuclear medicine. Of these 330 patients, 19 patients with confirmed familial occurrence of TC (21% men, 79% women; age median 60 yrs; follow-up 1-70 months, median 40,5 months) and 311 (17% men, 83% women; age median 43,5 yrs; follow-up 1-416 months, median 20 months) with confirmed abscence of familial ocuurrence were selected in the study. Tumor size, multifocality and multilobularity, local invasiveness, occurence of metastases to regional lymph nodes and distant metastases at the moment of diagnosis were analized. In group of patients with familial occurrence tumor size median was 12.5 mm (2-80), seven patients (37%) had papillary microcarcinoma, multicentricity was found in five (26%) while capsule infiltration was present in three (15.8%) patients. Metastases to regional lymph nodes were present in five patients (26%), while no distant metastases were noticed. In group of patients without familial occurrence tumor size median was 11 mm, 141 patients (45.3%) had papillary microcarcinoma, multicentricity was found in 95 (30.5%) while capsule infiltration was present in 38 (12.2%) patients. Metastases to regional lymph nodes were present in 80 patients (25.7%), while 9 (2.9%) cases of distant metastases were noticed. We haven't noticed a significant difference in clinical features of PTC between patients with and without familial occurrence of thyroid cancer.

30.

KLINIČKE ZNAČAJKE PAPILARNOG KARCINOMA ŠTITNJAČE U BOLESNIKA S POJAVOM RAKA ŠTITNJAČE U OBITELJI

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Obiteljski oblik medularnog karcinoma štitnjače je dobro poznat klinički entitet. Pojavnost papilarnog karcinoma štitnjače u obitelji je također zabilježena i predmet je znanstvenog istraživanja, a prema do sada objavljenim radovima obiteljski tip pokazuje agresivnije ponašanje od sporadičnog oblika. Cilj rada je utvrditi utječe li pozitivna obiteljska anamneza raka štitnjače na klinička obilježja papilarnog karcinoma štitnjače. U razdoblju od 1962 do 2007 godine u Klinici za onkologiju i nuklearnu medicinu evidentirano je 330 bolesnika kod kojih je postavljena patohistološka dijagnoza papilarnog karcinoma štitnjače. U istraživanje je uključeno 19 bolesnika s potvrđenom obiteljskom anamnezom raka štitnjače (21%) muškarci; 79% žene, medijan 60 god, raspon praćenja od 1-70 mjeseci (medijan 40,5 mjeseci) te njih 311 (17%) muškarci, 83% žene, medijan 43,5 god., raspon praćenja od 1-416 mjeseci (medijan 20 mjeseci) kod kojih anamnestički nije utvrđeno postojanje raka štitnjače u obitelji. Analizirane su veličina tumora, multifokalnost, bilateralnost, lokalna invazivnost tumora, zahvaćenost limfnih čvorova te prisutnost udaljenih metastaza u trenutku postavljanja dijagnoze. U skupini papilarnih karcinoma povezanih s obiteljskom anamnezom medijan veličine tumora iznosi 12,5 mm (2 – 80 mm). U sedmero bolesnika (37%) utvrđen je papilarni mikrokarcinom. Multicentričnost je pronađena u petoro (26%), dok je tumor probio kapsulu štitnjače bio prisutan u troje (15,8%) bolesnika. Limfni čvorovi bili su zahvaćeni u 5 slučajeva (26%). Udaljene metastaze nisu bile prisutne u ovoj skupini bolesnika. U bolesnika s negativnom anamnezom raka štitnjače u obitelji medijan veličine tumora iznosi 11 mm. Papilarni mikrokarcinom je utvrđen u 141 bolesnika (45,3%). Multicentričnost je pronađena u 95 (30.5%), dok je proboj kapsule štitnjače zabilježen u 38 (12.2%) bolesnika. Limfni čvorovi su u ovih bolesnika bili zahvaćeni u 80 (25,7%) slučajeva. Udaljene metastaze su bile prisutne u 9 slučajeva (2,9%). U našem istraživanju nismo utvrdili značajnu razliku u kliničkim obilježjima papilarnog karcinoma između skupina s pozitivnom i negativnom obiteljskom anamnezom raka štitnjače.

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RISK FACTORS FOR OSTEOPOROSIS IN FEMALE PATIENTS WITH DIFFERENTIATED THYROID CANCER

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Although some authors suggest that a suppressive dose of L-thyroxine may play a role in reducing bone mass in patients with differentiated thyroid cancer (DTC), awareness of the multietiologic origin of osteoporosis should be essential in interpretation. The aim of this study was to evaluate the contribution of additional risk factors for osteoporosis development. This study included 57 postmenopausal female patients aged 50-81 (median 64) years with DTC treated at our institution and referred for DEXA due to suspected osteoporosis. TSH values detected during suppressive therapy were less than 0.1 mU/L. A subject was considered to have osteoporosis if the lumbar or hip T-score was =-2.5. According to T-score values, patients were divided into two groups: 18 patients with and 39 patients without osteoporosis. Bone mineral density measurement was performed by a dual-energy x-ray absorptiometry (DEXA, Hologic QDR-1000) densitometer, which uses an x-ray tube as the radiation source. Measurements were taken at lumbar spine (L1-L4) and left hip. According to T-score values, of 57 study patients 18 (31.6%) had osteoporosis, 16 (89%) of them at lumbar region, one at femoral neck and lumbar spine and one at all three regions (femoral neck, total hip and lumbar). Seven (39%) patients with osteoporosis were aged 65 or older (*vs.* 28%), with a longer duration of postmenopause (more than 20 years in 33% *vs.* 23%) and 44% had low or normal BMI (=26) compared to 28% of patients without osteoporosis. The duration of L-thyroxin therapy was not longer in patients with osteoporosis (median 3 years compared to 4.5 yrs). The results of our study indicated that older age, longer duration of postmenopause and lower BMI influenced the development of osteoporosis in patients with DTC using suppressive doses of L-thyroxine treatment, and should be reviewed in the evaluation of bone density.

31.

RIZIČNI ČIMBENICI ZA OSTEOPOROZU U BOLESNICA S DIFERENCIRANIM KARCINOMOM ŠTITNJAČE

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Iako neki autori ukazuju da supresivna doza L-tiroksina može imati ulogu u smanjenju koštane mase u bolesnica s diferenciranim karcinomom štitnjače (DKŠ), svijest o postojanju višebrojnih čimbenika u nastanku osteoporoze trebala bi biti linija vodilja u interpretaciji nalaza mineralne gustoće kosti. Cilj ove studije bila je procjena doprinosa dodatnih čimbenika rizika za razvoj osteoporoze. U studiju je bilo uključeno 57 postmenopauzalnih bolesnica u dobi od 50-81 godine (medijan 64 godine) s DKŠ koje su liječene u našoj Klinici te su upućene na denzitometriju (DEXA) zbog sumnje na osteoporozu. Vrijednosti TSH registrirane tijekom supresije bile su niže od 0.1 mU/L. Dijagnoza osteoporoze postavljena je ako je u području lumbalne kralježnice ili kuka T vrijednost = -2,5. S obzirom na T vrijednosti bolesnice su podijeljene u dvije skupine: 18 u kojih je utvrđena osteoporoza i 39 bolesnica bez osteoporoze. Mjerenje mineralne gustoće kosti (BMD) izvedeno je prema načelu dvoenergetske apsorpciometrije x-zraka (DEXA) Hologic QDR-1000 denzitometrom. Učinjena su mjerenja u području lumbalne kralježnice (L1-L4) i lijevog kuka. Uzimajući u obzir T vrijednost, 18 od 57 ispitanih bolesnica (31,6%) imalo je osteoporozu. U njih 16 (89%) osteoporoza je utvrđena u lumbalnoj regiji, kod jedne bolesnice u području vrata bedrene kosti i L-kralježnice, a u jedne u sve tri navedene regije (vrata bedrene kosti, kuka i lumbalnoj regiji). Usporedbom dviju skupina bolesnica, onih s i bez osteoporoze, utvrđeno je da je u prvoj skupini 7 (39%) bilo u dobi od 65 godina ili više (u usporedbi s 28% bolesnica bez osteoporoze), s trajanjem postmenopauze >20 godina u 33% bolesnica u prvoj skupini (23% u drugoj), dok ih je 44% imalo niži ili normalan indeks tjelesne mase (=26), a prema 28% bolesnica bez osteoporoze. Trajanje terapije L-tiroksinom u bolesnica koje su imale osteoporozu nije bilo dulje u usporedbi s drugom skupinom bolesnica (medijan 3 godine prema 4,5 godine). Rezultati naše studije ukazuju na to da starija dob, duljina trajanja postmenopauze i niža vrijednost indeksa tjelesne mase utje-

ču na razvoj osteoporoze u bolesnica s DKŠ koje uzimaju supresivnu terapiju L-tiroksinom te navedeni čimbenici trebaju biti uključeni u procjenu koštane gustoće u takvih bolesnica.

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INCREASING INCIDENCE OF THYROID CARCINOMA IN CROATIA – CHERNOBYL YES OR NO?

