Thyroid cancer – treatment options

Ritter, Roman

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Roman Ritter

Thyroid Cancer – Treatment Options

Graduation Thesis

Zagreb, 2021

This graduation thesis was written at the Department of Nuclear Medicine, Clinical Hospital Centre, Zagreb, mentored by prof.dr.sc. Dražen Huić and was submitted for evaluation during the academic year 2020/2021.

ABBREVIATIONS

IHC – Immunohistochemistry

RT-PCR – Reverse Transcriptase Polymerase Chain Reaction

TPO – Thyroid Peroxidase

COX-2 – Cyclooxygenase-2

onfFN – Oncofetal Fibronectin

HMGI – High-Mobility Group I

CT – Computerized Tomography

MR – Magnetic Resonance

PET – Positron Emission Tomography

FDG – ^{18}F-fluorodeoxyglucose

Tg – Thyroglobulin

FVPTC – Follicular Variant of Papillary Thyroid Carcinoma

RAI – Radioiodine Ablation

EBRT – External Beam Radiotherapy

WBS – Whole-Body Scan

Table of Contents

Abstract

Thyroid cancer is rapidly increasing in incidence, yet the mortality rate remains relatively constant. Given its' favorable prognosis and great success in treatment of the most common types, it is currently debated, whether the incidence rise should change the way the screening is performed and affect the established treatment guidelines. In this literature review four of the most prominent thyroid gland cancers and their management options are presented; papillary, follicular, medullary and anaplastic carcinomas. The appropriate approach to surgical management for thyroid cancer is discussed, as some researchers advocate partial and others total thyroidectomy. There are advocates of prophylactic central cervical lymph node dissection through radical procedures, whereas other experts recommend lymphadenectomy in only specific cases. Radioactive iodine application in both treatment (ablation) and diagnosis (scanning) are also debated in terms of their specificity, sensitivity, dosage and conjunction with other methods. Chemotherapy is currently actively researched, as the traditional cytotoxic drugs are giving way to newer targeted agents, that promise to both decrease the rates of adverse effects and assist in treatment of poorly differentiated aggressive cancers. For palliation of terminally ill patients and management of distant metastases with unfavorable prognoses external beam radiation is traditionally used and continues to serve as a back-up therapy in cases of iodine-negative tumours. Additionally, follow-up strategies are briefly presented to give an overview of up-to-date research data, that reflects the extent of management success and the improvement in the quality of life.

Keywords: Thyroid cancer, thyroidectomy, radioactive iodine ablation, chemotherapy, external beam radiation

Sažetak

Učestalost karcinoma štitnjače brzo raste, ali stopa mortaliteta ostaje relativno konstantna. S obzirom na njegovu povoljnu prognozu i veliki uspjeh u liječenju najčešćih vrsta, trenutno se raspravlja o tome bi li porast učestalosti trebao promijeniti način provođenja probira i utjecati na utvrđene smjernice liječenja. U ovom radu, predstavljena su četiri najznačajnija karcinoma štitnjače i njihove mogućnosti liječenja; papilarni, folikularni, medularni i anaplastični karcinomi. Raspravlja se o prikladnom pristupu kirurškom liječenju karcinoma štitnjače, jer neki istraživači zagovaraju djelomičnu, a drugi totalnu tireoidektomiju. Postoje zagovornici profilaktičke disekcije centralnih cervikalnih limfnih čvorova koristeći se radikalnim postupcima, dok drugi stručnjaci preporučuju limfadenektomiju samo u određenim slučajevima. O primjeni radioaktivnog joda u liječenju (ablacija) i dijagnozi (skeniranja) također se raspravlja u pogledu njegove specifičnosti, osjetljivosti, doziranja i povezanosti s drugim metodama. Kemoterapija se trenutno aktivno istražuje, dok tradicionalni citotoksični lijekovi ustupaju mjesto novijom ciljanom terapijom, koja obećava smanjenje stope štetnih učinaka kao i pomoć prilikom liječenja slabo diferenciranih agresivnih karcinoma. Za palijativnu skrb neizlječivih bolesnika i liječenje udaljenih metastaza s nepovoljnim prognozama, tradicionalno se koristi vanjsko zračenje i nastavlja služiti kao rezervna terapija u slučaju tumora koji su jod negativni. Također, ukratko su predstavljene strategije praćenja pacijenata radi boljeg pregleda najnovijih podataka istraživanja, koji odražavaju opseg uspjeha terapije kao i poboljšanje kvalitete života.

Ključne riječi: Karcinom štitnjače, tireoidektomija, radioaktivna jodna ablacija, kemoterapija, vanjsko zračenje

Introduction

There are four major types of thyroid cancer, some of which are much more common than others, depending on the epidemiological situation of a given geographic area. How these cancers are treated, what and which surgery is necessary, and whether or not radioactive iodine, some sort of chemotherapy, or additional therapies are needed, depends on which type of thyroid cancer is presented. In order to recognize and plan a therapy course a definite diagnosis must be established using a variety of diagnostic procedures or their combination and appropriate methodology. When a suspicion for new neoplastic disease arises, not only a presence of the lesion needs to be visually confirmed, but also a histopathological evaluation must be performed. This enables not only the establishment of the type of thyroid cancer, but also assists in staging. Typing and staging have great importance in how they affect the planning of the therapy and the prediction of the outcome. In the following literature review epidemiology, presentation, diagnosis, treatment options and follow-up of thyroid cancer will be discussed.

EPIDEMIOLOGY

Incidence

Cancer of the thyroid gland is the most common endocrine malignancy. It accounts for 1.9% of all newly diagnosed tumours in the United States (excluding melanomas and in situ carcinomas), which translates to approximately 25,690 new cases annually (1). The incidence of thyroid cancer increased from 7.1 per 100,000 in 2000 to 17.6 per 100,000 in 2013 (2) and the reason for the sharp surge is currently debated, but inclined to be caused by improvement in diagnostic techniques, such as fine-needle aspiration (FNA) and ultrasonography, yet some argue, that the reason might be overscreening, as the detected tumours are incidental and occult (3, 4). The age-adjusted incidence rate was 11 per 100,000 persons in 2006, with a 3-fold higher rate in women; female to male ratio of 16.3:5.7 (5). The worldwide incidence varies geographically, with South Korea being the highest over 260 cases per 100 000 women aged 50-59 in 2008–2012 (a 24.2% increase in the past two decades), while Croatia having 35 cases per 100 000 women aged 55–64 years (6). Geographic differences can be explained in part by volcanic eruption activity and the resulting ash, because fluoride found there is inhibiting iodine symporter and subsequently altering uptake, such is the case in Hawaii and Iceland (7). Thyroid cancer is very rare in children under the age of 15. Annual U.S. incidence in this population is 0.2 per 100,000 girls and 0.09 boys (8). The annual incidence of thyroid cancer increases with age, peaking between 100 and 120 per million by the age of 50 to 80 (2).

Prevalence

The prevalence varies sharply among geographical areas, statistical methodology applied and population. At the 1927 International Conference on Goiter Carl Wegelin proposed, that thyroid cancer was more common in areas of endemic goiter, with frequency at autopsy varying from 1.04 percent in central Switzerland, an endemic region, to 0.09 percent in Berlin, a non-endemic region (9). Reports of autopsies vary from 0.03% to over 2% and even as high as 35.6% in Finland, when microcarcinomas

are taken into account (7, 10). The wide scatter of the results comes from the differences in histopathological protocols.

Foci less than 1 cm in diameter can be defined as papillary microcarcinomas, which can be further classified as “tiny” (5–10-mm diameter) and “minute” carcinomas (<5-mm diameter; 10). Minute papillary carcinomas are considered clinically benign and rarely exhibit any pathologic course. However, reports of distant metastases that arise from minute papillary carcinomas occasionally emerge (11).

Mortality

Over the course of the past 50 years the mortality from thyroid cancer has been decreasing. For the male population at the annual rate of -2% to -3%, with an exception for United States, where it took up in the ‘80s, and for the female population at the rate of -2% to -5%, again with the exception for U.S., UK and Australia, where it similarly increased thereafter (12). Between 2008-2012, most countries had mortality rates (age-standardized, world population) between 0.20 and 0.40/100,000 men and 0.20 and 0.60/100,000 women, where the highest were in Latvia, Hungary, the Republic of Moldova and Israel (over 0.40/100,000) for men and in Ecuador, Colombia and Israel (over 0.60/100,000) for women (11).

Distribution by Histological Type

The proportion between two main types of differentiated thyroid cancer, namely follicular and papillary depends on the dietary iodine uptake (13). Papillary cancers prevail in iodine-sufficient regions e.g., Iceland, where the proportions were 85% with papillary and 15% with follicular cancer from 1955 through 1984 (14), while in Bavaria, Germany, an iodine-deficient region, the proportions were 35% papillary and 65% follicular during 1960–1975 (15). The introduction of iodine supplementation in the endemic goiter regions resulted in an increased proportion of papillary cancers, while still improving the life expectancy (16).

Medullary carcinomas comprise nearly 5–10% of thyroid carcinomas, while 80% are sporadic and 20% familial MEN-II related. The sporadic form affects females in their

50-60’s and 50% more common than in males. MEN Ila-related medullary carcinomas present in the first and second decades of life, and MEN IIb-associated present during the first decade of life. Familial non-MEN medullary thyroid carcinomas present in the 6th decade and beyond (17).

The remainder of thyroid gland malignancies account to anaplastic cancer. Its’ incidence has declined and contributed to the reduction in overall thyroid cancer mortality. The peak incidence of anaplastic cancer is in the 7th decade with the female to male ratio of 1.5 (18).

HISTOPATHOLOGY

One cannot underestimate the importance of pathology of thyroid cancer as its' role is fundamental in the pathogenesis, management and the prospect for the patient. Thus, the histological features, essential for the classification of different tumours must be henceforth reviewed.

The term "follicular" might be confusing, as it is extensively used in many ways. All thyroid carcinomas, with the exception for medullary type, arise from follicular epithelium – the functional cell type of the thyroid gland. Another usage for the term "follicular" is a specific architectural form, synonymous with "acinar" or "vesicular". Finally, one recognizes follicular carcinoma as a distinct type of thyroid cancer.

One more important note has to be made about the capsule, to which pathologists may refer with a different regard. Normal thyroid anatomy presupposes an almost invisible, a few cells of thin layer organ capsule, which is often absent in some regions. This arbitrary toponym is used as a point of reference to classify tumours that invade beyond the organ's margins, although some prefer the usage of "extrathyroidal extension". The second capsule, namely the tumour capsule – a fibrous layer around the neoplastic epicenter, is what becomes relevant when talking about the evaluation of specific subtypes of cancers, e.g., minimally invasive follicular and Hürthle cell carcinomas (19).

