The evaluation of prognostic factors in differentiated thyroid cancer

Ph.D. Thesis

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1. List of abbreviations

99mTc-MIBI: technetium-99m methoxy-isobutyl-isonitrile

AJCC: American Joint Committee on Cancer

anti-Tg: thyroglobulin antibody

anti-TPO: thyroperoxidase antibody

ATA: American Thyroid Associtation

CT: computed tomography

DTC: differentiated thyoid carcinoma

ETA: European Thyroid Association

FDG/PET: fluorodeoxyglucose-positron emission tomography

FNAB: fine needle aspiration biopsy

FTC: follicular thyroid carcinoma

FT-UMP: follicular tumor of uncertain malignant potential

HE: hematoxylin and eosin

MEES: Hungarian Health Care Standards

MRI: magnetic resonance imaging

NIFTP: noninvasive follicular thyroid neoplasm with papillary nuclear features

NPV: negative predictive value

PET: positron emission tomography

PNST: peripheral nerve sheath tumors

PPV: positive predictive value

PTC: papillary thyroid carcinoma

RAI: radioiodine

RECIST: Response Evaluation Criteria In Solid Tumors

rhTSH: recombinant human TSH

SPECT/CT: single-photon emission computed tomography

SPSS: Statistical Package for the Social Sciences

T3: triiodothyronine

T4: thyroxine

Tg: thyroglobuline

TKI: tyrosine kinase inhibitor

TNM: tumor-node-metastasis

TSH: thyroid-stimulating hormone

UICC: Union for International Cancer Control

US: ultrasound

WBS: whole-body scan

WDT-UMP: well differentiated tumor of uncertain malignant potential

WHO: World Health Organization

2. Differentiated thyroid cancer

2.1. Definition and classification

Thyroid cancer is rare among human malignancies, account for approximately 1-2% of all malignancies, but it is the most frequent endocrine cancer [1]. A new pathological classification was introduced in 2017 by the World Health Organization (WHO) (Table 1). Papillary (PTC) and follicular (FTC) thyroid cancers, also known as differentiated thyroid carcinomas (DTC), belong to the primary thyroid tumors and derive from the thyroid follicular epithelial cells. The word 'differentiated' refers to that the cancer cells look and act in some respects like normal thyroid cells. PTC and FTC account for more than 90% of all thyroid cancers. The DTC have a relatively good prognosis with proper treatment, the 10-year survival is above 90% [2], however, there are several cases in which rapid progression and poor outcome can be perceived. There is an urgent requirement to better understand biological behavior of thyroid cancers, and to find reliable prognostic factors. In the 2017 WHO classification, the borderline thyroid tumors have been distinguished for the first time {follicular tumor of uncertain malignant potential (FT-UMP), well differentiated tumor of uncertain malignant potential (WDT-UMP), noninvasive follicular thyroid neoplasm with papillary nuclear features (NIFTP)}. Borderline tumors are equivalent to carcinoma in situ in other organs. They are placed between follicular adenoma, follicular carcinoma or follicular variant of PTC. In the new classification 15 variants of PTC are described. Many of them have worse prognosis than the classical variant. The exact prognostic significance of the rare variants is not well-characterized. The Hobnail variant was introduced as a new entity. FTC are grouped being minimally invasive, angioinvasive and widely invasive. Hürthle-cell tumors are categorized as a separate entity. This category includes Hürthle-cell adenoma and Hürthle-cell carcinoma which were previously classified as oncocytic variants.

Table 1 - Classification of malignant thyroid tumors (WHO 2017) [3]

Follicular adenoma

Hyalinizing trabecular tumour

Other encapsulated follicular patterned thyroid tumours

- Follicular tumours of uncertain malignant potential
- Well differentiated tumour of uncertain malignant potential
- Noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Papillary thyroid carcinoma

- Papillary carcinoma
- Follicular variant of PTC
- Encapsulated variant of PTC
- Papillary microcarcinoma
- Diffuse sclerosing variant
- Tall cell variant
- Cribriform-morular variant
- Hobnail variant
- Papillary carcinoma with fibromatosis/fasciitis-like stroma
- Solid/trabecular variant
- Spindle cell variant
- Clear cell variant
- Warthin like variant
- Columnar cell variant of PTC
- Oncocytic variant of PTC

Follicular thyroid carcinoma

- FTC, minimally invasive
- FTC, encapsulated angioinvasive
- FTC, widely invasive