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Ionizing irradiation is the only one epidemiological and experimentally proved initial and favoring factor of thyroid carcinogenesis. Our aim is to prove or reject Chernobyl disaster as one of the causes of the increasing incidence of thyroid cancer (TC) in Croatia. We ground our project on the methods and data of hydrometeorology, molecular biology, epidemiology, histopathology, and clinics. If a share of "Chernobyl TC" in our population is demonstrated, it will be possible to anticipate and predict the forthcoming increase in TC incidence, especially in those born 1966-1986 that were most sensitive to ionizing radioactivity at the time of nuclear accident. The Institute of Medical Research in Zagreb has concluded that there is no dose threshold below which no harmful effects could be expected to appear. GIS software enables areal interpolation of data, evaluation of the quantity of precipitation and concentration of radioisotopes in precipitation, and their soil deposition, for Croatia as a whole. There is positive correlation between radioiodine deposition at the time of Chernobyl disaster and the increase in the number of new cases of TC. Epigenetic changes occur early in the process of tumorigenesis of papillary TC, since the entry of these genes is disordered not only in tumor tissue but also in normal tissue. Autoimmune thyroiditis, benign nodules and adenomas are often found in tumor surrounding tissue of "Chernobyl TC", which was a statistically significant finding in our material. The sensitivity of thyroid gland to ionizing radiation declines with age. In the group born 1966-1986, after the period of latency, the incidence of TC significantly rises compared to other age groups, especially control group of patients with all tumor seats. Geographic distribution of radioiodine deposition, pre- and post-Chernobyl pathologic findings of TC surround-

32.

PORAST INCIDENCIJE KARCINOMA ŠTITNJAČE U REPUBLICI HRVATSKOJ – ČERNOBIL DA ILI NE?

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Ionizirajuće zračenje jedini je eksperimentalno i epidemiološki dokazani čimbenik koji započinje i potiče tireoidnu kancerogenezu. Naš je cilj dokazati ili isključiti černobilsku katastrofu kao jedan od uzroka porasta incidencije karcinoma štitne žlijezde (KŠŽ) u Republici Hrvatskoj (RH). Projekt temeljimo na podacima i metodama hidrometeorologije, molekularne biologije, epidemiologije, patohistologije i klinike. Dokaže li se udio „černobilskih" KŠŽ u našoj populaciji, moguće je anticipirati i projicirati porast incidencije KŠŽ u životnom vijeku, poglavito u onih rođenih 1966.-1986., najosjetljivijih na ionizirajuće zračenje u doba nuklearne katastrofe. Institut za medicinska istraživanja u Zagrebu zaključuje kako ne postoji prag doze ispod kojeg se ne mogu pojaviti kasniji štetni učinci. Program GIS omogućuje prostornu interpolaciju podataka, procjenu količine oborina, koncentracije radionuklida u oborinama i njihove depozicije na tlu za cijelo područje RH. Postoji pozitivna korelacija između depozicije radio-joda u vrijeme černobilske katastrofe i porasta broja novootkrivenih KŠŽ. Epigenetske promjene događaju se rano u procesu tumorigeneze papilarnih KŠŽ, jer je upis ovih gena poremećen ne samo u tkivu tumora, nego i u netumorskom tkivu. U „černobilskim" KŠŽ čest je nalaz autoimunog tireoiditisa, benignih nodula i adenoma u okolini tumora, što smo našli statistički značajnim i u našem materijalu. Osjetljivost štitne žlijezde na ionizirajuće zračenje opada s dobi. U onih rođenih 1966.-1986. učestalost KŠŽ nakon vremena latencije značajno raste spram ostalih dobnih skupina, pogotovo spram kontrolne skupine svih sijela tumora. Geografska distribucija depozicije radio-joda, prije- i poslije-černobilski histološki nalazi parenhima uokolo KŠŽ, te značajan porast KŠŽ u rizičnim skupinama upućuju na černobilsku katastrofu kao mogući razlog porasta incidencije KŠŽ u RH.

ing parenchyma, and a significant increase in the incidence of TC in the risk groups indicate that Chernobyl accident could be a potential cause of the increased TC incidence in Croatia.

33.

INSULAR CARCINOMA – A RARE CASE OF POORLY DIFFERENTIATED THYROID CARCINOMA

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Insular carcinoma of the thyroid is a rare type of thyroid malignancy that occurs sporadically in 4%-7% of all malignant diseases of the region. This tumor occupies an intermediate position between well-differentiated and undifferentiated or anaplastic carcinomas in terms of behavior and morphology. Herein we report a case of insular carcinoma of the thyroid for the first time described at our Department of Cytology. A 71-year-old female patient presented to our hospital with a grossly visible and palpable mass of the neck accompained by inspiratory stridor. The specimen obtained with US-guided fine needle aspiration was stained with MGG. Surgical material was paraffin embedded and H&E stained. The sections were subsequently immunohistochemically analyzed. Cytologic examination established the diagnosis of poorly differentiated carcinoma. Histopathological analysis showed nests of atypical monomorphic tumor cells, with hyperchromatic nuclei and scant cytoplasm forming a characteristic insular growth pattern. Immunohistochemistry confirmed intensive reaction to thyroglobulin and focal intensity for TTF-1. Staining reaction to cytokeratin was extremely scant and of low intensity. Uniformly negative immunohistochemical reaction in sections stained by calcitonin, CD34, FVII and LCA eventually confirmed the diagnosis of insular carcinoma. Insular carcinoma is a very rare and relatively new histologic type of carcinoma, therefore difficult to make a precise cytologic diagnosis. This is probably due to the finding of undifferentiated cells that may mislead the interpretation and diagnosis of anaplastic carcinoma, especially when a larger number of giant cells are present. With precisely defined criteria, cytologic findings should point to the possibility of insular carcinoma to the pathologist.

33.

INZULARNI KARCINOM - RIJETKI SLABO DIFERENCIRANI KARCINOM ŠTITNJAČE

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Inzularni karcinom štitnjače je rijedak tip malignog tumora koji se pojavljuje sporadično u 4%-7% malignih bolesti ove regije. Ovaj tip tumora svojim biološkim ponašanjem i morfologijom zauzima intermedijarno mjesto između dobro i slabo diferenciranog ili anaplastičnog karcinoma. Prikazujemo slučaj inzularnog karcinoma štitnjače prvi put opisanog u našoj Službi za citologiju. Žena u dobi od 71 godine došla je u našu bolnicu s velikom vidljivom palpabilnom masom na vratu praćenom inspiracijskom stridorom. Uzorak dobiven citološkom punkcijom pod kontrolom UZV obojen je prema May-Grunwald-Giemsi. Kirurški materijal je uklopljen u parafin i obojen hemalaun eozinom. Dodatni rezovi su zatim imunohistokemijski analizirani. Citološkom analizom je postavljena dijagnoza slabo diferenciranog karcinoma. Patohistološkom analizom su nađena gnijezda monomorfnih atipičnih tumorskih stanica s hiperkromatskim jezgrama i oskudnim citoplazmama koje su tvorile znakovit inzularni način rasta. Imunohistokemijska analiza je potvrdila intenzivnu pozitivnu reakciju na tireoglobulin i žarišnu reakciju na TTF-1. Reakcija na citokeratin je bila krajnje oskudna i slabog intenziteta. Ujednačeno negativna reakcija na kalcitonin, CD34, FVII i LCA je konačno potvrdila dijagnozu inzularnog karcinoma. Inzularni karcinom je vrlo rijedak i relativno nov histološki tip karcinoma, pa je prema tome teško postaviti preciznu citološku dijagnozu. Uzrok je možda i u čestoj prisutnosti nediferenciranih stanica koje mogu povesti interpretaciju u krivom smjeru, te dovesti do postavljanja dijagnoze anaplastičnog karcinoma, poglavito kada je prisutan veći broj orijaških stanica. Uz precizno definirane kriterije citološki nalaz bi mogao patologu ukazivati na mogućnost da se radi o inzularnom karcinomu.

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EVALUATION OF MALIGNANCY RISK IN BENIGN THYROID NODULES AFTER PERCUTANEOUS ETHANOL

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Minimally invasive methods are widely used in the treatment of patients with benign thyroid nodules, especially cystic ones. The most common minimally invasive method is percutaneous ethanol injection (PEI). This type of treatment is associated with a very low percentage of complications and with good results (50% shrinkage of nodule volume in more than 90% of patients). Despite the fact that the method has been used in clinical practice for 25 years now, there is still some concern that it may cause malignancy. The aim of our study was to evaluate the malignancy risk in thyroid nodules treated by PEI. A group of 25 patients with euthyroid nodular goiter were studied. The size of the nodules was more than 3 cm in one of the dimensions. Before treatment, fine needle aspiration biopsy (FNA) was performed to prove the benign nature of the nodules. PEI was performed under sonography control (5-10 times in each patient). The mean volume of instilled 95% ethanol was 30% of the nodule volume. Second FNA was performed after a period of 1-5 years of PEI treatment in 21 patients. Four patients where PEI failed to prove effective underwent operative therapy followed by histology. In our group of patients there was no case of malignancy. Second FNA showed the same diagnosis as the first one ("colloid nodule") in 21 of 21 patients. Histologic examination revealed colloid goiter with a diffuse sclerotic process and without any features of malignancy in four patients.

34.