Differentiated Thyroid Cancer: Papillary Carcinoma

One of the main classifications of follicular neoplasms is based on their level of differentiation. As the tumours appear well differentiated one can further subdivide them into two major groups: the papillary and follicular carcinomas.

Papillary carcinoma is distinguished by nuclear changes, such as enlargement, pseudoinclusions, hypochromasia, grooves and marked nucleoli. When fixated in formalin and cleared of chromatin the nucleus shows "Orphan Annie eyes", as well as less specific calcifications called Psammoma bodies (which should hint to look for

microcarcinomas; 19). The classic variant of this tumour has arborising papillae with fibrovascular centers.

Majority of papillary cancers do not possess a capsule and invade the parenchyma, but in around 10% of cases there is a defined fibrous capsule, otherwise presenting with a typical architecture (20). The reason why the encapsulated variant is distinct is that its' prognosis is usually better than other follicular subtypes.

As discussed above, sometimes the terminology might be ambiguous, such is the case with a follicular variation of papillary carcinoma. Its' architecture is composed of follicles, similar to follicular adenomas, yet the nuclear changes are identical to the classic papillary type of thyroid cancer (20).

In addition to nuclear changes and papillary structure some types exhibit a large cytoplasm, which makes the cells twice or more as tall. If these elongated cells comprise at least 70% of the total number it is considered a Tall Cell variant, which usually also has mitoses (19).

Rarely a papillary carcinoma shows marked sclerosis, psammoma bodies and lymphocytic infiltrates, usually involving the whole lobe or even entire gland. Because of its' specific appearance it is called Diffuse Sclerosing variant, or the aggressive variant, extending more often than the others extrathyroidally.

Differentiated Thyroid Cancer: Follicular Carcinoma

Not to be confused again with the nomenclature, follicular carcinoma is different from a follicular variant of papillary type. The follicular one is subdivided into two major variants – the Follicular and Hürthle cell. The follicular group lacks the aforementioned nuclear changes, present in papillary type, classified as either minimally or widely invasive.

The minimally invasive follicular carcinoma is macroscopically similar to follicular adenoma, yet surrounded by a well-marked fibrous capsule, unlike the latter. The tumour normally consists of microfollicles with colloid or tumour nests and diagnosed by at least one of the two criteria: invasion outside the tumour capsule, and/or invasion into neighboring blood vessels. (21)

The widely invasive carcinoma can be grossly differentiated from benign tumours by a visible to the naked eye invasion. Capsule, which is thick in the minimally invasive variant, may be indistinguishable. Aside from the similar microfollicular colloid aggregates and solid nests widely invasive carcinoma may present necrosis and mitotic activity.

Medullary Carcinoma

Medullary carcinoma arises in the middle to upper 1/3 of the thyroid – an anatomical location of the C cells. It most often arises sporadically, yet in 20% of cases it is a part of hereditary syndrome, which is more commonly bilateral and multifocal (19). Macroscopically it is well defined and usually doesn't have a capsule. Microscopically medullary carcinoma may take non-specific patterns, seen in other malignancies, yet the most common appearance is solid or with nests resembling insular carcinoma.

The cells of the tumour are spindled or plasmacytoid. Characteristically they contain pink amyloid aggregates on H&E preparations in around 80% of cases, that can be confirmed with Congo Red stain. The amyloid is revealed by polarized light after the staining, showing light green coloration. Specific, but positive in only about 80% of cases, is the immunohistochemical staining for calcitonin. Additionally, one can use neuroendocrine markers, such as chromogranin.

Undifferentiated Thyroid Cancer: Anaplastic Carcinoma

This thyroid carcinoma arises from the follicular epithelium and characterized by minimal or no differentiation, hence anaplastic. It invades widely into the perithyroidal tissues and may entirely replace the thyroid parenchyma at the time of diagnosis. Macro- and microscopically anaplastic carcinoma shows hemorrhagic regions and appears necrotic. Cytologically there is usually a pattern or a mixture of patterns, varying between spindle, squamoid and pleomorphic cells.

The spindle pattern is similar to a high-grade undifferentiated sarcoma, squamoid resembles a squamous cell carcinoma and pleomorphic, sometimes called Giant Cell, shows odd cell shapes. Nevertheless, it readily reveals malignancy and challenges

the definition of the tissue origin, as the tumour is seldom positive for specific markers. In this case clinical history becomes crucial for the determination of pathogenesis, as anaplastic carcinoma may be primary, dedifferentiated or a secondary tumour. (22)

DIAGNOSIS

Solitary Nodule

In clinical practice one frequently stumbles upon palpable nodules that require a thorough assessment. A high proportion of these findings is multinodular, despite being initially considered as solitary. Autopsy reports show up to 50% prevalence of thyroid nodules and ultrasound check-ups identify those in 13-40% of patients, that do appear clinically silent (21). In order for the nodule to be recognized by palpation its' size must reach 1 cm in diameter, otherwise smaller lesions are found on ultrasound examinations and are dubbed incidentalomas.

The differential diagnosis of a nodular finding may be attributed to a wide range of pathologies. Most of these would be colloid adenomas or simple follicular adenomas with the prevalence of 27-60% and 26-40% respectively (22). Based on the relative iodine absorbance by these tumours on a radionuclide scanning one can classify those as "hot", when they exhibit hyperfunction. Their prevalence is around 5% and there is an association with the size of the tumour and clinically significant hyperthyroidism. For instance, out of all cases with nodules smaller than 3 cm hypothyroidism was found in 2% of them, whereas in nodules greater than 3 cm hypothyroidism was found in 20% of the cases (23). Classically elevations of both T3 and T4 are seen in these autonomous lesions, yet sometimes only one of the iodothyronine subtypes may be pronounced. Rarely undetectable changes in the levels of thyroid hormones can be assessed only with a sensitive serum assay, which is why it is no rule that the toxic nodules would always exhibit apparent elevations in aforementioned molecules.

Among all the palpable nodules 10-14% represent malignancies (23, 24). Out of those majority (70-75%) are papillary carcinomas, followed by follicular (20-25%) and finally 3-5% medullary and anaplastic carcinomas. Autopsy reveals occult thyroid malignancies in 6% of cases in U.S. whose clinical significance is negligible (25).

Physical Evaluation and History

The most important risk factor for thyroid cancer formation is the patient's exposure to radiation. In order to assess its' outcome, it is crucial to determine the age at which the exposure occurred, the body region and the characteristics, such as type and dosage. The radiation causes thyroid neoplasia with a linear relationship up to 1800 rad. 16-29% of patients in U.S. who received head and neck irradiation in their childhood presented palpable nodules, among which one third were carcinomas (26). It is important to mention, that external irradiation for treatment of Hodgkin's lymphoma of more than 2000 rad or from iodine-131 for toxic goiter doesn't appear to be causing development of thyroid carcinoma.

Accelerated thyroid enlargement in women with Hashimoto's thyroiditis, especially above 50 years of age, thyroid lymphoma should be suspected. Radiologically these lesions are "cold", often accompanied by diabetes. Medullary carcinoma should be suspected as a part of MEN syndrome, when there is a family history of mucosal abnormalities, hypercalcemia or pheochromocytoma. Rarely a familial incidence of benign goiter or deaf mutism may be connected to Pendred's syndrome, increasing a chance of malignancy (22).

Although clinical symptoms are more prevalent in malignant tumours only 5-10% of cases exhibit signs of lymphadenopathy, hard nodules, pain, tenderness and/or vocal cord paralysis, all of which should raise suspicion of cancerous formation.

Fine-Needle Aspiration

This method is considered the best preoperative procedure for acquiring histopathological samples. The highest success is achieved using 22-25-gauge needles, yielding in the same time the lowest complication rate (27). False negative results usually stand at 1% and false positives at 2%. Despite not being a true needle biopsy, that is still sometimes used, FNA delivers a significantly lower morbidity (28). In order to improve the results of the procedure it is performed under ultrasound guidance. The goal is to acquire cellular material for further cytologic analysis, which helps to distinguish between benign, suspicious and malignant nodules. Overall, in the past decades the application of this method helped to reduce undesired surgical

thyroidectomies by 50%, which carries a great health and economic value (29). Another way FNA can be used is to sample lymph nodes and to measure thyroglobulin mRNA for an additional cytologic evaluation (30).

This is a minimally invasive procedure, different from needle biopsy, and considered very safe. It uses a syringe holder and plastic hub needles. There is no suction, which is essential, as the aspirated material is suspected to cause seeding.

In order to execute the procedure, we would require:

1) A syringe holder or a handle which is integral. An example would be the Cameco Syringe Pistol or the Aspir Gun.
2) Disposable plastic syringes of 10 or 20 cc. volume.
3) Disposable needles ranging from 22 to 25 gauge with a length of 1 to 1.5 inch with plastic hubs.
4) Frosted end glass slides.
5) Hemacytometer cover glass. This would be used to smear the aspirated sample on the glass slide.
6) Staining solution, commonly used one is the Diff-Quik stain.

Before the procedure begins, the patient would anesthetize the desired area with a simple ice pack. Once it is done the procedure goes as follows:

1) The nodule is pinched between the fingers of the nondominant hand.
2) The skin is disinfected using ethyl alcohol.
3) The skin is pierced perpendicularly.
4) The needle is moved back and forth until fluid is seen in the hub, if this doesn't happen, then suction might be applied using the plunger.
5) When there is 2-3 cc of aspirate, or 10 cc if the lesion firm release the plunger and withdraw the needle.
6) The aspirate clots promptly, therefore a rapid preparation of the smear is important.
7) The slide can be examined by the pathologist.

A thorough following of the steps ensures a quality preparation and yields accurate results for the establishment of a correct diagnosis.

Cytological and Biochemical Markers

The results obtained by the microscopic histopathological examination after preparation of the tissue using FNA procedure do not always deliver a definite diagnosis. Often (in 10-30% of the cases) the conclusions are ambiguous and thus require further study to avoid unnecessary surgical intervention, which otherwise leads to 75% of the patients undergo a removal of a benign lesion. In order to prevent this and identify a correct etiology a number of biochemical and molecular markers can help to discern a malignancy.