Hürthle (oncocytic) cell tumours

- Hürthle cell adenoma
- Hürthle cell carcinoma

Poorly differentiated thyroid carcinoma

Anaplastic thyroid carcinoma

Squamous cell carcinoma

Medullary thyroid carcinoma

Mixed medullary and follicular thyroid carcinoma

Mucoepidermoid carcinoma

Sclerosing mucoepidermoid carcinoma with eosinophilia

Mucinous carcinoma

Ectopic thymoma

Spindle epithelial tumour with thymus-like differentiation

Intrathyroid thymic carcinoma

Paraganglioma and mesenchymal / stromal tumours

- Paraganglioma
- Peripheral nerve sheath tumors (PNST)
  - *Schwannoma*
  - *Malignant PNST*
- Benign vascular tumours
  - *Haemangioma*
  - *Cavernous haemangioma*
  - *Lymphangioma*
- Angiosarcoma
- Smooth muscle tumours
  - *Leiomyoma*
  - *Leiomyosarcoma*
- Solitary fibrous tumour

Hematolymphoid tumours

- Langerhans cell histiocytosis
- Rosai-Dorfman disease
- Follicular dendritic cell sarcoma
- Primary thyroid lymphoma

Germ cell tumours

- Benign teratoma
- Immature teratoma
- Malignant teratoma

Secondary tumours

The poorly DTC is also a separate entity, defined as malignant follicular cell neoplasia with limited evidence of follicular cell differentiation. Its clinical behavior is intermediate between well-differentiated DTC and anaplastic carcinoma. The wide diversity of biological behavior of thyroid tumors is well represented in the new classification [3].

The most common system used to describe the size and extent of the DTC in the surrounding tissues is the tumor-node-metastasis (TNM) classification.

1) **T** indicates the size of the primary tumor and whether it has grown into nearby areas.
2) **N** describes the extent of spread to nearby (regional) lymph nodes.
3) **M** indicates whether the cancer has spread (metastasized) to other organs of the body (the most common sites of spread of thyroid cancer are the lungs, the liver, and the bones).

The Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) have adopted the 8th TNM classification system, which is available from January 1, 2018 (Table 2 and 3). Several modifications have been included in the updated 2017 TNM staging system, which are the followings:

1) The age at diagnosis cutoff was raised from 45 to 55 years of age.
2) Regional lymph node metastases and microscopic extrathyroidal extension were removed from the definition of T3 disease.
3) T3a is a new category for tumors >4 cm confined to the thyroid gland.
4) T3b is a new category for tumors of any size demonstrating gross extrathyroidal extension into strap muscles.
5) Level VII lymph nodes, previously classified as lateral neck lymph nodes (N1b) were reclassified as central neck lymph nodes (N1a) to be more anatomically consistent and to facilitate uniform coding for tumor registrars, clinicians, and researchers.

6) The presence of distant metastases in older patients is classified as IVB, rather than IVC disease.

Compared with the 7th edition, the changes downstage many patients into lower stages, more accurately reflecting their lower risk of thyroid cancer mortality. The new, updated system classifies fewer patients as having stage III or IV disease, but conveys a poorer prognosis for those who do [4].

Table 2 - TNM Classification System for Differentiated Thyroid Cancer (8th edition) [4]

Tx	Primary Tumor Cannot be Assessed
T0	No evidence of primary tumor
T1	Tumor size maximum 2 cm, limited to the thyroid
T1a	Tumor size maximum 1 cm, limited to the thyroid
T1b	Tumor size >1 cm up to a maximum of 2 cm, limited to the thyroid
T2	Tumor size >2 cm up to 4 cm, limited to the thyroid
T3	Tumor size >4 cm, limited to the thyroid, or any tumor with macroscopic extrathyroidal extension (Musculus sternohyoideus, Musculus sternothyreoideus, Musculus omohyoideus)
T3a	Tumor size >4 cm, limited to the thyroid
T3b	Any tumor with macroscopic extrathyroidal extension (M. sternohyoideus, M. sternothyreoideus, M. omohyoideus)
T4a	Any tumor size with extrathyroidal extension beyond the thyroid capsule and invasion of subcutaneous soft tissue, larynx, trachea, esophagus and/or recurrent laryngeal nerve
T4b	Any tumor size with invasion of prevertebral fascia, mediastinal vessels or carotid artery
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
N1a	Lymph node metastases unilateral in level VI or upper mediastinum
N1b	Metastases in other unilateral, bilateral or contralateral cervical lymph nodes (level I, II, III, IV and V) or retropharyngeal
Mx	Distant metastases not assessed
M0	No distant metastases
M1	Distant metastases

Table 3 - TNM Classification System for Differentiated Thyroid Cancer (8th edition) [4]

Patient age < 55 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Patient age 55 years or older			
Stage I	T1a, T1b, T2	N0	M0
Stage II	T3	N0	M0
	T1, T2, T3	N1	M0
Stage III	T4a	Any N	M0
Stage IV/A	T4b	Any N	M0
Stage IV/B	any T	Any N	M1

2.2. Epidemiology

The worldwide incidence of thyroid cancer has continuously increased during the last few decades. This rise can be attributed to the increased diagnosis of occult cancers through the use of neck ultrasound and other techniques of diagnostic neck imaging [5-9]. Although the use of improved techniques leads to earlier and more accurate diagnosis, it may result in overdiagnosis and overtreatment [7].