EVALUACIJA RIZIKA MALIGNITETA U BENIGNIM ČVOROVIMA ŠTITNJAČE NAKON PERKUTANE INJEKCIJE ETANOLA

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Minimalno invazivne metode se široko primjenjuju u liječenju bolesnika s benignim čvorovima štitnjače, osobito cističnim. Najčešće primjenjivana metoda je perkutana injekcija etanola (PIE). Ovaj oblik terapije uzrokuje vrlo mali postotak komplikacija i dobre rezultate (50%-tno smanjenje volumena čvora u više od 90% bolesnika). Unatoč činjenici da se navedena metoda primjenjuje u kliničkoj praksi tijekom 25 godina, još uvijek postoji sumnja na mogućnost uzrokovanja maligniteta. Cilj studije bio je procijeniti rizik maligniteta u bolesnika s čvorovima štitnjače koji su liječeni pomoću PIE. Istraživanje je uključivalo 25 bolesnika s eutiroidnom nodularnom gušom. Veličina čvorova bila je veća od 3 cm u jednoj od dimenzija. Prije liječenja učinjena je citološka punkcija radi utvrđivanja benigne naravi čvorova. PIE je učinjena pod kontrolom ultrazvuka (5-10 puta u svakog bolesnika). Srednji volumen injiciranog 95%-tnog etanola iznosio je 30% volumena čvora. Druga citološka punkcija učinjena je nakon razdoblja od 1-5 godina od terapije PIE u 21 bolesnika. U 4 bolesnika u kojih PIE nije bila učinkovita učinjen je operacijski zahvat i histološka analiza. U skupini naših bolesnika nije utvrđen niti jedan slučaj maligniteta. Ponovljena citološka punkcija potvrdila je prvotnu dijagnozu („koloidni čvor") u 21 od 21 bolesnika. Histološka analiza u 4 bolesnika utvrdila je koloidnu gušu s difuznim sklerotičnim procesom, bez znakova maligniteta.

35

OUR EXPERIENCE IN THE TREATMENT AND FOLLOW-UP OF FAMILY MEMBERS WITH MEN IIA SYNDROME

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After 25-year follow up in family members with MEN IIA syndrome, we evaluated the effects of early treatment. During this period, we identified 25 relatives. Eleven of them underwent total thyroidectomy; in 8 patients histopathologic reports showed medullary thyroid carcinoma, and in 3 young patients (aged 23-27 yrs) C-cell hyperplasia. The mean age of all relatives at the time of operation was 25.1 (16-41 yrs). Three relatives underwent bilateral adrenalectomy for pheochromocytoma. All patients who underwent surgical intervention after 1982 (since when serum calcitonin level has been measured) had high serum calcitonin concentrations, either baseline or provoked (pentagastrin, alcohol). All these patients were positive on RET mutation testing. In 2 relatives moderately elevated calcitonin levels were measured postoperatively, without evidence for metastates. In 4 relatives screening for pheochromocytoma was performed. No parathyroid adenoma/carcinoma was found in any of the family members. RET mutation testing was performed in 15 relatives in 1989 at the Institute of Cancer Research, Sutton Surrey, UK. Since 1994, RET mutation testing in another 15 relatives was performed at Department of Molecular Medicine, Ruđer Bošković Insititute in Zagreb. The youngest relatives (born 1993-2007) underwent RET mutation analysis. Test results were positive in two (born in 1988 and 2000), and baseline calcitonin level was elevated in one of these subjects. The parents have not yet made decision on surgical intervention recommended by us. Our results are mostly consistent with other reports on the treatment and follow up of relatives with MEN IIA syndrome.

35.

NAŠA ISKUSTVA U DUGOVREMENOM PRAĆENJU I LIJEČENJU ČLANOVA PORODICE SA SINDROMOM MEN IIA

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Nakon 25-godišnjeg praćenja članova porodice sa sindromom MEN IIA ispitali smo učinke ranog liječenja bolesti. U tom razdoblju pratimo 25 srodnika od kojih je kod 11 učinjena totalna tireoidektomija: u 8 bolesnika dokazan je medularni karcinom štitnjače, u 3 mlađih C-stanična hiperplazija (23-27 god.). Prosječna dob svih srodnika u vrijeme operacije bila je 25,1 (16-41) godina. U 2 srodnika učinjena je obostrana adrenalektomija zbog feokromocitoma. Svi bolesnici koji su operirani nakon 1982. godine, otkad mjerimo koncentraciju kalcitonina, imali su prijeoperacijski povišene vrijednosti kalcitonina bazalno ili u stimulacijskim testovima (pentagastrin, alkohol). Također je u svih operiranih dokazana genetska opterećenost. Umjereno povišenu vrijednost kalcitonina nakon operacije, a bez uvjerljivih dokaza metastaza pratimo u 2 srodnika. Mogući razvoj feokromocitoma pratimo u 4 srodnika. Niti u jednog od srodnika nije dokazan adenom-karcinom paratireoideja. Ispitivanje nasljednih mutacija proto-onkogena RET u 15 srodnika provedeno je 1989. godine u Insitute of Cancer Research, Sutton Surrey, UK. Jednaka ispitivanja u 15 srodnika sprovode se od 1994. godine u Zavodu za molekularnu medicinu Instituta "R. Bošković" u Zagrebu. U najmlađem naraštaju od 8 srodnika (rođeni 1993.-2007. god.) u 7 srodnika učinjena je RET analiza. Dvoje rođenih 1998. i 2000. godine su dokazano genetski opterećeni, u jednoga je izmjerena i povišena bazalna vrijednost kalcitonina. Roditelji zasad dvoje oko operacijskog liječenja. Naši rezultati su većinom u skladu s brojnim izvješćima o liječenju i praćenju srodnika sa sindromom MEN IIA.

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AXILLARY LYMPH NODE METASTASES IN PAPILLARY THYROID CARCINOMA – A CASE REPORT

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Papillary thyroid carcinoma usually metastasizes to regional lymph nodes and eventually to lungs and bones. We report on a case of axillary lymph node metastases of papillary thyroid carcinoma in a 24-year-old woman. In 1998, the patient noted an increase in size of a nodule in the right supraclavicular region. Ultrasonography and FNA were performed and the patient was diagnosed with metastases of the papillary thyroid carcinoma bilaterally in the neck lymph nodes. Initial surgical treatment included total thyroidectomy with bilateral functional dissection of the neck. Original diagnosis was confirmed by histopathologic findings with detection of primary tumor in the right thyroid lobe. Postoperative diagnostic radioiodine scintigraphy revealed pathological uptake in the right axillary region, in addition to remnant tissue in thyroid bed. Upon ruling out contamination, multiple suspicious lymph nodes were described by ultrasonography of the axilla and confirmed as metastases of papillary carcinoma by subsequent FNA. Then the patient underwent radioiodine therapy and received 9250 MBq (250 mCi) of activity in total, in two applications. In March 1999, diagnostic radioiodine scintigraphy showed pathological uptake in the right axillary region to persist, and the patient underwent surgery with tumorectomy of the axillary metastases. Metastases were confirmed histologically in 3 of 7 lymph nodes examined. Six months after the operation, the patient received another radioiodine therapeutic dose of 3700 MBq (100 mCi) of activity. In June 2000, the patient still had the finding of pathological uptake in the right axillary region on diagnostic radioiodine scintigraphy, therefore reoperation (evacuation) of the right axilla was performed. The patient was free of the disease (US, ^{131}I scintigraphy) at all subsequent follow-up visits (last follow up on July 17, 2007). This case confirms that papillary thyroid cancer can occasionally spread to axillary lymph nodes. Therefore, careful clinical examination of the axilla is recommended in patients with thyroid cancer. Also, thyroid cancer must be considered on differential diagnosis of axillary mass.

36.

AKSILARNE METASTAZE KOD PAPILARNOG KARCINOMA ŠTITNJAČE – PRIKAZ SLUČAJA

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Papilarni karcinom štitnjače većinom metastazira u regionalne limfne čvorove, a ponekad u pluća i kosti. Navodimo slučaj metastaza papilarnog karcinoma štitnjače u aksilarne limfne čvorove u žene stare 24 godine. Bolesnica je 1998. godine primijetila povećani limfni čvor u desnoj supraklavikularnoj regiji. Ultrazvučno te citološkom punkcijom dokazane su metastaze papilarnog karcinoma štitnjače obostrano u limfnim čvorovima vrata. Bolesnici je učinjena totalna tireoidektomija s bilateralnom funkcionalnom disekcijom vrata. Patohistološki nalaz potvrdio je prvotnu dijagnozu, uz utvrđen primarni tumor u desnom režnju štitnjače. Poslijeoperacijskom scintigrafijom ^{131}I prikazalo se patološko nakupljanje radioaktivnog joda u projekciji desne aksile, uz nakupljanje u prednjoj vratnoj regiji, koje je odgovaralo ostatnom tkivu štitnjače. Nakon isključenja kontaminacije, ultrazvukom aksile opisani su multipli suspektni limfni čvorovi kod kojih je naknadno učinjenom citološkom punkcijom potvrđen nalaz metastaza papilarnog karcinoma. U bolesnice je nakon toga u dva navrata provedena radiojodna terapija, kojom je ukupno primila 9250 MBq (250 mCi) aktivnosti ^{131}I. U ožujku 1999. godine u bolesnice je kontrolnom scintigrafijom ^{131}I ponovno zabilježeno patološko nakupljanje radioaktivnog joda u desnoj aksili te je učinjena tumorektomija aksilarnih metastaza koje su potvrđene patohistološki u 3 od 7 pregledanih limfnih čvorova. Šest mjeseci nakon operacije u bolesnice je još jednom provedena radiojodna terapija dozom od 3700 MBq (100 mCi) aktivnosti. U lipnju 2000. godine kontrolnom scintigrafijom ^{131}I ponovno je bilo prisutno patološko nakupljanje radioaktivnog joda u projekciji aksile, pa je u bolesnice ponovno učinjen operacijski zahvat (evakuacija) desne aksile. U bolesnice od tada više nema znakova bolesti (ultrazvučno, scintigrafijom ^{131}I); zadnja redovita kontrolna obrada učinjena je 17. srpnja 2007. Ovaj slučaj pokazuje da se papilarni karcinom štitnjače može ponekad proširiti i u aksilarne limfne čvorove. Stoga se preporuča detaljan pregled aksile u bolesnika s rakom štitnjače. Također treba razmotriti rak štitnjače u diferencijalnoj dijagnostici aksilarne mase.