Galectin-3, a β-galactoside-binding lectin, playing a role in adhesion, cell cycle and apoptosis, was proposed as a valuable marker. Immunohistochemical staining (IHC) showed that both follicular and papillary cancers were positive for Gal-3, whereas the benign tumours appeared negative (31). In order to confirm its' presence both IHC and reverse-transcriptase polymerase chain reaction (RT-PCR) can be used. For IHC the results of a subsequent study yielded 100% sensitivity and 98% specificity (32), moreover, when the examination included minimally invasive tumours, which are problematic for standard FNA technique, this method was found to improve the sensitivity from 75% to 89% (33). RT-PCR establishment for this marker resulted in an increase of sensitivity, yet the specificity decreased under an acceptable threshold, for the gene expression is found in all of the tumours, rendering it unusable (34). Gal-3 IHC is available and useful for determination of thyroid malignancies.

Telomerase, an enzyme found is stem cells and lymphocytes, regenerates chromosomal ends that are unstable. After each cell division the lagging strand fails to complete its' synthesis, thus shortening occurs. In order to prevent cells from becoming senescent telomerase replenishes these endings. This mechanism is absent in terminally differentiated cells, such as epithelium, but exists in malignant ones, facilitating their immortalization. The development of the methodology to use telomerase as a biomarker began with a TRAP (telomerase repeat amplification protocol) – a PCR study, where no activity was detected in benign tumours in contrast with 61% of malignant ones. Unfortunately, follow up studies found a high variability in sensitivity and specificity of the assay in the distinguishment of the malignant from benign tumours, additionally to insufficient amount of material extracted by the FNA (35). Because of that the detection of telomerase activity was proposed to be assessed

by RT-PCR of the human telomerase gene (hTERT). The results of FNA specimens investigated using hTERT RT-PCR showed 93% sensitivity and 90% specificity, which serves as a helpful tool for malignancy evaluation (36).

Thyroid Peroxidase (TPO) is an enzyme, that facilitates thyroglobulin iodination, oxidation and iodothyronine coupling. It is suggested that in the progression of adenomatous lesions to cancerous its' function is lost. For this reason, TPO was examined as a biomarker for malignancy assessment using IHC staining. The obtained results showed an inversely proportional correlation between the cellular atypia and TPO expression (37). Furthermore, another study's findings presented a 100% sensitivity and 99% specificity, proving the TPO IHC staining a reliable method for distinguishing between benign and malignant nodules (38).

Cyclooxygenase-2 (COX-2) facilitates the formation of prostaglandins from arachidonic acid when induced in pro-inflammatory state by growth factors, oncogenes and carcinogens. Some associations were found between the presence of COX-2 on IHC staining and thyroid cancer, as well as the presence of COX-2 mRNA, although currently its' usefulness in diagnostic evaluation is yet to be confirmed (39).

Cadherins are glycoproteins, involved in cytoarchitecture and adhesion. A member of this group, E-cadherin, plays a role in tumour suppression. It was found to be downregulated in aggressive and undifferentiated carcinomas, but its' usefulness was proven in prognosis of the disease. A more important for diagnosis marker is the CD44 – cell surface glycoprotein, a known hyaluronic acid receptor. In malignant tissue it is altered, giving off isoforms among which is CD44v. Attempts to use isoforms v2, v3 and v6 yielded mixed results, showing a variable sensitivity and specificity rendering it inadequate as a standalone marker (40). However, the usage of CD44v6 in conjunction with Galectin-3 improved the specificity to 98% and sensitivity to 88%, resulting in 97% diagnostic accuracy, which does prove its' usefulness in the aforementioned conditions (41).

Oncofetal Fibronectin (onfFN) are glycoproteins found in extracellular matrix that serve as adhesion macromolecules. It was demonstrated after RT-PCR amplification, that onfFN expression is significantly increased in anaplastic and papillary carcinoma specimens (42). In a follow-up study the same team of researches

demonstrated a sensitivity of 96.9% and 100% specificity for RT-PCR onfFN assay (43). This a useful marker in papillary malignancy, although it doesn't distinguish follicular adenoma from carcinoma.

RET is a proto-oncogene encoding for tyrosine kinase, usually not expressed in a normal thyroid gland. The RET/PTC mutation is specific to papillary carcinoma, which suggested its' usage in the diagnosis of said tumour. Notable is that patients who underwent radiation exposure show RET/PTC mutation in both benign and malignant lesions (44). Despite its' high specificity for papillary carcinoma RET/PTC marker is still questionable in the diagnostic domain and requires further research (45).

High-Mobility Group I (HMGI) represents a family of embryonic proteins that serve as chromatin organization regulators. It is specifically found in thyroid malignancies (46). A study conducted a wide research of histological samples and determined both 100% sensitivity and specificity for IHC and RT-PCR, which showed a rather inspiring future for this marker to be diagnostically applied (47).

BRAF is the infamous serine-threonine kinase that leads to a malignant transformation. $BRAF^{V599E}$ is a specific mutation for papillary cancer, that isn't found it a normal thyroid. In FNA samples of said tumours this mutation was found in 50% of cases, where there was ultimately none in benign lesions (48). The superior specificity of those findings, although being not as frequent, may serve as a helpful tool for preoperative decision making.

The investigation of potential markers continues and their number grows every year. To emphasize the extent of ongoing research a number of promising biochemical findings, such as Epithelial Membrane Antigen, CD57, NM23, Aurora B, Ceruloplasmin, CK19 and many others might be listed. Current application of verified TPO and Galectin-3 is only the beginning. A combination of dozens and even hundreds of genes can be applied to cross-match the specimens for their identification and clearly, it is anticipated that FNA sample molecular markers will be utilized ever more.

Radionuclide Imaging

Thyroid scintigraphy is nuclear imaging of the thyroid gland in the neck. Also called a thyroid scan, this test can provide important information about the shape of the thyroid as well as the level of its function. Its' principle is based on the fact that nodules with a low malignant potential exhibit a high uptake of radioiodine, compared to normally functioning tissue. Another important feature is the low or absent uptake of the iodine tracer by cancerous lesions.

The radiopharmaceuticals that are commonly used are Iodine-131, Iodine-123 and technetium-99m pertechnetate.

^{131}I is produced from either bombardment by neutrons or recycling of fuel rods from a nuclear power plant. Its' half-life is eight days and undergoes a β-decay. It can be used for uptake measurement, imaging as well as for therapy.

^{123}I is made in a cyclotron using either a (p,5n) technique, which delivers a pure isotope with almost no admixtures of other types, or (p,2n) that has some high-energy gamma radiation, which provides a poorer image quality and higher irradiation dosage. Its' half-life is 13.6 days and decays through electron capture.

^{99m}Tc is extracted from molybdenum-99. Its' half-life is only 6 hours, which requires either a swiftly available transport to the hospital, or presence of a generator in the facility itself.

Because of high dose absorbance Iodine-131 isn't used anymore for scanning purposes. For scintigraphy with Iodine-123 we use dosages of 200-400 uCi (7.4-14.8 MBq) and the image is taken from 6 to 24 hours after the administration. For Technetium the dosage is around 10 mCi (370 MBq) and the imaging is performed shortly after 20-30 minutes (49). In order to capture the image a gamma camera with a pinhole collimator is used. An important remark has to be made on the phenomenon of "parallax" – a geometrical distortion that can alter the anatomical location, if the angles are not taken into an account when using a collimator. Thus, we need to use topographical markers on the skin. The positions in which the scan is made are anterior, left-anterior oblique and right-anterior oblique. The results help to assess

whether the nodule is hot, warm, cold, intermediate normo- or hyperfunctioning and the image completion is finalized within 30 minutes to an hour.

A study, interpreting the results of the scan, found cold nodules in 21% of patients aged 15 to 16 and in 44% of patients aged 65 and above. Thyroid cancer was found in 25% of cold nodules in the 45-65 ages group and in 25% of 65 and older (50). When the nodule is designated as intermediate, normofunctioning or warm it usually means that no abnormality was found or the function cannot be assessed. Posterior nodules can be obstructed by the normal anterior tissue, or inversely a small anterior lesion can become invisible on the background of underlying normal gland, thus cold nodules may appear warm on the scan. A report showed that about 9% of intermediate results were actually malignant (51).

Hot nodules symbolize an increased uptake. It usually means that they are hypertrophic and are under the control of thyrotropin or they can be functioning autonomously if they are dysregulated. Rarely, in 1-4% of cases such nodules harbor malignancies and will be designated as “coexisting thyroid cancer and hyperfunctioning nodule” (51). This can be explained by either their coexistence in the same gland but different positions, hyperfunctioning nodule close to an adenoma, hyperfunctioning carcinoma or a large tumour that competes with a normal tissue for the iodine uptake. Sometimes an appearance of “owl’s eye” is seen when a cold nodule is found within an autonomous hyperfunctioning area (52).

Radioiodine scans differ from ^{99m}Tc scans in that the former represents organification of iodine, while the latter signifies trapping of the tracer within the tissue. This represents a discordance between the results of the two scans, which occurs in around 5-8% of the cases (53). The argument for usage of one of the two exists. On one hand Iodine-123 yields a superior image quality, however some advocate for the usage of Technetium because of its’ low cost and rapid imaging within the first 30 minutes after administration. Although if only the Technetium scan is performed without any subsequent Iodine-123 evaluation then there is a risk to miss a malignancy in 1 in 1000 cases.

Despite the valuable utility of scintigraphy in the past, its’ role today is being surely replaced by FNA technique. One of the reasons is the insufficient ability to triage

preoperative patients to either undergo a surgery or get a further FNA examination. Not to be mistaken, scintigraphy is still valuable in assessment of hyperthyroidism, suppressed TSH or supportive in inadequate results of biopsy sampling.

Ultrasonic Imaging

Ultrasonography represents a prominent method of thyroid gland imaging and outlines the presence of nodular lesions before it is found by palpation. It possesses a great real time resolution power, undoubtfully safe, low cost and widely available. Ultrasound scanning is a subjective art; skill improves with experience. A diligent search for the solution to the clinical problem is required. The principle lies in intermittent generation of a pulse of sound wave energy that reflects from the tissue and received by the probe. The amplified frequency currently used lies between 5 and 15 MHz, which enables penetration of the tissue up to 5 cm deep and allows high resolution of structures as small as 2 mm in diameter. To minimize the distortion and provide better quality linear transducers are preferred over sector ones. In regards to the weaknesses of ultrasonography it is necessary to mention large tumours, that could cause issues with depth penetration, distortion caused by air-filled structures such as trachea, calcified deposits and substernal location of tumours. For the acquisition of the best results the patient needs to be lying supine with his neck maximally extended. Any anatomical abnormalities must be noted and the nodules of interest palpated. Scanning begins from the xiphoid process up to the chin. Tumours in patients with thyroid cancer must be examined in both transverse and longitudinal planes. One shouldn’t neglect the examination of carotid sheath for identification of enlarged lymph nodes, while adenopathy can be distinguished from esophagus when the patient is asked to swallow water, as the image is obtained in real time and the movement is seen on the screen.