In the United States, the number of diagnosed thyroid cancer cases increased significantly between 2000 and 2005, with the most common subtype being DTC. According to earlier reports, predominantly young people (20 to 40 years) were affected, but in the last decade people with the age group 45 to 65 were the most affected. The continuous increase in incidence was demonstrated in all age groups. On average, in one in two hundred and fifty people the disease is randomly detected, however the microscopic form of the disease without any clinical relevance is even more common. During the autopsy, microscopic thyroid cancer was found in 13% of patients. In the United States, there were projected to be 56 870 new cases of thyroid cancer, while there was an estimated 2010 deaths from thyroid cancer in 2017.

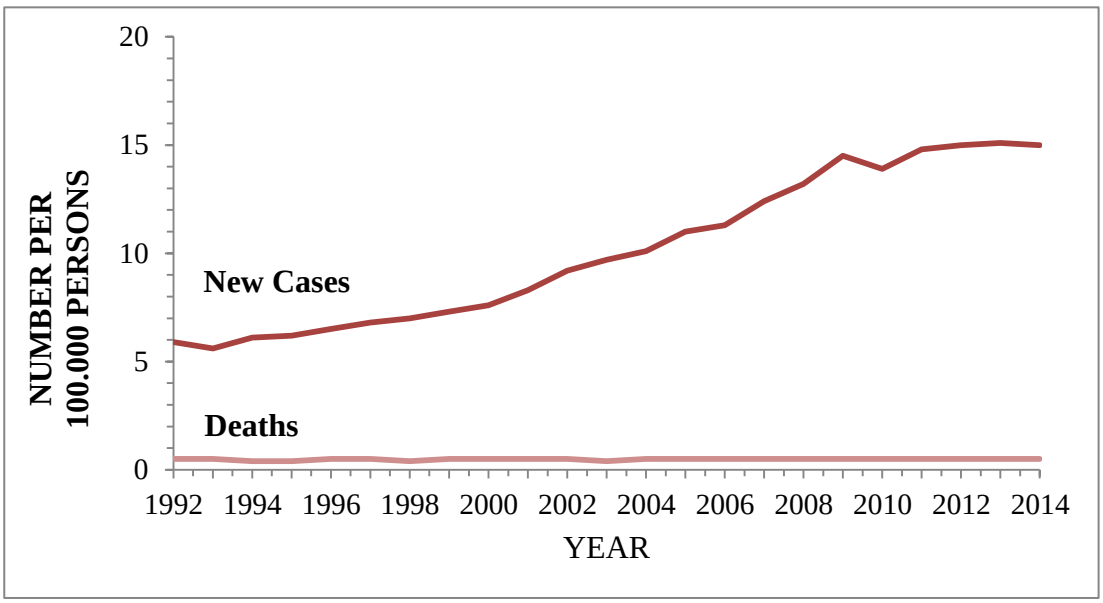


Figure 1 - Incidence and mortality data between 1992 and 2014 in the United States [10]

The incidence of thyroid cancer prior to the mid 1990s was relatively stable, approximately 5/100 000. The incidence then increased to 15/100000 in 2014, according to the last available data (Figure 1) [10]. Women have seen the highest increase in incidence, with 22.2 new cases per 100 000 people diagnosed in 2014. Between 2007 and 2013 the 5-year survival rate was 98.2%. The rise in incidence has been due almost entirely to PTC [11].

The international incidence trends are similar regarding the increasing incidence of thyroid cancer. In high income and developing countries the incidence of thyroid cancer has tripled or more over the past 30 years (Figure 2) [12]. Higher access to health care can be one of the main driver of increased detection, however a real increase also should be considered.

In Hungary, in the 1980's 240 new cases were found per year, while in 2014 approximately 800 new cases were registered by the National Cancer Registry and Biostatistics Center [13].