37.

CLINICAL AND HISTOPATHOLOGIC FEATURES OF THYROID CARCINOMA IN PATIENTS TREATED AT DEPARTMENT OF ONCOLOGY AND NUCLEAR MEDICINE, SESTRE MILOSRDNICE UNIVERSITY HOSPITAL, ZAGREB, CROATIA

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The aim is to present clinical and histologic characteristics of thyroid cancer (TC) patients treated at University Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital, Zagreb, from 1988 till 2007. From 1962 to 2007, a total of 1478 patients with TC were treated at University Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital, Zagreb. A total of 859 patients treated from 1988 till 2007 were included in the study (21% male and 79% female), of which 712 (82.9%) had papillary, 61 (7.1%) follicular, 48 (5.6%) medullary, 10 (1.2%) medullary with differentiated TC component, 13 (1.5%) Hürthle cell and 10 (1.2%) anaplastic TC. Histopathologic findings were obtained from Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, and University Hospital for Tumors, Zagreb. Patients with papillary TC (18% male and 82% female; age median 48 years) had less advanced disease with median tumor size of 12 mm, regional lymph node metastases in 24.2% and distant metastases in 5.2% of cases. Patients with follicular TC (26.2% male and 73.8% female; age median 49 years) had median tumor size of 12 mm, regional lymph nodes metastases in 8.1% and distant metastases in 18% of cases. Patients with medullary TC (44.7% male and 55.3% female; age median 55.5 years) had median tumor size of 22 mm, regional lymph node metastases in 52.1% and distant metastases in 27.1% of cases. The data obtained in our study regarding the prevalence of different histologic subtypes and clinical presentation of thyroid carcinoma patients are in line with data from other centers and those from the literature.

37

KLINIČKA I PATOHISTOLOŠKA OBILJEŽJA RAKA ŠTITNJAČE U BOLESNIKA LIJEČENIH U KLINICI ZA ONKOLOGIJU I NUKLEARNU MEDICINU KLINIČKE BOLNICE "SESTRE MILOSRDNICE", ZAGREB

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Cilj je prikazati patohistološka i klinička obilježja raka štitnjače u trenutku postavljanja dijagnoze u bolesnika liječenih u Klinici za onkologiju i nuklearnu medicinu KB "Sestre milosrdnice" u razdoblju od 1988. do 2007. godine. U razdoblju od 1962. do 2007. godine u Klinici za onkologiju i nuklearnu medicinu KB "Sestre milosrdnice" ukupno je evidentirano 1478 bolesnika liječenih od karcinoma štitnjače. U istraživanje je uključeno 859 bolesnika (21% muškarci, 79% žene) liječenih u Klinici od 1988. do 2007. godine, od kojih 712 (82,9%) s papilarnim, 61 (7,1%) s folikularnim, 48 (5,6%) s medularnim, 10 (1,2%) s miješanim medularno-diferenciranim, 13 (1,5%) s karcinomom Hürthleovih stanica te 10 (1,2%) s anaplastičnim karcinomom štitnjače. Patohistološki nalazi su dobiveni iz Kliničkog zavoda Ljudevit Jurak KB "Sestre milosrdnice" i Službe za patologiju Klinike za tumore. Bolesnici s papilarnim karcinomom (18,% muškarci, 81,7% žene; medijan dobi 48 godina) su imali manje uznapredovalu bolest s medijanom veličine tumora od 12 mm, zahvaćenošću regionalnih limfnih čvorova od 24,2% te učestalosti udaljenih metastaza od 5,2%. U skupini bolesnika s folikularnim karcinomom (26,2% muškarci, 73,8% žene; medijan dobi 49 godina) medijan veličine tumora je iznosio 32,5 mm, regionalni limfni čvorovi su bili zahvaćeni u 8,1%, dok su udaljene metastaze bile prisutne u 18% bolesnika. U skupini bolesnika s medularnim karcinomom (44,7% muškarci, 55,3% žene; medijan dobi 55,5 godina) medijan veličine tumora je iznosio 22 mm, regionalni limfni čvorovi su bili zahvaćeni u 52,1%, dok su udaljene metastaze bile prisutne u 27,1% bolesnika. Dobiveni podaci o učestalosti pojedinih patohistoloških tipova karcinoma štitnjače i njihovim kliničkim obilježjima u skladu su s podacima iz drugih centara, odnosno s podacima iz literature.

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GALECTIN-3 EXPRESSION IN FINE NEEDLE ASPIRATES OF CYTOLOGICALLY INDETERMINATE LESIONS OF THE THYROID

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Many patients with thyroid lesions are surgically treated only for diagnostic purposes because it is often difficult to make decisive preoperative diagnosis regarding malignancy based on cytologic analysis. Galectin-3 has been proposed as a tumor marker that could improve accuracy of preoperative diagnosis of thyroid lesions. The aim was to determine diagnostic accuracy of galectin-3 as a marker for preoperative diagnosis of malignancy in cytologically indeterminate lesions of the thyroid. RT-PCR analysis of galectin-3 expression was performed on RNA isolated from fine-needle aspirates. Only the samples obtained from patients with cytologically indeterminate thyroid lesions were analyzed. Results were evaluated against the postoperative histopathologic diagnosis. A total of 79 samples from patients with cytologically indeterminate lesions of the thyroid (cytologic diagnosis: 13 cellular follicular lesion, 22 follicular neoplasm, 24 suspected follicular neoplasm, 13 suspected papillary carcinoma, and 7 Hürthle cell tumor) were analyzed. Based on postoperative histopathology, 15 of 79 (19.0%) samples were malignant (12 papillary carcinoma, 1 follicular carcinoma, 1 Hürthle cell carcinoma and 1 medullary carcinoma), and 64 (81%) samples were benign (23 nodular goiter, 30 follicular adenoma, 7 Hürthle cell adenoma and 4 Hashimoto's thyroiditis). Overall, 36 out of 79 samples (46%) were positive for galectin-3. The specificity, sensitivity, positive predictive value and negative predictive value of galectin-3 in distinguishing between malignant and benign lesions were 0.58, 0.60, 0.25, and 0.86, respectively. Accordingly, galectin-3 showed a relatively high negative predictive value, but low specificity, sensitivity and positive predictive value as a marker for preoperative diagnosis of malignancy in cytologically indeterminate thyroid lesions.

38.

EKSPRESIJA GENA ZA GALEKTIN-3 U PUNKTATIMA CITOLOŠKI NEODREĐENIH PROMJENA ŠTITNJAČE U POGLEDU MALIGNOSTI

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Mnogi bolesnici s lezijama štitnjače operiraju se u dijagnostičke svrhe, jer je često teško postaviti jasnu prijeoperacijsku dijagnozu glede malignosti na temelju citološke analize. Galektin-3 se istražuje kao tumorski biljeg koji bi mogao povećati točnost prijeoperacijske dijagnostike lezija štitnjače. Cilj je bio odrediti dijagnostičku točnost galektina-3 kao biljega malignosti u prijeoperacijskoj dijagnostici u skupini citološki neodređenih lezija štitnjače u pogledu malignosti. Ekspresija gena za galektin-3 analizirana je metodom RT-PCR u punktatima štitnjače dobivenim aspiracijskom biopsijom tankom iglom. Analizirani su samo uzorci dobiveni od bolesnika s citološki neodređenim lezijama štitnjače u pogledu malignosti. Rezultati su uspoređivani s obzirom na patohistološku dijagnozu. Obrađeno je 79 uzoraka od bolesnika s citološki neodređenim lezijama štitnjače u pogledu malignosti (citološka dijagnoza: 13 celularnih folikularnih promjena, 22 folikularna tumora, 24 suspektna folikularna tumora, 13 suspektnih papilarnih karcinoma i 7 tumora Hürthleovih stanica). Patohistološka analiza je pokazala da je 15 od 79 (19%) uzoraka bilo zloćudno (12 papilarnih karcinoma, 1 folikularni karcinom, 1 karcinom Hürthleovih stanica te 1 medularni karcinom), a 64 (81%) uzoraka dobroćudno (23 nodularne strume, 30 folikularnih adenoma, 7 adenoma Hürthleovih stanica te 4 Hashimotova tireoiditisa). Vrijednost galektina-3 bila je pozitivna u ukupno 36 od 79 uzoraka (46%). Specifičnost, osjetljivost, pozitivna prediktivna vrijednost i negativna prediktivna vrijednost galektina-3 kao biljega za razlikovanje malignih od benignih lezija bile su redom 0,58; 0,60; 0,25 i 0,86. Galektin-3 je pokazao relativno visoku negativnu prediktivnu vrijednost, ali nisku specifičnost, osjetljivost i pozitivnu prediktivnu vrijednost kao biljeg za prijeoperacijsku dijagnozu malignih lezija među citološki neodređenim lezijama štitnjače u pogledu malignosti.