Doppler imaging enhances the visualization with qualitative and quantitative analysis of the blood flow. The indication is both of the direction of flow by phase shift and the velocity by frequency shift. It is useful to rate the degree of vascularization in order to differ blood vessels from cystic spaces and hypoechoic nodules. Investigation of cervical lymph nodes with colour flow Doppler revealed a significant difference in

the vascular patterns, distinguishing benign and malignant lymphadenopathy with 93% sensitivity and 86% specificity (54). Otherwise, besides the usefulness in detection of diffuse hyperemia in patients with Grave's disease, Doppler imaging in cancer evaluation is being investigated (55).

Ultrasound-Assisted FNA is usually reserved for a range of specific conditions (56):

1) Exceptionally deep nodules in overweight, muscular or thick-framed patients.

2) Exceptionally small nodules.

3) Nonpalpable lesions.

4) Incidentalomas with risk factors.

5) Complex degenerated nodules.

6) Nonpalpable adenopathy.

There is a variety of transducers, that can assist in a certain type of sampling. The examples would be attachable needle guides or special biopsy probes. Sonography was found to be useful in aspiration of 45% of previously nonpalpable nodules, while 52% were identified only with the usage of ultrasound (57).

Ultrasonic imaging is extremely valuable in the follow up of postoperative thyroidectomy, because it can detect growing nodules way before it can be palpated, periodic screening of recurrent carcinoma, assist in surgical management and reveal residual tissue, all of which is discussed in the relevant chapters. However, by itself it cannot substitute conventional methods of diagnosis. The correlation between ultrasonic findings and histopathological analysis is only partial. Sonography doesn't reliably differentiate benign and malignant lesions, although advancements were recently made yielding 88% sensitivity and 91% specificity when using Thyroid imaging reporting and data system (TI-RADS) (58). Automatic and objective models, like the Deep Learning Radiomics of Thyroid (DLRT) for the differential diagnosis of benign and malignant thyroid nodules from ultrasound images are being currently employed with some remarkable results (59). Diagnostic imaging field is currently at the verge of revolutionary changes brought by ever growing number of neural network-

based models. It is anticipated in the near future, that many modalities will be reviewed. The increasing number of methods for data extraction are promising to utilize previous observations to deliver more precise results both qualitatively and quantitatively.

Computerized Tomography (CT) and Magnetic Resonance (MR) Imaging

Over the years, there has been an increase in the discovery of thyroid cancers, likely because of the marked increased utilization of CT and MR imaging. The application of both imaging methods of the head and neck has led to the incidental discovery of thyroid nodules, that may be as great as 20% of patients being diagnosed with thyroid cancer. As discussed previously, these incidentalomas may be found in up to 40% of the population, which raises a question as to when incidental lesions should be evaluated further for a possible thyroid cancer is extremely controversial and difficult, given the high prevalence of thyroid lesions detected by both CT and MRI. The primary role of MR and CT in the evaluation of thyroid cancer is in the follow-up of recurrent thyroid cancer.

CT is in principle an x-ray beam generator with a detector, that after a series of irradiations calculates and presents using algorithms a multidimensional image of numerous tissue slices. The total time taken to perform the modality may be under a minute. In order to enhance image quality and differ the structures of interest from the rest of the tissue contrasts can be used. However, a scintigraphic evaluation by iodine-123 can heavily alter those results for as much as 3 to 8 weeks. The advantages of CT scanners are widespread availability, ability to perform 1-3mm thick slices, flexible planar formatting and evaluation of invasion of cancer into the adjacent structures (60). The major drawbacks however are the aforementioned inability to use iodine contrast in patients undergoing therapy for thyroid cancer and obviously the radiation exposure that in itself holds a malignancy inducing potential. For those reasons, the early evaluation by CT scanning and follow up is rarely used, although CT guided radio-frequency ablation and cryotherapy is an extremely useful application.

MR differs from CT in that it doesn't use x-rays, which eliminates the risk of exposure to ionizing radiation as well as the ability to perform images in all planes without reformation. It uses a principle of electromagnetic wave generation to induce a change in the magnetic spin of the hydrogen atoms. Once the electromagnetic field is restored, relaxation of hydrogen emits its' own field, that can be captured and presented as an image of potentially molecular resolution of any depth. MR imaging typically uses T1 and T2-weighted modalities. To simplify, T1 is good for outlining structures and T2 for exposing ongoing changes in tissues. In regards to thyroid tumours the diffusion sequence modality is worth mentioning, where it helps to detect high-grade tumours such as anaplastic thyroid carcinoma (61). To enhance the detalization one uses a gadolinium contrast, unlike iodine in CT. The disadvantage of the method lies in its' slow performance and the relationship between time and resolution. For acquisition of high-quality image, the patient may need to be incapacitated for up to an hour. Pacemakers, tattoos containing metals and cochlear implants all make it incompatible with MR imaging. The cost effectiveness is inferior to CT, because for detection of 2-3 mm lymph nodes a very expensive "closed" type MR may be needed. In the follow up procedures CT is preferred over MR, yet if there is a need in cross-sectional imaging of adenopathy and evaluation of recurrence and metastasis MR is superior to CT (62).

Positron Emission Tomography

(PET) is the injection of a radionuclide, such as ^{18}F-fluorodeoxyglucose (FDG), that emits positrons. After the said positron contacts an electron a process of annihilation occurs, that results in a production of two electrons of 511 keV each. A positron camera captures these events and thus rendering of an image is possible. In order to provide accurate results by attenuation correction a CT is used, hence the common PET/CT abbreviation.

In regards to radiopharmaceuticals, usage relevant to thyroid cancer, the aforementioned FDG is widely used in oncology. Because it's essentially a glucose, it is taken up by the cells, metabolized and remains inside. For the reason that cancer cells have an increased energy demand, tracing of glucose allows for the detection of

these tumours after 1 to 2 hours. In the occasional patient with autoimmune thyroid disease, the uptake of FDG can be focal and misinterpreted as a malignancy in the thyroid (65). There is another promising isotope, Iodine-124 that has an increased resolution, allows better localization of metastasis compared to conventional imaging, confirms recurrence after surgery and could provide accurate dosimetry prior to treatment with Iodine-131 (63).

PET with FDG is a valuable test to help manage patients who have an elevated thyroglobulin (Tg) level with cancers that cannot trap iodine. The test can identify cancer sites and lead to a change in therapy in 30–60%. Optimal handling of thyroid malignancy conventionally depends on excisional success and Iodine-131 treatment. When there is a discrepancy between measured Tg and a negative scintigraphic scan we speak of an uncertainty, whether to schedule another radioiodine session or to look for a more reassuring imaging. This is where FDG-PET/CT is starring with a supreme detalization, confidence and low false positive interpretation rate (64).

The prognostic value of PET scan patient’s follow-up is discussed in the relevant chapter.

TREATMENT OPTIONS

A variety of treatment plans are available for patients with thyroid cancer. Some are standard and some are experimental. A treatment clinical trial is a research study meant to help improve current modalities or obtain information on new treatments for patients with cancer. As these show to be better, than the standard treatment, the new ones may become the standard. Generally, the planning depends on the type of cancer (invasive or non-invasive), staging, spread and markers. It involves a multidisciplinary approach – surgeons, endocrinologists, radiologists and nuclear medicine specialists.

Surgery

Papillary carcinoma has ultimately the best prognosis. First consideration that has to be made is whether the excision will be complete, namely total thyroidectomy with isthmectomy or partial. The broad recommendation for surgery is the total lobectomy. The reason is that even the smallest, less than 1 cm, cancers have a recurrence rate of 6-8%, while the mortality is still very low – 0.2% (66). When the lesions are greater than 1 cm complete thyroidectomy is recommended to almost any patient, because the recurrence and mortality rates increase proportionally. Approximately 75% of all patients are approaching surgery when diagnosed at low risk by the TNM (tumour, lymph nodes, metastasis) staging and the mortality is overall less than 5% (67). The problem with partial thyroidectomy is that statistically a multifocal and bilateral involvement occurs in 30-87% of patients, which renders the excision insufficient, increasing the risk of recurrence (68). Another point against partial approach is the reason that the postoperative management involves the assessment of tumour removal by serum thyroglobulin levels measurement and radioiodine scanning. It makes complete resection more efficient and what is more important – if the tumour reoccurs, the success rate of its' treatment with radioactive iodine drops down from 70 to only 7%, which clearly makes it way more serious than before (69). Total thyroidectomy eliminates the need for reoperation, that automatically lowers the complication rate and the need to operate on the scar tissue. The case, where a near-

total thyroidectomy is performed, is usually when the surgeon isn't sure about the viability of the parathyroid gland or the recurrent laryngeal nerve. Some thyroid tissue is left on the said structures of the contralateral side of the tumour and ablated with radioiodine postoperatively. This approach together with a subsequent thyrotropin suppression therapy gives best results in both survival and recurrence (68). Before the thyroid excision ultrasound is used to identify the lesion and lymphadenopathy. In the process of thyroidectomy, the surgeon palpates the neck lymph nodes and removes all the central and adjacent to tumour ones. If the lateral nodes are found on palpation – ipsilateral modified radical neck dissection should be performed.

There are postoperative staging scores for differentiated cancers – AGES and MACIS. To mention one, MACIS stands for Metastases, Age, Completeness of resection, Invasion and tumour Size. The scoring system is believed to help in prediction of 20-year disease specific mortality.

Follicular carcinoma is different from the more common follicular adenoma in its' invasion of organ capsule and vessels. They tend to be encapsulated and unifocal. In contrast with papillary tumours, that metastasize into the regional lymph nodes, follicular cancers involve lymph nodes in less than 10% of cases, but more often exhibit hematological spread into lungs and bones (70). Usually when a young patient is diagnosed with follicular cancer and multiple lymph node metastasis it appears that in fact, he might have the follicular variant of papillary thyroid carcinoma (FVPTC) (71). The prognosis for follicular cancer is generally worse: 5-year and 10-year disease-free survival rates are 88.4% and 75.3%, respectively (72). This difference is connected to the older age and more advanced stage at the diagnosis. Tumour size and presence of distant metastases are the most important factors. Tumours larger than 4 cm with angioinvasion and/or extensive capsular invasion would have the worst prognosis.

A subtype of follicular cancer – Hürthle cell tumour is considered malignant when presented with angioinvasion, distant metastases and capsular invasion. It tends to be multifocal and invade regional lymph, like the papillary cancer, and often reoccur after irradiation. The mortality rate for this variant is 24% against 12.6% for the classic follicular cancer, as mentioned above (73).