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CD44v6 AS A MARKER FOR PREOPERATIVE DIAGNOSIS OF CYTOLOGICALLY INDETERMINATE LESIONS OF THE THYROID

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CD44v6 is investigated as a molecular marker that could help make preoperative diagnosis of malignant thyroid lesions in cases in which decisive preoperative diagnosis regarding malignancy can't be made based on cytological analysis. The aim was to determine diagnostic accuracy of CD44v6 as a marker for preoperative diagnosis of malignant lesions in the group of cytologicaly indeterminate lesions of the thyroid. Samples obtained by fine-needle aspiration of thyroid lesions were analyzed. CD44v6 expression in the samples was analyzed by RT-PCR. CD44v6 expression was analyzed only in samples obtained from patients with cytologically indeterminate thyroid lesions. The results were evaluated against the postoperative histopathological diagnosis. A total of 79 samples from patients with cytologically indeterminate lesions of the thyroid were analyzed. Cytological diagnoses were: 13 cellular follicular lesion, 22 follicular neoplasm, 24 suspected follicular neoplasm, 13 suspected papillary carcinoma, and 7 Hurthle cell tumor. Based on preoperative histopathology, 15 of 79 (19.0%) samples were malignant (12 papillary carcinoma, 1 follicular carcinoma, 1 Hurthle cell carcinoma, and 1 medullary carcinoma), and 64 (81%) samples were benign (23 nodular goiter, 30 follicular adenoma, 7 Hurthle cell adenoma, and 4 Hashimoto's thyroiditis). Overall, 41 out of 79 samples (52%) were positive for CD44v6. CD44v6 as a marker for diagnosis of malignant thyroid lesions showed specificity of 0.48; sensitivity of 0.53; positive predictive value of 0.19, and negative predictive value of 0.82. Accordingly, CD44v6 showed a relatively low specificity, sensitivity, and positive predictive value, but relatively high negative predictive value as a marker for preoperative diagnosis of malignant lesions in the group of cytologicaly indeterminate thyroid lesions.

39.

CD44v6 KAO BILJEG ZA PRIJEOPERACIJSKU DIJAGNOSTIKU CITOLOŠKI NEODREĐENIH PROMJENA ŠTITNJAČE U POGLEDU MALIGNOSTI

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CD44v6 se istražuje kao molekularni biljeg koji bi mogao pomoći u prijeoperacijskoj dijagnozi malignih lezija štitnjače kada se na temelju citološke analize ne može postaviti jasna dijagnoza glede malignosti. Cilj rada bio je odrediti dijagnostičku točnost CD44v6 kao biljega za prijeoperacijsko otkrivanje malignih lezija među citološki neodređenim lezijama štitnjače u pogledu malignosti. Analizirani su punktati štitnjače dobiveni aspiracijskom biopsijom tankom iglom. U punktatima se određivala ekspresija gena za CD44v6 metodom RT-PCR. Ekspresija gena za CD44v6 određivala se samo u uzorcima dobivenim od bolesnika s citološki neodređenim lezijama štitnjače u pogledu malignosti. Rezultati su uspoređivani s obzirom na patohistološku dijagnozu. Analizirano je 79 uzoraka od bolesnika s citološki neodređenim lezijama štitnjače u pogledu malignosti. Citološke dijagnoze su bile: 22 folikularna tumora, 24 suspektna folikularna tumora, 13 celularnih folikularnih promjena, 13 suspektnih papilarnih karcinoma i 7 tumora Hürthleovih stanica. Petnaest od 79 (19%) uzoraka je bilo maligno (1 medularni karcinom, 1 folikularni karcinom, 12 papi-larnih karcinoma te 1 karcinom Hürthleovih stanica), a 64 (81%) uzoraka benigno (30 folikularnih adenoma, 7 adenoma Hürthleovih stanica, 23 nodularne strume te 4 Hashimotova tireoiditisa) s obzirom na patohistološku dijagnozu. Vrijednost CD44v6 bila je pozitivna u ukupno 41 od 79 uzoraka (52%). CD44v6 je kao biljeg za dijagnozu malignih lezija štitnjače pokazao specifičnost od 0,48; osjetljivost od 0,53; pozitivnu prediktivnu vrijednost od 0,19; te negativnu prediktivnu vrijednost od 0,82. CD44v6 je pokazao relativno nisku specifičnost, osjetljivost i pozitivnu prediktivnu vrijednost, ali relativno visoku negativnu prediktivnu vrijednost kao biljeg za prijeoperacijsku dijagnozu malignih lezija među citološki neodređenim lezijama štitnjače u pogledu malignosti.

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MEDULLARY THYROID CARCINOMA WITH PARATHYROID ADENOMA

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Medullary thyroid carcinoma occurs in 10%-20% of cases as a component of the multiple endocrine neoplasia type II syndrome, which includes medullary thyroid cancer and pheochromocytoma. Medullary thyroid carcinoma occurs most commonly after age 50, with a higher prevalence in women, and shows dominant familial transmission. A patient with medullary thyroid carcinoma and parathyroid adenoma without pheochromocytoma, aged 60, height 188 cm and weight 87 kg is described. He first visited physician when he felt weakness and back pain. His general laboratory findings were normal for one year, and then we found hypercalcemia, elevated parathormone level and bilateral nephrolithiasis. He only had appendectomy in his medical history. His brother died from pituitary cancer. Echosonography showed parathyroid adenoma of the inferior right lobe and a hypoechogenic thyroid node ("cold" on scintigraphy; the patient refused fine-needle aspiration, FNA) in the right lobe of the euthyroid gland. Complete surgical extirpation of the adenoma (histologic finding was adenoma) and right thyroid lobotomy (histologic finding was medullary carcinoma) were performed. Parathormone and calcium levels were in the normal range postoperatively. Eighteen months later, the patient was hospitalized for severe cervical spondylosis and lumbar ischialgia with arterial hypertension, tachycardia and angina. Physical examination showed normal findings, and so were laboratory findings except for high erythrocyte sedimentation rate (ESR) 35/74, signs of sideropenic anemia: E $4.6x10^{12}$/L (4.3-5.7 $x10^{12}$/L), Hb 124 (138-175 g/L), Hct 37.7 (41-53), MCV 81.8 (86.0-100.0 fL), Fe 7.4 (16.1-25.1 mmol/L), TIBC 42.6 (43-73.34 µmol/L), UIBC 35.2 (30.4-51.8 µmol/L), index of saturation 0.17 (0.33), mild hyperkalemia 5.3 (3.6-5.2 mmol/L) and hypertriglyceridemia 2.57 (0.11-2.10 mmol/L). The values of thyroid and parathyroid hormones and thyroglobulin were normal; calcitonin could not be measured at the time. Echosonography of the thyroid gland showed a hypoechogenic node in the left lobe, 5.3x6.9 mm in size, "cold" on scintigraphy, without enlarged lymph

40.

MEDULARNI KARCINOMOM ŠTITNJAČE S ADENOMOM PARATIREOIDNE ŽLIJEZDE

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Medularni karcinom štitnjače se pojavljuje kao dio sindroma tipa II multiplih endokrinih adenomatoza u 10%-20% svih slučajeva sa primarnim hiperparatireoidizmom i feohromocitomom, najčešće nakon 50. godine života, nešto češće kod žena. Prenosi se dominantno unutar familije. U radu je prikazan pacijent sa medularnim karcinomom štitnjače i adenomom paraštitne žlijezde, bez feohromocitoma, star 60 godina, visok 188 cm, težak 87 kg, prvi put se javio ljekaru zbog opće slabosti i bola u krstima. Godinu dana je imao uredne laboratorijske i druge kliničke nalaze, a onda je ustanovljena povećana vrijednost serumskog kalcijuma i parathormona, kao i obostrana nefrolitijaza. Od ranijih bolesti je imao apendektomiju. U porodičnoj anamnezi brat je umro od „tumora hipofize". Ehosonografski i scintigrafski ustanovljen je adenom donje desne paratireoidne žlijezde i hipoehogeni nodus (scintigrafski hladan, pacijent nije pristao na punkciju) u desnom režnju eutireoidne štitnjače. Urađena je ekstirpacija adenoma (patohistološki nalaz, adenom) in toto i desna lobektomija štitnjače (patohistološki nalaz, medularni karcinom). Postoperativno parathormon i kalcijum u referentnim granicama (ref. gr.). Nakon 1.5 godine hospitaliziran je zbog teške spondiloze vratne kičme i lumboišialgije, sa arterijskom hipertenzijom, tahikardijom i anginoznim tegobama. Fizikalni nalaz je uredan. Od laboratorijskih nalaza SE povišena: 35/74, znaci sideropenične anemije: E 4.6x1012/l (4,3-5,7 x1012/L, Hb 124 (138-175 g/L), Hct 37.7 (41-53), MCV 81,8 (86,0-100,0 fL), Fe 7,4 (16,1-25,1 mmol/L), TIBC 42,6 (43-73,34 umol/L), UIBC 35,2 (30,4-51,8 umol/L), indeks zasićenja 0,17 (0,33), kalijum 5,3 (3,6-5,2 mmol/L), trigliceridi 2,57 (0,11-2,10 mmol/L) uz ostale laboratorijske parametre u ref.gr. Hormonski status štitne i paraštitne žlijezde i vrijednost tireoglobulina u ref. gr. Nismo bili u mogućnosti raditi kalcitonin. Eho štitnjače: bez uvećanih limfonoda u području vrata, desni lobus štitnjače se ne prikazuje, u lijevom režnju hipoehogeni nodus veličine 5,3x6,9 mm, scintigrafski hladan. CT zdjelice je pokazao osteoplastične i osteolitične promjene na zdjeličnoj kosti, koje su najvjerovatnije posljedica hiperparatireoidizma koji

nodes in the neck. There were osteoblastic and osteolytic changes on CT of pelvic bones, probably caused by early hyperparathyroidism. Radionuclide skeleton scan showed no changes. The patient refused FNA of the "cold" node again, and he did not present any more. Had the patient undergone initial FNA of the node, the disease recurrence could have been obviated by total thyroidectomy.