The surgical management is similar to papillary cancer. Experts agree that total or near-total thyroidectomy should be conducted because of the risk of distant metastases and apparently more aggressive behavior of these tumors. A problem arises with Hürthle cell cancers, because the diagnosis is usually not made by the preoperative FNA. A preliminary scintigraphic scan in addition to TSH test is made if the lesion is smaller than 3 cm. If the nodule is hot – a watchful waiting strategy can be taken, for these nodules are rarely malignant, while if the nodule is cold – a total lobectomy is recommended. As discussed earlier these nodules harbor malignancy in 20% of cases. In half of those the diagnosis can be established during the surgery and confirmed by a frozen section of a lymph node. Near-total or subtotal thyroidectomy is not as effective as a total thyroidectomy for follicular thyroid cancer. The reason is that the remnant normal thyroid tissue usually has to be ablated before possible distant metastases can be detected with radioiodine scanning.

Most of the patients have minimal capsular involvement and their prognosis is so good, that thyroidectomy proves to be a definite treatment (74). But when there is angioinvasion, with or without capsular involvement, follicular cancer is considered moderately invasive. In patients with Hürthle cell cancers the surgeon should look for nodal metastases in central neck and tracheoesophageal groove. These metastases are often untreatable by radioiodine, thus a thorough ipsilateral central neck dissection should be performed to avoid tumor recurrence in this area.

Postoperatively these patients are treated is a similar fashion to papillary cancers. Serum thyroglobulin is repeated when the patient is rendered hypothyroid in preparation for radioiodine scanning or therapeutic treatment with Iodine-131. Solitary distant metastases should be removed surgically, and radioiodine should be used to destroy and ablate any residual microscopic disease.

Medullary carcinoma is treated preferably by total thyroidectomy and a thorough central neck dissection with or without the removal of upper thymus (75). On a preliminary ultrasound examination the parathyroid glands are noted and removed only if there is primary hyperparathyroidism or some abnormality. It is important, because in up to 40% of patients these findings will influence the plan of the surgery (77). If one of the glands shows devascularization, then it should be transplanted into the neck of the patients with medullary thyroid cancer and MENII-B syndrome. In

MENII-A patients, because of the risk of hyperparathyroidism, it should be transplanted into the forearm.

In patients with palpable central and\or cervical lymph nodes and tumours greater than 1.5 cm ipsilateral modified neck dissection is recommended. The 10-year survival rate for patients with these nodal metastases is 70% (76).

Family members with RET oncogene or the ones, that have calcitonin elevation to pentagastrin or calcium stimulation, should undergo central neck dissection and total thyroidectomy before the age of 6.

Postoperatively the patients are followed with carcinoembryonic antigen and calcitonin levels. MR and CT is used to detect recurrence in the neck and mediastinum. To locate liver, bone and lung metastases a selective venous catheterization of the hepatic and cervical veins can be useful (78).

Anaplastic carcinoma is one of the most aggressive and deadly malignancies. The median survival, as mentioned earlier, is around 6 months regardless of the therapy, where patients die of suffocation from local tumour invasion. At presentation the patients have a large 5 – 10 cm fixed mass and around 30% have distant, often pulmonary, metastases (79). Most also have some well-differentiated thyroid cancer. Rarely, 1% of differentiated cancers would transform into anaplastic carcinoma.

Once anaplastic cancer is diagnosed, no curative treatment is likely. A slightly better prognosis stands for younger patients. Age less than 60, isolated thyroid tumour, female sex, surgical resection and external beam therapy were found to be favorable prognostic factors (80).

When conducting a thyroidectomy in these patients, the least involved lobe should be removed first, because it helps the surgeon to navigate around trachea. After the debulking surgery of this thyroid tumour radiation and chemotherapy with doxorubicin suggests a slightly better outcome (81).

Radiotherapy Ablation

Radioiodine ablation (RAI) refers to the destruction of residual macroscopically normal thyroid tissue in the thyroid bed after near-total thyroidectomy in patients with well-differentiated thyroid carcinoma. The behavior of follicular lesions appears to differ from papillary regarding prognostic factors associated with tumor recurrence and survival, as mentioned earlier, nevertheless, and despite the above clear differences between these two cancers, for all practical purposes, they are similarly regarded in terms of radionuclide imaging, ablation, and treatment. The objectives are to increase the sensitivity of whole-body scans (WBS) and help to interpret serum thyroglobulin levels in follow-up studies, decrease the recurrence rates and increase survival (82).

In order for RAI therapy to be effective, the patient must have a high level of thyrotropin in the blood. If the levels are insufficient or the thyroid gland is removed there are two ways to prepare the patient for RAI: 1) Cessation of thyroid hormone adjuvants for several weeks, which causes hypothyroidism and stimulates pituitary gland to release thyrotropin. This induction is temporary, but often causes symptoms like tiredness, depression, weight gain, constipation, muscle aches, and reduced concentration. 2) Endogenous thyrotropin (Thyrogen), which can supress thyroid hormone for a long period of time. This drug is given daily for 2 days, followed by RAI on the 3rd day. Most doctors additionally recommend a low iodine diet for 1 or 2 weeks before treatment. This means avoiding foods that contain iodized salt and red dye, as well as dairy products, eggs, seafood, and soy (90).

Following surgical therapy for differentiated thyroid cancer, it is needed to determine whether RAI remnant ablation should be indicated. This decision depends on two considerations; first, recurrence rates and mortality for differentiated thyroid cancer are low, at 14 and 5% over 25 years, respectively (84). Second, vast majority of patients present with intrathyroidal, node-negative disease, with lesions smaller than 2 cm. Lastly, RAI therapy in itself carries a risk of malignant transformation due to radiation exposure and an increasing number of younger patients with small tumours is being recognized.

In a wide study of US. Air Force and Ohio State University, when post-thyroidectomy RAI was compared to simple surveillance, a reduction in reoccurrence (38 vs. 16%)

and mortality (8 vs. 3%) was noted (84). However, a comprehensive meta-analysis report from 2002 showed mixed results, where 4 series demonstrated a lower recurrence rates for RAI patients, while 6 others noted no significant difference (85). Another literature review after analyzing this conflicted data summarized that: 1) RAI is not indicated in tumours smaller than 1 cm, no extrathyroidal invasion and other pathological high-risk features. 2) RAI is indicated in cases of distant metastases and marked extrathyroidal extension (86).

Dose selection comes down to the choice between dosimetric calculation and fixed dose. The American Thyroid Association states that dosimetric methods are reserved for patients with renal insufficiency, children, elderly and cases with pulmonary metastases. Dose fixed are safer and easier to implement, which makes it the most common, empiric approach (87).

Dose employment is universally agreed to be between 30 mCi (1.1 GBq) and 100 mCi (3.7 GBq). Two multi-institutional randomized trials enrolled patients with primary tumours with T1 to T3 stages, both with and without regional lymph node involvement and no distant metastases. They reported an 85 to 90% ablation success rate, using the aforementioned doses (88, 89).

Dose efficacy in a Polish randomized trial did not demonstrate differences between 30, 60 and 100 mCi in local recurrence rate at a 10-year follow up (91).

Dose toxicity, reported in the two randomized trials (88, 89), found higher rates of nausea, neck pain, lacrimal gland dysfunction, salivary gland dysfunction, and altered taste in patients treated with dosage of 100 mCi, compared to 30 mCi. The major long-term toxicities of RAI included secondary primary malignancies, sialadenitis, nasolacrimal duct obstruction, and infertility, however long-term follow-up of cohorts treated with 30 and 100 mCi doses of RAI will be necessary to determine absolute and differential risk (92).

The management of differentiated thyroid cancer is evolving as new data become available. Long-term cancer control rates between dose levels remain uncertain, that is why the risks and benefits of different doses need to be attributed to each patient, adjusting the therapy based upon clinicopathologic features and concerns. High-risk patients, including those gross extrathyroidal extension, lymph node involvement,

subtotal thyroidectomy, or with sufficient iodine uptake, higher-dose RAI therapy appears to provide better rates of ablation and cancer control.

External Beam Radiotherapy

External beam radiotherapy (EBRT) is the most common type of radiation therapy used for cancer treatment. It is limited to the usage in high-risk patients and depends on the histologic type and clinical stage of the thyroid cancer. EBRT is often used for cancers that don't take up iodine and have an extrathyroidal spread. This method delivers high-energy x-ray or electron beams to a patient's tumor. Beams are usually generated by a linear accelerator and targeted to destroy cancer cells while sparing surrounding normal tissues.

Well-differentiated cancer patients with residual tumours after attempted surgical resection do not usually benefit from RAI, thus an absorbed dose of 100 Gy is necessary to destroy a small tumour and 80 Gy to eliminate neck nodes in 74% of patients with masses less than 2 g (93). Reports suggests, that a good control is possible in patients with gross residual disease, where surgery was unsuccessful or impossible. Examples are invasion into prevertebral fascia, carotid artery and situations where loss of function is highly estimated.

EBRT as an adjuvant therapy may benefit patients with a higher risk of local recurrence and who are more likely to die from their disease. In a study, where 70 patients were identified as a high-risk group, of whom 47 received EBRT and 23 did not, discovered a higher cause-specific survival (81.0% vs 64.6%) and local-regional relapse-free rate (86.4% vs 65.7%) in patients who received beam therapy (94). In the absence of randomized data, there is still sufficient evidence to recommend EBRT, in addition to standard therapy in high-risk patients, defined as older than age of 45 with evidence of extrathyroidal invasion and gross or microscopic residual disease after resection.

Patients who have lymph node metastases with extra nodal capsular extension and local invasion of adjacent soft tissues are at high risk of disease recurrence and poorer prognosis. Although one study didn’t show a difference in survival after irradiation of

the neck nodes, local-regional relapse-free rate in patients who received external-beam RT was significantly better - 95.2% vs 67.5% respectively (95).

In treatment of distant metastases RAI therapy usually achieves a good level of success, but only 3% of bone metastases were found to show a curative rate after the ablation. High dose (50 Gy in 25 fractions) may be appropriate for a long-term control of such secondaries (96). The role of EBRT in controlling gross residual disease after surgery and in unresectable disease is being evaluated with every new study. In patients with symptomatic recurrent disease with poor performance or widespread incurable disease a shorter course irradiation may be effective to control local symptoms, such as pain, skin ulceration, and obstruction.

Medullary carcinoma with gross residual disease doesn't seem to benefit from EBRT much. No survival benefit of adjuvant irradiation with positive nodes was found, except for some improvement in local-regional relapse-free rate (97).