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OUR FIRST EXPERIENCE IN THE USE OF RECOMBINANT HUMAN TSH (yhTSH) IN FOLLOW-UP OF PATIENTS WITH DIFFERENTIATED CARCINOMA OF THE THYROID

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Recombinant human TSH (rhTSH) has found application in the monitoring and management of patients with persistent or recurrent thyroid cancer, obviating the need to render the patient hypothyroid. rhTSH has not yet been approved in Croatia. The present study was designed 1) to show our experience in managing patients with thyroid cancer with the use of rhTSH, and 2) to simulate and compare direct cost of rhTSH procedure with the conventional l-thyroxin withdrawal procedure in working patients. Since 2004, twelve adult patients with papillary and follicular thyroid cancer requiring radioiodine whole body scanning (WBS) received rhTSH. In all of them, prior treatment procedure consisted of total thyroidectomy followed by ablative therapy with radioiodine. The patients themselves or their employer paid the full cost of rhTSH. The recommended procedure was followed: 24 h after the second intramuscular injection of rhTSH, 185 MBq (5mCi) I-131 were administered, 48 h later I-131-WBS was performed, and serum TSH and Tg levels were measured. The quality of life of our patients was unchanged during rhTSH procedure, in contrast to hypothyroidism induced by thyroid hormone withdrawal. The only adverse events to rhTSH were mild nausea and headache recorded in one patient. In our group of patients, we found no abnormal WHS or increase in Tg level. RhTSH yielded a WHS similar in quality to thyroid hormone withdrawal. Absence from work in active patients was only 5 days with rhTSH method, while in case of conventional levothyje operativno riješen, sa zaostalim promjenama u strukturi kosti. Scintigrafija skeleta je urednog nalaza. Pacijentu je preporučena punkcija suspektnog nodusa štitnjače, koju je odbio. Nije se javio na kontrolu. Da je pacijent pristao odmah na punkciju hladnog čvora, urađena bi bila totalna tireoidektomija i spriječen recidiv.

41.

NAŠA ISKUSTVA U PRIMJENI REKOMBINANTNOG HUMANOG TSH U PRAĆENJU BOLESNIKA S RAKOM ŠTITNJAČE

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Rekombinantni humani TSH (rh-TSH) danas ima svoje mjesto u praćenju i liječenju bolesnika s diferenciranim rakom štitnjače, a bez prethodnog izostavljanja terapije levotiroksinom. Cilj rada bio je 1) pokazati naša iskustva u primjeni rh-TSH, te 2) na simulaciji usporediti cijenu prirpravka i stvarnu cijenu troškova odsutnosti s posla radno aktivnog bolesnika. Od 2004. godine pomoću rh-TSH ispitano je 12 bolesnika s diferenciranim rakom štitnjače. Bolesnici su sami ili u suradnji s radnom organizacijom platili troškove rh-TSH. Primijenjena je prihvaćena shema ispitivanja uz pomoć rh-TSH: 24 h od druge i.m. injekcije 0.9 mg rh-TSH davana je probna doza 5 mCi I-131, a 48 h poslije rađena je scintigrafija cijelog tijela i određivanje Tg u serumu. Pripravak su bolesnici dobro podnosili bez neželjenih pojava. U ovih bolesnika scintigrafija cijelog tijela nije pokazala patoloških nalaza, a nisu zabilježene ni patološke vrijednosti Tg. Scintigrafija cijelog tijela kvalitativno i kvantitativno nije pokazala odstupanja od scintigrama rađenih na uobičajeni način kod bolesnika bez levotiroksina. Izostanak s posla kod ispitivanih bolesnika je bio 5 dana, dok je kod bolesnika uz prethodno izostavljanje levotiroksina bio i do 2 mjeseca. Simulacija cijene postupka uz klasično izostavljanje levotiroksina kod naših bolesnika sa cijenom postupka uz pomoć rh-TSH jasno pokazuje da je metoda uz pomoć rh-TSH i jeftinija. Naravno da na osnovi naše sporadične primjene rh-TSH nije moguće izvoditi konačne zaključke, te se zasad treba držati preporuka iz literature. Cijena pripravka je glavna prepreka za širu primjenu rh-TSH. Međutim, simulacijom je pokazano da je metoda rh-TSH u konačnici jeftinija od klasične metode kod radno aktivnih osoba. Možda je vrijeme

roxin withdrawal it was even 2 months. Cost comparison analysis clearly showed the rhTSH procedure to be less expensive. A greater number of patients and longer period of evaluation of rhTSH procedure are needed for more reliable conclusions to make. For the time being, recommendations from the literature should be followed. The relatively high cost of rhTSH is considered the main factor hampering its use, however, eventually rhTSH is less expensive. It appears that time has come to initiate discussion with the Croatian Institute of Health Insurance to cover rhTSH procedure by insurance.

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DIFFERENTIATION OF CYSTIC LESIONS WITH FINE NEEDLE ASPIRATION BIOPSY OF THE THYROID GLAND

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Introduction: Palpable nodules in the thyroid gland are present in 8% to 15% of the total population. The prevalence of cysts in the palpable nodule is 30% to 40%, while the incidence of malignancies in composite cists is up to 10%. Malignant tumors of the thyroid gland account for approximately 85% of all endocrinologic carcinomas and thus the evaluation of the thyroid gland is of utmost importance. Early diagnostic assessment of the suspect thyroid cysts may ensure timely diagnosis of malignancies.

Aim: Assessment of the malignant potential of the thyroid cystic lesions dependent on the macroscopic aspirate appearance and thyroglobulin concentration within the cyst.

Subjects and Methods: Workup of all patients with palpable cystic lesions of the thyroid gland was performed. Of the 124 subjects 91 (73%) were women and 33 (27%) were men. Their mean age was 48.56 ± 1.34 years. All subjects underwent clinical and ultrasound examination. Ultrasonographic aspiration biopsy of the lesion and scintigraphy of the thyroid gland were performed

Results: In all subjects the concentration of thyroid hormones was within normal values. Scintigraphy with 99mTc-pertehnetate reveled "cold" nodules in 120 subjects and in 4 moderately cold nodules. The ultrasonographic structure of the nodules presented anechoic in

pokrenuti inicijativu preko Društva za bolesti štitnjače kako bi HZZO priznao metodu rh-TSH.

42.

RAZLIKOVANJE CISTIČNIH TVORBI ASPIRACIJSKOM PUNKCIJOM ŠTITNJAČE

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Palpabilni čvorovi u štitnoj žlijezdi javljaju se kod 8% do 15% ukupne populacije. Udio cista u palpabilnom čvoru iznosi 30% do 40%, dok je učestalost malignoma u kompliciranim cistama i do 10%. Među endokrinološkim zloćudnim tumorima maligni tumori štitne žlijezde čine oko 85%, stoga je procjena čvorova štitne žlijezde od neprocjenjive važnosti. Rana dijagnostička obrada sumnjivih cista štitnjače može osigurati pravodobnu dijagnozu malignoma. Cilj studije bila je procjena malignog potencijala cistične lezije štitnjače u ovisnosti o makroskopskom izgledu aspirata i unutarcističnoj koncentraciji tireoglobulina. Obrađeni su ispitanici s palpabilnom cističnom tvorbom štitne žlijezde. Od ukupno 124 ispitnika bila je 91 (73%) žena i 33 (27%) muškarca. Prosječna dob bila je 48,56±1,34 godine. Svi su ispitanici podvrgnuti kliničkom i ultrazvučnom pregledu, a pod kontrolom ultrazvuka učinjena je aspiracijska punkcija lezije. Kod svih se ispitanika učinio scintigrafski pregled štitne žlijezde. Koncentracija hormona štitnjače je u svih ispitanika bila unutar normalnih vrijednosti. U 120 ispitanika čvor se scintigrafski s 99mTc-pertehnetatom prikazao „hladno", a u četiri „relativno hladno". Ultrazvučna struktura čvorova je bila anehogena kod 46 (37,1%), anehogena sa solidnim dijelom u 68 (54.8%) te hipoehogena s anehogenim dijelom u 10 (8,1%) ispitanika. Izgled aspirata procijenili smo makroskopski kao čokoladni (59,7%), sukrvav (10,5%) ili žut (29,8%). U sedmoro (5,6%) ispitanika sa cističnom tvorbom štitnjače

46 (37.1%) subjects, anechoic and in part solid in 68 (54.8%) and hypo echoic and in part anechoic in 10 (8.1%) of the subjects. Aspirates were assessed microscopically as brownish (59.7%), bloody (10.5%) and yellow (29.8%).

Malignant tumors were diagnosed in 7 (5.6%) subjects with thyroid cystic lesions. The average concentration of thyroglobulin was higher in cysts with malignant tumors.

Conclusion: The obtained results point out the paramount importance of analyzing the cyst content because of the undemanding procedure and reliable findings.