The treatment for metastatic disease is usually palliative and includes supportive measures, analgesic drugs, and possibly, hormonal therapy, chemotherapy, and local radiation. Unfortunately, neither the liver nor large volumes of the lung tolerate EBRT well. Thus, RT is usually reserved for painful bone metastases, where a dose of 2000 cGy in five daily fractions or 3000 cGy in 10 fractions would typically result in pain relief. Single large lung metastases causing hemoptysis or obstruction may also respond to EBRT.

Anaplastic carcinoma overall shows an improvement in survival of patients treated with adjuvant EBRT or concurrent radiochemotherapy vs. surgery alone. No prospective randomized controlled trials have been undertaken and there is no consensus on optimal management of small intrathyroidal anaplastic cancer or incidentally found tumours following surgery. After complete or near-complete resections, the best results in terms of both local control and survival appear to be achieved with the combination of surgery, EBRT and chemotherapy. A study examined 516 patients and identified age younger than 60 years, extent of disease, and the association of surgery and EBRT as positive prognostic factors. Best results are reported after maximum surgical debulking and postoperative radiotherapy (98). Since anaplastic carcinoma has a low response to chemotherapy, the irradiation

regimen for patients with good performance is 60 Gy in 40 fractions over 4-week course, with 2 fractions of 1.5 Gy daily.

In contrast with papillary and follicular carcinoma, the prognosis for patients who have developed distant metastases from anaplastic thyroid cancer is extremely poor. Therefore, external-beam radiation has an important role in palliation of bone metastases. Similarly, in patients with brain metastases, whole-brain radiation should be considered, except in the elderly, who do not tolerate such a procedure (98).

Chemotherapy

When other conventional methods, like surgery and ablation, fail, chemotherapy is being used as a single or part of combined modality in therapy of metastatic or locally advanced thyroid cancer. Mainly it is employed in anaplastic carcinoma but also used in around 20% of iodine uptake negative differentiated carcinomas. In differentiated thyroid carcinoma chemotherapy has been considered for decades to be the only systemic therapy with palliative purpose. A recent systematic review revealed that is has not been possible to find solid evidence about the efficacy of cytotoxic therapy, the results indicated that it may have some effectiveness, although this should be proven with well-designed studies using modern drugs (99).

Doxorubicin is an anthracycline, one of the earliest chemotherapeutic drugs that was reported in thyroid cancer treatment back in 1974. In the present time it is considered to be most effective at a dosage of 60 mg/m^2, while an increase in dosage to 75 and even 90 mg/m^2 can yield an additional response (100). The most important toxicity is the doxorubicin induced cardiomyopathy. The most important prediction factor for the treatment success is the patient's performance status (101). Drug's usage in combination with other chemotherapeutic agents doesn't appear to have any advantage.

Epirubicin is analogous to doxorubicin with less cardiotoxicity, yet dose limiting myelosuppression. The drug was in a study in combination with carboplatin (75 and 300 mg/m^2 respectively) achieving one complete remission, five partial and seven stable courses of disease (102).

Cisplatin makes cross-links between DNA, killing the tumour cell. In a study 5 out of 13 responded to the drug in a setting of all main thyroid types (103). Its' main toxicities are myelosuppression, nephrotoxicity and ototoxicity.

Paclitaxel stabilizes microtubules, thus inhibiting mitotic spindle and cell division. In 10 out of 20 patients with anaplastic cancer, that took part in a study, response was achieved after a continuous 96-hour infusion (104). The toxicities are myelosuppression and peripheral neuropathy.

Vandetanib is a tyrosine kinase inhibitor or RET, VEGFR-2 and EGFR. A randomized trial of patients with metastatic medullary or advanced differentiated cancer showed a 83% 6 months progression-free survival in contrast to 63% in the placebo group (105). Overall survival was not affected.

Cabozantinib is an oral tyrosine kinase inhibitor of Met, VEGFR-2, KIT, RET, Tie-2 and FLT3. Out of 330 patients enrolled in a 2013 trial the group that received the drug showed 11.2 months of progression-free survival, compared to 4 in the placebo group. Adverse effects included hypocalcemia, hypertension, fatigue and diarrhea.

Cytotoxic agents remain important as a component of multimodality therapy for anaplastic thyroid cancer. However, targeted agents have emerged as frontline therapy for the majority of patients with advanced differentiated or medullary thyroid cancers. To name a few, Pazopanib, Sorafenib and Sunitinib are ongoing clinical trials and show some promising results in the future treatment of thyroid cancer.

Follow-up

The assessment for the risk of recurrence and death can vary from annual ultrasound examinations and PET-CT to thyrotropin stimulated WBS and thyroglobulin measurements. In order to evaluate the patient's outcome and group him according to the relative risks the following factors are considered:

1) Overall health status, age and sex.
2) Characteristics of the tumour, such as size, multifocality, histological grade, localisation and/or extent of invasion and distant metastases.
3) Previous interventions, such as surgery and RAI.
4) Relative success of said intervention/s.

Once the factors are taken into account some scoring system can be applied to plan the follow-up and support. The value of these scoring systems is suggestive and helps to detect atypical cases that require a comprehensive approach.

An important part of post treatment assessment is the definition of recurrent and persistent disease. A level of serum thyroglobulin beyond 2 ng/mL in a patient that underwent total thyroidectomy and radioiodine ablation without the evidence of tumours on cross-sectional imaging is defined as biochemically persistent or recurrent. Clinically persistent or recurrent disease means a patient with identifiable on imaging tumours after being disease-free upon completion of therapy. In a large study, involving 1,503 patients that underwent total or near-total thyroidectomy, the anatomic recurrence rate was 0.6%, but the persistent disease rate was around 14% (107).

The frequency of check-ups relies on the previously collected data and staging, so the high-risk patients will receive a suitable surveillance, while low-risk would be monitored relatively seldom. Patients with one or more deteriorating factors are likely to benefit from radioiodine ablation and undergo a more attentive surveillance. Current guidelines include AJCC/UICC (American Joint Cancer Committee/Union Internationale Contre le Cancer) staging, which classifies patients as low, intermediate or high-risk of recurrent or persistent disease based on the characteristics discussed above, discarding only the response level to the previous therapy (108).

WBS yields very limited information and are found to be contradictory in their efficacy. In no case did the thyrotropin-stimulated WBS show the site of persistent tumour in a retrospective study (110). But before discarding this evaluation method it is important to note that:

1) No anti-Tg antibodies should be present (exclusion of around 25% differentiated thyroid carcinoma patients)
2) The Tg essay must be sensitive enough to detect elevation levels of 1 ng/mL
3) The previous WBS must be negative
4) The patient must belong to the low-risk group

Current guidelines suggest WBS for usage in long-term follow up of intermediate or high-risk group patients (108).

Ultrasound is found to be useful in detection of recurrent thyroid cancer in both the gland and the regional lymph nodes. It's application also assists FNA biopsy and Tg-needle washout. The rate of recurrence, discovered on FNA examinations in patients underwent thyroidectomy and RAI, was 10.3% after a mean of 45 months. Many had unstimulated serum Tg less than 2 ng/mL and WBS didn't detect most of the new lesions, while ultrasound showed a sensitivity of 94.1% (111). Negative predictive value of thyroid hormone withdrawal (Tg less than 1 ng/mL) in a neck ultrasound was 98.8% at 12 moths, whereas WBS wasn't informative (112). Ultrasounds shows a clear superiority over WBS, when it comes to low-risk patients with undetectable serum Tg.

rhTSH application in thyroid cancer surveillance is a major improvement. It has been shown to significantly reduce number of sick leaves in comparison to traditional thyroid hormone withdrawal. Among patients, who underwent near-total thyroidectomy and remnant ablation, with a thyroid hormone suppressive therapy of less than 5.0 ng/mL, 89% had THST-Tg levels less than 1 ng/mL. After rhTSH administration 18% had Tg above 2 ng/mL, yet on WBS only about 50% of these had positive results (113). A subsequent prospective study of 107 differentiated thyroid carcinoma patients with a median follow-up of about 3 years showed that a single rhTSH-Tg of less than 0.5 ng/mL had an approximately 98 % likelihood of identifying patients free of disease (114).

FDG-PET is recommended in Tg-positive, RAI scan-negative patients with an elevated Tg value higher than 10 ng/mL in order to localize recurrence. Well-differentiated cancer cells take up iodine and are amenable to Iodine-131 therapy, while less well differentiated cancer cells do not take up iodine but do concentrate FDG. In contrast, patients who are iodine negative as well as FDG-PET negative appear to have a good prognosis. When the radioiodine scan is negative, identification of a focal FDG-PET lesion can make surgery an option. The sensitivity of the scan is high and the images identify sites of cancer that lead to a change in management in 20–60% of the cases. Newer PET radionuclides such as Iodine-124 have potential for better lesion detection and more accurate dosimetry prior to therapy with Iodine-131.

Conclusion

As in every medical field, there are no closed chapters. Thyroid cancer, being one of the most common, greatly affects the lives of millions of people across the world. Understanding the pathogenesis of the disease is relevant as ever. As the new data emerges every year, changes in our approach to both diagnosis and treatment of thyroid lesions imminently come to improve the outcome and the burden of the disease. Since the introduction of nuclear medical therapies in the 40's of the last century radioactive iodine still means a great deal in making thyroid cancer one of the best treated oncologic diseases. Classic surgical excision and the subsequent remnant ablation remain the most important approach in the management of thyroid cancer, while the recent research aims to improve the details of those procedures and their appropriate application. The evidence shows how each method proves to be useful, whether it is external beam therapy, cytotoxic agents or a combination of surgery and RAI, if the understanding of the ingoing pathology is thoroughly established. Early recognition, proper typing and staging with an assistance of advanced imaging determines which therapy will be used and how exactly will it be applied. When all these necessary preconditions are met, one can expect the success to be maximal in respect to the individual patient's condition.

Acknowledgments

I would like to thank my mentor prof.dr.sc. Dražen Huić for the academic assistance and guidance, Alexandra Elbakyan for her contribution to science and my family and friends for their support along the way of my medical studies and the writing of this thesis.