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CYTOMORPHOLOGICAL FEATURES OF MEDULLARY CARCINOMA OF THE THYROID

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Medullary carcinoma is malignant tumor of the thyroid gland showing C cell differentiation. It accounts for 5%-10% of all thyroid malignancies. Up to 25% of these tumors are heritable, associated with germline mutations of the RET proto-oncogene. The etiology of sporadic form is unknown. Virtually all medullary carcinomas produce calcitonin and serum levels of the hormone are typically increased. Ten-year survival rate is about 75%. This study included smears of cytologically diagnosed medullary carcinoma obtained by FNAC of 3311 nodules in 2007 patients during a 7-year period at Department of Cytology, Sestre milosrdnice University Hospital. Aspirations were performed mostly under US guidance using a 23-gauge needle and 10-ccm syringe. Smears were stnined by standard method according to MGG and analyzed under a light microscope. In some cases immunocytochemistry was performed. The aim of the study was to evaluate morphological pictures of medullary carcinoma. Out of 108 thyroid gland tumors, cytology diagnosed medullary carcinoma in 6 (5.5%) cases, two of which had histopathologic diagnosis. The most common cytologic features were the presence of dispersed cell pattern, eccentric nuclei, neuroendocrine chromatin pattern, nuclear pleomorphism, bi- or multinucleation, red cytoplasmic granules, and amphophylic cytoplasm. It is important to diagnose medullary carcinoma preoperatively. According to the literature, the dijagnosticiran je zloćudni tumor. Prosječna koncentracijaa tireoglobulina bila je veća u cistama sa zloćudnim tumorom. Dobiveni rezultati ukazuju na neprocjenjivu vrijednost analize sadržaja ciste zbog jednostavnosti izvođenja i pouzdanosti nalaza.

43.

CITOMORFOLOŠKE ZNAČAJKE MEDULARNOG KARCINOMA ŠTITNJAČE

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Medularni karcinom je maligni tumor štitnjače koji pokazuje C staničnu diferencijaciju. Javlja se u 5%-10% svih malignoma u štitnjači. Do 25% medularnih karcinoma je nasljedno, udruženo s mutacijama RET protoonkogena. Etiologija sporadičnog oblika je nepoznata. Gotovo svi medularni karcinomi proizvode kalcitonin, što dovodi do povećane razine ovoga hormona u serumu. Desetogodišnje preživljenje je oko 75%. Ovaj rad obuhvaća razmaze citološki dijagnosticiranih medularnih karcinoma dobivenih citopunkcijom 3311 čvorova u 2007 bolesnika tijekom 7-godišnjeg razdoblja na Odsjeku za citologiju Kliničke bolnice “Sestre milosrdnice”. Punkcije su u većini slučajeva bile ultrazvučno vođene. Rabile su se igle od 23 gauge i šprice od 10 ccm. Razmazi su bojani standardnom metodom po MGG i analizirani svjetlosnim mikroskopom. U nekim slučajevima učinjena je imunocitokemija. Cilj rada bio je učiniti pregled morfoloških značajka medularnog karcinoma. Od 108 tumora štitnjače citološki je dijagnosticirano 6 medularnih karcinoma (5,5%), od kojih su 2 imala patohistološku dijagnozu. Najčešće citološke značajke bile su: pojedinačne stanice s periferno smještenom jezgrom, struktura kromatina tipa neuroendokrinih tumora, pleomorfizam jezgre, bi- i multinukleacija, crvena citoplazmatska granula i amfofilija citoplazme. Medularni karcinom važno je dijagnosticirati prijeoperacijski. Najnižu citopatološku korelaciju, prema literaturi, nalazimo za

lowest cytopathological correlation is found in this type of tumor. It is understandable because of the existance of 12 morphological variants according to WHO. Immunocytochemistry is useful , yet some novel methods will be of interest.

44

SERUM THYROGLOBULIN, I-131 WHOLE BODY SCAN AND NECK ULTRASONOGRAPHY IN THE FOLLOW-UP OF LOW RISK PATIENTS WITH DIFFERENTIATED THYROID CANCER

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The aim of this retrospective study was to assess the utility of serum thyroglobulin (TG), (131) I-whole body scan (WBS) and neck ultrasonography (US) in the follow up of low risk patients with differentiated thyroid cancer (DTC). The study included 121 consecutive patients with DTC submitted to total thyroidectomy and subsequent (131) I thyroid ablation between 1992 and 2002 at our department (Osijek University Hospital). Patients with uptake outside the thyroid bed on the postablative (131) I- WBS (high-risk patients) were excluded from the study. The routine procedure in the follow up of DTC was based on serum Tg measurements during thyroid hormone withdrawal (Tg-off), diagnostic (131) I-WBS and neck US. The mean follow up period was 8.2+/-3.6 years. Clinically persistent or recurrent disease was diagnosed in 16 of 121 patients (13.2%). Serum thyroglobulin (Tg-off) was elevated (Tg >2 ng/mL) in 13 patients with recurrence (sensitivity: 81%), (131) I-WBS was positive (uptake outside the thyroid bed) in 4 patients with recurrence (sensitivity: 25%) and neck US identified (confirmed by fine-needle aspiration cytology) 12 patients with recurrent disease (sensitivity: 75%). Neck US identified 3 (18.7%) patients that were not previously detected by serum Tg and (131) I-WBS (Tg (-), (131) I WBS (-)). The combined use of serum thyroglobulin (Tg-off) and neck US detected all patients with recurrence of DTC. Serum thyroglobulin levels (Tg-off) and neck US were sufficient diagnostic tools for detection of persistent or recurrent disease in the follow up of low risk patients with DTC. The routine use of diagnostic WBS in the follow up of low risk patients did not show significant clinical benefit.

44.

SERUMSKI TIREOGLOBULIN, SCINTIGRAFIJA CIJELOG TIJELA JODOM-131 I ULTRAZVUK VRATA U PRAĆENJU NISKO RIZIČNIH BOLESNIKA S DIFERENCIRANIM KARCINOMOM ŠTITNJAČE

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Svrha prikazane retrospektivne studije bila je ocijeniti korisnost dijagnostičkih metoda: serumskog tireoglobulina (Tg), scintigrafije cijelog tijela jodom-131 (SCT I-131) i ultrazvuka (UZV) vrata u praćenju nisko-rizičnih bolesnik s diferenciranim karcinomom štitnjače (DKŠ). Studija je obuhvatila 121 uzastopnog bolesnika s DKŠ koji su bili podvrgnuti totalnoj tiroidektomiji i ablacijskoj terapiji jodom-131 u periodu od 1992. do 2002. god. u našem centru (Klinička bolnica Osijek). Bolesnici koji su na poslije-ablacijskom scintigramu cijelog tijela (I-131) imali patološko nakupljanje aktivnosti izvan tiroidnih ostataka bili su isključeni iz studije (tzv. visoko-rizični bolesnici). Standardni postupak u praćenju DKŠ temeljio se na mjerenju serumskog Tg u uvjetima izostavljene terapije hormonima štitnjače (Tg-off), dijagnostičkoj scintigrafiji cijelog tijela jodom-131 i UZV vrata. Prosječno razdoblje praćenja bilo je 8,2+/-3,6 godina. Klinički ustrajna odnosno recidivirajuća bolest dijagnosticirana je u 16 od 121 (13,2 %) bolesnika. Serumski tireoglobulin (Tg-off) je bio povišen (Tg >2 ng/mL) u 13 od 16 bolesnika s dokazanim recidivom (osjetljivost : 81%), scintigrafija cijelog tijela (I-131) je bila pozitivna (nakupljanje aktivnosti izvan tiroidnih ostataka) u 4 od 16 bolesnika s recidivom (osjetljivost: 25%), dok je UZV vrata (potvrđeno nalazom citološke punkcije) identificirao 12 bolesnika s recidivom (osjetljivost: 75%). UZV vrata je zasebno identificirao 3 bolesnika s recidivom (18,7%) koji nisu bili otkriveni serumskim Tg i scintigrafijom cijelog tijela (I-131). Kombinirana upotreba samo serumskog Tg (Tg-off) i UZV vrata otkrila je sve bolesnike s recidivom DKŠ. Mjerenje serumskog tireoglobulina (Tg-off) i UZV vrata bili su dovoljan dijagno-

stički alat za otkrivanje ustrajne ili recidivirajuće bolesti u praćenju nisko-rizičnih bolesnika s DKŠ. Rutinska upotreba dijagnostičke scintigrafije cijelog tijela (I-131) nije imala značajnu kliničku korist u praćenju nisko-rizičnih bolesnika.

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UNDIFFERENTIATED (ANAPLASTIC) THYROID CARCINOMA

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Undifferentiated-anaplastic thyroid carcinoma (ATC) is one of the most aggressive tumors in human medicine. The aim of the study was to analyze basic demographic characteristics, the possibility of surgical treatment and survival of patients with ATC. Study group consisted of patients with ATC treated at the Center of Endocrine Surgery during the 1993-2005 period. During the study period, ATC was found in 150 patients (96 female and 54 male), median age 67 (range 38-89) years. More than 50% of patients were over 60 years old. In patients operated on, diagnosis was based on histopathology results (n=74). In patients without surgery, diagnosis was based on cytologic analysis. Pre-existence of differentiated thyroid cancer was found in almost 70% of patients operated on for ATC. Radical surgery (total thyroidectomy) was performed in about 20% of patients, most frequently tumor reduction, rarely open biopsy and tracheotomy. Every patient received transcutaneous radiotherapy. Survival was one week to 70 months (5 months on an average) from the time of ATC diagnosis. One-year survival was 16%, and included only patients operated on. Despite multimodal therapy, patients with ATC have poor prognosis. A little longer survival can only be expected in the group of operated patients.

45.

NEDIFERENCIRANI (ANAPLASTIČNI) KARCINOM ŠTITNJAČE

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Nediferencirani anaplastični karcinom štitnjače je jedan od najagresivnijih tumora u ljudi. Cilj ovog istraživanja bio je analizirati osnovne demografske karakteristike, mogućnost kirurškog liječenja te preživljenje u bolesnika s anaplastičnim karcinomom. Analiziranu skupinu činili su bolesnici s dijagnozom anaplastičnog karcinoma štitnjače liječeni u Centru za endokrinu kirurgiju od 1993. do 2005. godine. U navedenom razdoblju utvrđeno je 150 bolesnika (96 žena i 54 muškaraca, medijan dobi 67 godina) s anaplastičnim karcinomom koji su liječeni u Centru za endokrinu kirurgiju. Više od 50% njih bili su stariji od 60 godina. Dijagnoza je potvrđena patohistološkim nalazom nakon operacije (n=74). U bolesnika koji nisu bili operirani dijagnoza je utvrđena citološkom punkcijom. U gotovo 70% bolesnika operiranih zbog anaplastičnog karcinoma diferencirani karcinom štitnjače već je bio prisutan. Radikalna operacija (totalna tireoidektomija) je učinjena u 20% bolesnika. Najčešća operacija bila je redukcija tumora, dok su se ostali zhavati, kao što su otvorena biopsija i traheotomija, rjeđe primjenjivali. U svakog bolesnika provedena je transkutana radioterapija. Preživljenje je bilo od 1 do 70 mjeseci (u prosjeku 5 mjeseci) od trenutka postavljanja dijagnoze. Jednogodišnje preživljenje iznosilo je 16% i to samo u bolesnika koji su bili liječeni operativnim putem. Bolesnici s anaplastičnim karcinomom štitnjače imaju vrlo lošu prognozu usprkos multimodalnoj terapiji. U operiranih bolesnika može se očekivati neznatno dulje preživljenje.

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PAPILLARY MICROCARCINOMA – PATHOLOGIC CHARACTERISTICS AND CLINICAL PRESENTATION

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Papillary microcarcinoma (PTMC), defined as a papillary thyroid cancer ≤1 cm according to WHO, is a clinical entity with a high prevalence, often as the result of clinical introduction of highly accurate diagnostic tools currently available (real-time ultrasound with fine-needle aspiration cytology). Various disagreements are present regarding the risk potential of PTMC, and consequentially therapeutic approach as well as follow up. In our material of 236 patients with PTMC presented and operated during the 26-year period (1980-2006) at Sestre milosrdnice University Hospital, we investigated some of pathological characteristics and clinical behavior of this specific group of PTC patients; we also discuss some of the important issues relevant to the development of therapeutic strategies. Results showed aggressive behavior of some chosen parameters in a significant number of subjects, a tendency to muticentricity and locoregional spread.

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THYROID CANCER MORTALITY RATE IN BELGRADE, SERBIA, 1993-2002

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Thyroid cancer is a relatively rare tumor, however, its incidence shows an increase in most countries. Yet, the increase in the incidence is not fraught with thyroid cancer mortality. The aim of this study was to estimate thyroid cancer mortality in Belgrade during the 1993-2002 period. The survey was based on unpublished mortality data of the Municipal Statistical Office in Belgrade. The proportion and standardized mortality rates were used. Thyroid cancer mortality accounted for 0.09% of all deaths (0.12% in female and 0.06% in male) and

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PAPILARNI MIKROKARCINOM – PATOLOŠKE OSOBITOSTI I KLINIČKA PREZENTACIJA

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Napredak medicinskih tehnologija te njihova brza klinička primjena dovode do bitnih pomaka u ranom otkrivanju patoloških promjena te prepoznavanju rizičnih lezija štitnjače. Upravo zahvaljujući brzom razvoju i primjeni takvih tehnologija (prije svega visokofrekventnog ultrazvuka) postoji tendencija dijagnosticiranja papilarnog karcinoma u ranom stadiju te posredno povećane incidencije novo dijagnosticiranih karcinoma male veličine. Ta skupina bolesnika ispunjava kriterije papilarnog mikrokarcinoma (tumori ≤1 cm) koji kao poseban entitet predstavlja već dulje vrijeme predmet kontroverza kako u procjeni rizičnosti lezije, tako i u terapijskom pristupu te praćenju. U našem materijalu papilarnog mikrokarcinoma prezentiranom na Klinici za ORL i kirurgiju glave i vrata tijekom 26 godina (1980.-2006., 236 bolesnika) prikazujemo neke od osobitosti papilarnog mikrokarcinoma te procjenu značenja u tom sve značajnijem segmentu tumorskih bolesti štitnjače. Rezultati pokazuju agresivno ponašanje tumora u značajnom broju slučajeva, sklonost multicentričnosti kao i lokoregionalnom širenju bolesti.

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STOPA SMRTNOSTI RAKA ŠTITNJAČE U BEOGRADU, SRBIJA, 1993.-2002.

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Rak štitnjače je relativno rijedak tumor, no primijećen je porast njegove incidencije u većini zemalja. Ipak, ovo povećanje incidencije raka štitnjače nije praćeno porastom njegove stope smrtnosti. Cilj ove studije bio je istražiti stopu smrtnosti raka štitnjače u Beogradu u periodu od 1993. do 2002. godine. Istraživanje je temeljeno na neobjavljenim podacima o smrtnosti Gradskog ureda za statistiku u Beogradu. Korištene su proporcijske i standardizirane metode. Smrtnost od raka štitnjače činila je 0,09% svih smrti (0,12% u žena i 0,06%

0.42% of cancer mortality (0.59% in female and 0.28% in male) in Belgrade from 1993 to 2002. The mean standardized mortality rate of thyroid cancer was 0.53 per 100.000 (0.62 in female and 0.37 in male). Age adjusted mortality rates were low up to the age group of 50 years, then sharply increased, reaching highest value in the oldest age group. Thyroid cancer mortality in Belgrade is low, greater in female than in male population, and there is no noticeable difference from other countries. The results obtained are in line with literature data.

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HYPERTHYROIDISM AND THYROID CARCINOMA

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Hyperthyroidism is rarely a presenting feature of thyroid carcinoma. This association is also a very rare one. Usually it is seen when the diagnosis of tumor has already been established, as in metastatic differentiated carcinoma. Our patients mainly present with small thyroid carcinomas. In such a setting, hyperthyroidism brings patients to the doctor and the tumor is an occasional finding on routine work-up. This may happen in autoimmune hyperthyroidism as well as in toxic multinodular goiter. We present a rare case of hyperthyroidism in multinodular goiter which appeared to be tumor tissue. The patient was a 65-year-old female with great "hot" nodules on pertechnetate scan. FNAB revealed well differentiated follicular and papillary carcinoma. After a short course of thyrostatic therapy, the patient underwent total thyroidectomy and radioiodine ablation as routine procedures. Histopathology indicated poorly differentiated carcinoma of the left lobe. The patient received suppressive levothyroxine therapy. The tumor recurred. Repeat FNAB showed mixed follicular and papillary carcinoma. She was reoperated on two more occasions with resection of the trachea, followed by external neck radiotherapy. Histopathology indicated undifferentiated and follicular carcinoma. Now, seven years after the diagnosis, the patient is well and in good condition so far. This case stresses the necessity of detailed examination of every hyperthyroid patient no matter how obvious the diagnosis may seem at first sight.

u muškaraca) te 0,42% smrti od raka (0,59 u žena i 0,28% u muškaraca) u Beogradu od 1993. do 2002. Prosječna strandardizirana stopa smrtnosti raka štitnjače je iznosila 0,53 na 100.000 stanovnika (0,62 u žena i 0,37 u muškaraca). Dobno standardizirane stope smrtnosti bile su niske za skupine s manje od 50 godina, s naglim porastom iznad 50 godina. Najviše dobno standardizirene stope smrtnosti utvrđene su u najstarijim skupinama. Stopa smrtnosti raka štitnjače u Beogradu je niska, viša je u žena nego u muškaraca, i bez veće razlike u odnosu na druge zemlje. Dobiveni rezultati odgovaraju podacima iz literature.

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HIPERTIREOZA I RAK ŠTITNJAČE

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Hipertireoza je rijetko prvi znak raka štitnjače. I inače se ove dvije bolesti rijetko javljaju zajedno. Obično se hipertireoza nađe kad je tumorska bolest već ustanovljena, kao u metastatskom diferenciranom karcinomu. Naši bolesnici s hipertireozom i rakom štitnjače uglavnom imaju male tumore. Obično se jave zbog hipertireoze i tumor štitnjače je slučajan nalaz. Nalazimo ih u autoimunoj hipertireozi i toksičnoj multinodoznoj guši. Prikazujemo rijedak slučaj hipertireoze u multinodoznoj guši za koju se ispostavilo da je tumor. Bolesnica u dobi od 65 godina došla je zbog hipertireoze. Scintigrafija tehnecijem je pokazala velike "vruće" čvorove. Citološka punkcija je pokazala dobro diferencirani folikularni i papilarni karcinom. Nakon kratkog liječenja tireostaticima bolesnica je operirana i dobila je radioaktivni jod. Patohistološka dijagnoza je bila slabo diferencirani karcinom u lijevom režnju. Bolesnica je dobivala supresivnu dozu levotiroksina. Tumor se vratio. Ponovljena citologija je opet ukazivala na miješani folikularni i papilarni karcinom. Bolesnica je ponovno operirana još u dva navrata s resekcijom traheje, nakon čega je provedeno vanjsko zračenje vrata. Patohistološki nalaz je i ovoga puta bio nediferencirani i folikularni karcinom. Danas, sedam godina nakon dijagnoze, bolesnica je dobro i bez znakova tumorske bolesti. Ovaj slučaj naglašava potrebu detaljnog pregleda svakog bolesnika s hipertireozom, bez obzira na to kako je jasno dijagnoza izgledala na prvi pogled.