References

1. Jemal A, Murray T, Ward E, et al. American Cancer Society. Cancer Statistics, 2005. CA Cancer J Clin 2005; 55:10–30.
2. Olson E, Wintheiser G, Wolfe KM, Droessler J, Silberstein PT. Epidemiology of thyroid cancer: A review of the National Cancer Database, 2000-2013. Cureus. 2019; 11:4127.
3. The epidemic of thyroid cancer in the United States: the role of endocrinologists and ultrasounds. Udelsman R, Zhang Y. Thyroid. 2014; 24:472–479.
4. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. Brito JP, Morris JC, Montori VM. BMJ. 2013; 347:4706.
5. Ortega J, Sala C, Flor B, Lledo S. Efficacy and cost–effectiveness of the UltraCision harmonic scalpel in thyroid surgery: an analysis of 200 cases in a randomized trial. J. Laparoendosc. Adv. Surg. Tech. A. 2004; 14:9–12.
6. Li M, Dal Maso L, Vaccarella S. Global trends in thyroid cancer incidence and the impact of overdiagnosis. Lancet Diabetes Endocrinol. 2020; 8:468–70.
7. Kim J, Gosnell JE, Roman SA. Geographic influences in the global rise of thyroid cancer. Nat Rev Endocrinol. 2020; 16: 17–29.
8. Parkin DM, Stiller CA, Draper GJ, Bieber CA. International incidence of childhood cancer. IARC Sci Publ 1988; 87: 1–401.
9. Wegelin C. Malignant disease of the thyroid gland and its relation to goiter in man and animals. Cancer Rev. 1928; 3:297.
10. Wartofsky L, Van Nostrand D, editors. Thyroid cancer: A comprehensive guide to clinical management. 3rd ed. New York, NY: Springer; 2016.
11. Strate SM, Lee EL, Childers JH. Occult papillary carcinoma of the thyroid with distant metastases. Cancer 1984; 54:1093–1100.
12. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, et al. Thyroid cancer mortality and incidence: a global overview: Thyroid Cancer Mortality and Incidence. Int J Cancer. 2015; 136:2187–95.
13. Lohrs U, Permanetter W, Spelsberg F, Beitinger M. Investigation of frequency and spreading of the different histological types of thyroid cancer in an endemic goiter region. Verhandl Dtsch Ges Pathol 1977; 61:268–274.

14. Hrafnkelsson J, Jonasson JG, Sigurdsson G, Sigvaldason H, Tulinius H. Thyroid cancer in Iceland 1955-1984. Acta Endocrinol 1988; 118: 566–572.
15. Lohrs U, Permanetter W, Spelsberg F, Beitinger M. Investigation of frequency and spreading of the different histological types of thyroid cancer in an endemic goiter region. Verhandl Dtsch Ges Pathol 1977; 61:268–274.
16. Farahati J, Geling M, Mader U, Mortl M, Luster M, Muller JG, et al. Changing trends of incidence and prognosis of thyroid carcinoma in lower Franconia, Germany, from 1981-1995. Thyroid 2004; 14:141–147.
17. Ledger GA, Khosla S, Lindor NM, Thibodeau SN, Gharib H. Genetic testing in the diagnosis and management of multiple endocrine neoplasia type II. Ann Intern Med 1995; 122:118–124.
18. Mazzaferri EL, Oertel YC. Primary malignant lymphoma and related lymphoproliferative disorders. In Mazzaferri EL, Samaan NA, editors. Endocrine Tumors. Cambridge, MA: Blackwell Scientific, 1993:348.
19. LiVolsi VA. Surgical pathology of the thyroid. London, England: W B Saunders; 1990.
20. Amdur RJ, Mazzaferri EL. Essentials of thyroid cancer management. Mazzaferri EL, Amdur RJ, editors. New York, NY: Springer; 2005. p.23
21. Burch HB. Evaluation and management of the solid thyroid nodule. Endocrin Metab Clin North Am 1995; 24:663–710.
22. Daniels GH. Thyroid nodules and nodular thyroids: A clinical overview. Comp Ther 1996; 22:239–250.
23. Hamburger JI. The autonomously functioning thyroid nodule: Goetsch's Disease. Endocr Rev 1987; 8:439–447.
24. Ridgway EC. Clinical evaluation of solitary thyroid nodules. In Braverman LE, Utiger RD, editors. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text, 9th ed. Philadelphia: Lippincott, Williams & Wilkins, 2004.
25. Sampson RJ, Woolner LB, Bahn RC. Occult thyroid carcinoma in Olmsted County, Minnesota. Prevalence at autopsy compared with that in Hiroshima and Nagasaki. Cancer 1974; 34:2070–2076.
26. Favus MJ, Schneider AB, Stachura ME, et al. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. N Engl J Med 1976; 294:1019–1025.

27. Oertel YC. Fine-needle aspiration of the thyroid. In Moore WT, Eastman RC, editors. Diagnostic Endocrinology, 2nd ed. St. Louis, MO: Mosby-Year Book, 1996; 211–228.
28. Harvey JN, Parker D, De P, Shrimali RK, Otter M. Sonographically guided core biopsy in the assessment of thyroid nodules. J Clin Ultrasound 2005; 33:57–62.
29. Singer PA. Evaluation and management of the thyroid nodule, Otolaryngol. Clin North Am 1996; 29:577–592.
30. Wagner K, Arciaga R, Siperstein A, et al. Thyrotropin receptor/thyroglobulin messenger ribonucleic acid in peripheral blood and fine-needle aspiration cytology: diagnostic synergy for detecting thyroid cancer. J Clin Endocrinol Metab 2005; 90:1921−1924.
31. Xu XC, el-Naggar AK, Lotan R. Differential expression of galectin-1 and galectin-3 in thyroid tumors. Potential diagnostic implications. Am J Pathol 1995; 147:815–822.
32. Bartolazzi A, Gasbarri A, Papotti M, et al. Application of an immunodiagnostic method for improving preoperative diagnosis of nodular thyroid lesions. Lancet 2001; 357:1644–1650.
33. Saggiorato E, Cappia S, De Giuli P, et al. Galectin-3 as a presurgical immunocytodiagnostic marker of minimally invasive follicular thyroid carcinoma. J Clin Endocrinol Metab 2001; 86:5152–5158.
34. Bernet VJ, Anderson J, Vaishnav Y, et al. Determination of galectin-3 messenger ribonucleic Acid overexpression in papillary thyroid cancer by quantitative reverse transcription-polymerase chain reaction. J Clin Endocrinol Metab 2002; 87:4792–4796.
35. Aogi K, Kitahara K, Buley I, et al. Telomerase activity in lesions of the thyroid: application to diagnosis of clinical samples including fine-needle aspirates. Clin Cancer Res 1998; 4:1965–1970.
36. Zeiger MA, Smallridge RC, Clark DP, et al. Human telomerase reverse transcriptase (hTERT) gene expression in FNA samples from thyroid neoplasms. Surgery 1999; 126:1195–1198.
37. Garcia S, Vassko V, Henry JF, De Micco C. Comparison of thyroid peroxidase expression with cellular proliferation in thyroid follicular tumors. Thyroid 1998; 8:745–749.

38. Christensen L, Blichert-Toft M, Brandt M, et al. Thyroperoxidase (TPO) immunostaining of the solitary cold thyroid nodule. Clin Endocrinol 2000; 53:161–169.
39. Lo CY, Lam KY, Leung PP, Luk JM. High prevalence of cyclooxygenase 2 expression in papillary thyroid carcinoma. Eur J Endocrinol 2005; 152:545−550.
40. Ermak G, Jennings T, Robinson L, et al. Restricted patterns of CD44 variant exon expression in human papillary thyroid carcinoma. Cancer Res 1996; 56:1037–1042.
41. Gasbarri A, Martegani MP, Del Prete F, et al. Galectin-3 and CD44v6 isoforms in the preoperative evaluation of thyroid nodules. J Clin Oncol 1999; 17:3494–3502.
42. Takano T, Matsuzuka F, Miyauchi A, et al. Restricted expression of oncofetal fibronectin mRNA in thyroid papillary and anaplastic carcinoma: an in situ hybridization study. Br J Cancer 1998; 78:221–224.
43. Takano T, Miyauchi A, Yokozawa T, et al. Preoperative diagnosis of thyroid papillary and anaplastic carcinomas by real-time quantitative reverse transcription-polymerase chain reaction of oncofetal fibronectin messenger RNA. Cancer Res 1999; 59:4542–4545.
44. Elisei R, Romei C, Vorontsova T, et al. RET/PTC rearrangements in thyroid nodules:studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. J Clin Endocrinol Metab 2001; 86:3211–3216.
45. Nakazawa T, Kondo T, Kobayashi Y, Takamura N, Murata S-I, Kameyama K, et al. RET gene rearrangements (RET/PTC1 and RET/PTC3) in papillary thyroid carcinomas from an iodine-rich country (Japan). Cancer 2005; 104:943–51.
46. Chiappetta G, Bandiera A, Berlingieri MT, et al. The expression of the high mobility group HMGI (Y) proteins correlates with the malignant phenotype of human thyroid neoplasias. Oncogene 1995; 10:1307–1314.
47. Czyz W, Balcerczak E, Jakubiak M, Pasieka Z, Kuzdak K, Mirowski M. HMGI(Y) gene expression as a potential marker of thyroid follicular carcinoma. Langenbecks Arch Surg 2004; 389:193–7.
48. Cohen Y, Rosenbaum E, Clark DP, et al. Mutational analysis of BRAF in fine needle aspiration biopsies of the thyroid: a potential application for the preoperative assessment of thyroid nodules. Clin Cancer Res 20004; 10:2761–2765.

49. Society of Nuclear Medicine Procedure Guideline for Thyroid Scintigraphy, version 2.0, approved February 7, 1999. Procedure Guidelines Manual, Society of Nuclear Medicine, 20003:29–32.
50. Borner W, Lautsch M, et al. Die diagnostiche bedeutung des “kalten Knotens” im schilddrusenszintigramm. Med Welt 1965; 17:892–897.
51. Ashcraft MW, Van Herle AJ. Management of thyroid nodules. II. Scanning techniques, thyroid suppressive therapy, and fine needle aspiration. Head Neck Surg 1981; 3:296–322.
52. Sandler MP, Coleman RE, Patton JA, et al. Diagnostic Nuclear Medicine, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2003.
53. Kusic Z, Becker DV, Saenger EL, et al. Comparison of technetium99m and iodine-123 imaging of thyroid nodules: correlation with pathologic findings. J Nucl Med 1990; 31:393–399.
54. Tschammler A, Wirkner H, Ott G, Hahn D. Vascular patterns in reactive and malignant lymphadenopathy. Eur Radiol 1996; 6: 473–480.
55. Fukunari N, Nagahama M, Sugino K, et al. Clinical evaluation of color Doppler imaging for the differential diagnosis of thyroid follicular lesions. World J Surg 2004; 28:1261−1265.
56. Solbiati L, Osti V, Cova L, Tonolini M. Ultrasound of thyroid, parathyroid glands and neck lymph nodes. Europ Radiol 2001; 11:2411−2424.
57. Deandrea M, Mormile A, Veglio M, et al. Fine-needle aspiration biopsy of the thyroid: comparison between thyroid palpation and ultrasonography. Endocr Pract 2002; 8:282–286.
58. Chen L, Zhang J, Meng L, Lai Y, Huang W. A new ultrasound nomogram for differentiating benign and malignant thyroid nodules. Clin Endocrinol (Oxf) 2019; 90:351–9.
59. Zhou H, Jin Y, Dai L, Zhang M, Qiu Y, Wang K, et al. Differential diagnosis of benign and malignant thyroid nodules using deep learning Radiomics of thyroid ultrasound images. Eur J Radiol 2020; 127:108992.
60. Seo YL, Yoon DY, Lim KJ, et al. Locally advanced thyroid cancer: can CT help in prediction of extrathyroidal invasion to adjacent structures? AJR. 2010; 195:240–4.

61. Kim S, Loevner L, Quon H, et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck. Clin Cancer Res. 2009;15:986–94.
62. King AD, Tse GM, Yuen EH, et al. Comparison of CT and MR imaging for the detection of extranodal neoplastic spread in metastatic neck nodes. Eur J Radiol. 2004; 52:264–70.
63. Marcus C, Whitworth PW, Surasi DS, Pai SI, Subramaniam RM. PET/CT in the management of thyroid cancers. AJR Am J Roentgenol 2014; 202:1316–29.
64. Crippa F, Alessi A, Gerali A, Bombardieri E. FDG-PET in thyroid cancer. Tumori 2003; 89:540–543.
65. Levy EG, Fatourechi V, Robbins R, Ringel MD. Thyroglobulin-positive, radioiodine-negative thyroid cancer. Thyroid 2001; 11:599–602.
66. Pearce EN, Braverman LE. Editorial: Papillary thyroid microcarcinoma outcomes and implications for treatment. J Clin Endocrinol Metab 2004; 89:3710−3712.
67. Hay ID. Papillary thyroid carcinoma. Endocrinol Metabol Clin North Am 1990; 19:545–576.
68. Loh K-C, Miller TR, Greenspan FS. Differentiated thyroid carcinomas. In Clark OH, Duh QY, Perrier ND, Jahan TM, editors. Endocrine Tumors. Hamilton, Ontario: BC Decker Inc., 2003:23–36.
69. Clark OH, Levin K, Zeng QH, et al. Thyroid cancer: the case for total thyroidectomy. Eur J Cancer Clin Oncol 1988; 24:305–313.
70. D'Avanzo A, Ituarte P, Treseler P, et al. Prognostic scoring systems in patients with follicular thyroid cancer: a comparison of different staging systems in predicting the patient outcome. Thyroid 2004; 14: 453–458.
71. Crile G Jr, Hazard JB. Relationship of the age of the patients to the natural history and prognosis of carcinoma of the thyroid. Ann Surg 1953; 138:33–38.
72. Ito Y, Hirokawa M, Higashiyama T, Takamura Y, Miya A, Kobayashi K, et al. Prognosis and prognostic factors of follicular carcinoma in Japan: importance of postoperative pathological examination. World J Surg 2007; 31:1417–24.
73. DeGroot LJ, Kaplan EL, Shukla MS, et al. Morbidity and mortality in follicular thyroid cancer. J Clin Endocrinol Metab 1995; 80: 2946–2953.

74. van Heerden JA, Hay ID, Goellner JR, et al. Follicular thyroid carcinoma with capsular invasion alone: a nonthreatening malignancy. Surgery 1992; 112:1130–1136; discussion 1136–1138.
75. Kebebew E, Kikuchi S, Duh QY, Clark OH. Long-term results of reoperation and localizing studies in patients with persistent or recurrent medullary thyroid cancer. Arch Surg 2000; 135:895–901.
76. Kebebew E, Clark OH, Medullary thyroid cancer. In Clark OH, Duh Q-Y, Perrier ND, Jahan TM, editors. Endocrine Tumors. Hamilton, Ontario: BC Decker Inc., 2003: 23–36.
77. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 2003; 134:946–955.
78. Gautvik KM, Talle K, Hager B, et al. Early liver metastases in patients with medullary carcinoma of the thyroid gland. Cancer 1989; 63: 175–180.
79. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. Cancer 2001; 91: 2335–2342.
80. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma: Treatment outcome and prognostic factors. Cancer 2005; 103:1330−1335.
81. Massart C, Barbet R, Genettet N, Gibassier J. Doxorubicin induces Fas-mediated apoptosis in human thyroid carcinoma cells. Thyroid 2004; 14:263–270.
82. Klain M, Ricard M, Leboulleux S, et al. Radioiodine therapy for papillary and follicular thyroid carcinoma. Eur J Nucl Med 2002; 29 (Suppl 2):S479–S485.
83. Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, Maurer MS, McIver B, Mullan BP, Oberg AL, Powell CC, van Heerden JA, Goellner JR: Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940–1999): temporal trends in initial therapy and long-term outcome in 2,444 consecutively treated patients. World J Surg 2002; 26:879–885.
84. Mazzaferri EL: Thyroid remnant ^{131}I ablation for papillary and follicular thyroid carcinoma. Thyroid 1997; 7:265–271.

85. Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC: A systematic review and meta-analysis of radioactive iodine remnant ablation for well-differentiated thyroid cancer: J Clin Endocrinol Metab 2002; 89:3668–3676.
86. Sacks W, Fung CH, Chang JR, Waxman A, Braunstein GD: The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. Thyroid 2010; 20:1235–1245.
87. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L: 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26:1–136.
88. Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridgi B, Bardet S, Leenhardt L, Astie D, Schvartz C, Vera P, Morel O, Benisvy D, Bournaud C, Bonichon F, Dejax C, Toubert ME, Leboulleux S, Ricard M, Benhamou E: Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med 2012; 366:1663–1673.
89. Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, Nicol A, Clark PM, Farnell K, McCready R, Smellie J, Franklyn JA, John R, Nutting CM, Newbold K, Lemon C, Gerrard G, Abdel-Hamid A, Hardman J, Macias E, Rogues T, Whitaker S, Vijayan R, Alvaraz P, Beare S, Forsyth S, Kadalayil L, Hackshaw A: Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med 2012; 366:1674–1685.
90. Radioactive iodine (radioiodine) therapy for thyroid cancer. CancerOrg n.d. https://www.cancer.org/cancer/thyroid-cancer/treating/radioactive-iodine.html
91. Kukulska A, Krajewska J, Gawkowska-Suwiriska M, Puch Z, Paliczka-Cieslik E, Roskosz J, Handkiewicz-Junak D, Jarzab M, Gubala E, Jarzab B: Radioiodine thyroid remnant ablation in patients with differentiated thyroid carcinoma (DTC): prospective comparison of long-term outcomes of treatment with 30, 60, and 100 mCi. Thyroid Res 2010; 3:9.
92. Andresen NS, Buatti JM, Tewfik HH, Pagedar NA, Anderson CM, Watkins JM. Radioiodine ablation following thyroidectomy for differentiated thyroid cancer: Literature review of utility, dose, and toxicity. Eur Thyroid J 2017; 6:187–96.

93. O' Connell M, Flower MA, Hinton PJ, et al. Radiation dose assessment in radioiodine therapy. Dose-response relationships in differentiated thyroid carcinoma using quantitative scanning and PET. Radiother Oncol 1993; 28:16–26
94. Brierley JD, Tsang RW, Panzarella T. Analysis of prognostic factors and effect of treatment from a single institution on patients treated over forty years. Thyroid 2003; 13.
95. Kim TH, Yang DS, Jung KY, et al. Value of external irradiation for locally advanced papillary thyroid cancer. Int J Radiat Oncol Biol Phys 2003; 55:1006–1012.
96. Brierley JD, Tsang RW. External-beam radiation therapy in the treatment of differentiated thyroid cancer. Semin Surg Oncol 1999; 16:42–49.
97. Martinez SR, Beal SH, Chen A, Chen SL, Schneider PD. Adjuvant external beam radiation for medullary thyroid carcinoma. J Surg Oncol. 2010; 102:175-178.
98. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer. 2005; 103:1330-1335.
99. Albero A, Lopéz JE, Torres A, de la Cruz L, Martín T. Effectiveness of chemotherapy in advanced differentiated thyroid cancer: a systematic review. Endocr Relat Cancer 2016; 23:71-84.
100. Gottlieb JA, Hill CS. Chemotherapy of thyroid cancer with Adriamycin: experience with 30 patients. N Engl J Med 1974; 290:193–197.
101. Shimaoka K, Schoenfeld D, DeWys W, et al. A randomized trial of doxorubicin vs doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985; 56:2155–2160.
102. Santini F, Bottici V, Elisei R, et al. Cytotoxic effects of carboplatinum and epirubicin in the setting of an elevated serum thyrotropin for advanced poorly differentiated thyroid cancer. J Clin Endocrinol Metab 2002; 87:4160–4165.
103. Hoskin PJ, Harmer C. Chemotherapy for thyroid cancer. Radiother Oncol. 1987; 10:187–94.
104. Ain KB, Egorin MJ, DeSimone PA. Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. Thyroid. 2000; 10:587–94.

105. Wells Jr SA, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012; 30:134–41.
106. Elisei R, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013; 31:3639–46.
107. Scuito R, Romano L, Rea S, et al. Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. Ann Oncol. 2009; 20:1728–35.
108. American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26:1–133.
109. Mazzaferri EL, Kloos RT. Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab. 2002; 87:1490–8.
110. Mazzaferri EL, Kloos RT. Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab. 2002; 87:1490–8.
111. Frasoldati A, Pesenti M, Gallo A, et al. Diagnosis of neck recurrences in patients with differentiated thyroid carcinoma. Cancer. 2003; 97:90–6.
112. Durante C, Attard M, Torlontano M, et al. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. J Clin Endocrinol Metab. 2010; 95:4882–8.
113. Wartofsky L. Management of low-risk well-differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. Thyroid. 2002; 12:583–90.
114. Kloos RT, Mazzaferri EL. A single recombinant human thyrotropinstimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab. 2005; 90:5047–57.

Biography

Roman Ritter was born in a family of medical doctors. While always feeling close to the medical field he consciously decided to take this path before his obligatory military recruitment in the Israeli Air Force. Even before the demobilization he began studying for the entrance exams, pursuing the options to study both in English and German. After completing a pre-medical course in Frankfurt, he attempted the entrance exams in both Goethe University and Innsbruck University, Austria. Unable to begin the semester for various reasons he finally began his studies at the medical faculty in Zagreb.