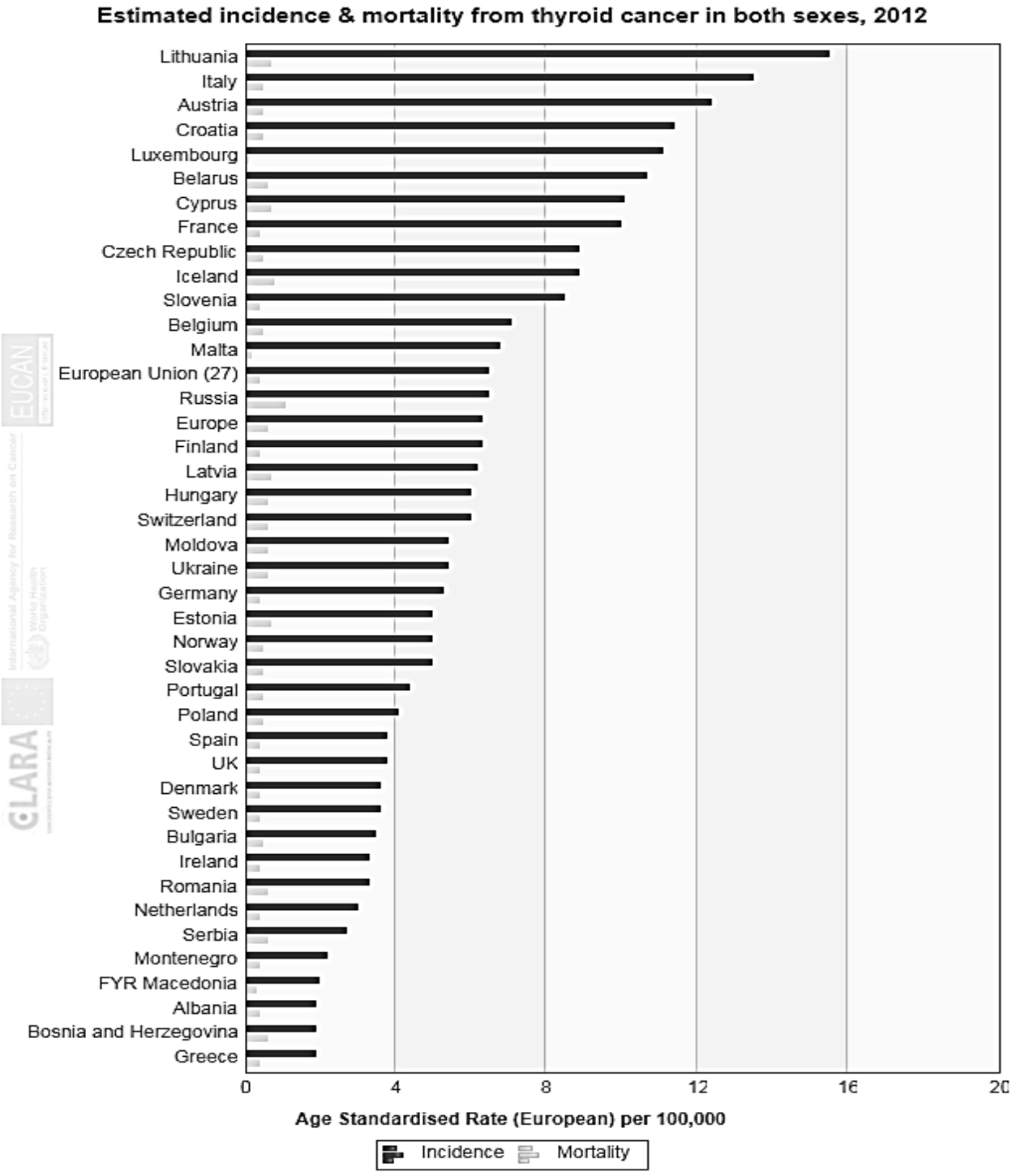


Figure 2 - The estimated incidence and mortality from thyroid cancer in both sexes in 2012 [12]

2.3. Etiology and pathogenesis

Although the etiology of thyroid cancer remains unknown and the reasons for the worldwide increase in its incidence are not well understood, exposure to ionizing radiation in childhood and a medical history of goitre or thyroid nodules have been consistently associated with an increased risk. Young children are more susceptible to ionizing radiation because of the accelerated growth of the thyroid at this age [14]. In many studies, the incidence of thyroid cancer among children (aged 0–14 years) increased remarkably after the Chernobyl disaster in 1986 in the Ukraine and Belarus [15-16]. Unlike childhood exposure, the evidence of deleterious effect of ionizing radiation in adult life and thyroid cancer is conflicting [15-17]. Areas such as French Polynesia, Hawaii, Iceland, New Caledonia, and the Philippines have the highest rates of thyroid cancer in the world, although they have not been affected by the nuclear fallout. These regions are characterized by the presence of numerous volcanos [18-19] and conjectures have been made that some factors in these volcanic areas may act as endocrine disruptors and carcinogens. However, how the volcanic environment may affect the carcinogenesis process in the thyroid is unknown.

Iodine intake is essential for the function of the thyroid and iodine deficiencies or excesses have been related to thyroid cancer, although not consistently [20]. Positive correlations between endemic areas for goitre, an abnormal enlargement of the thyroid gland caused by iodine deficiency, and thyroid cancer have been reported in England, Sweden, and Wales, but no such association was found in the USA. In contrast, regions where the intake of iodine is high, such as Hawaii and Iceland, have a high incidence of thyroid cancer, although exposure to volcanic activity could also explain the observed rates [21]. Iodine intake may influence the distribution of thyroid cancer by histological subtypes [6]; FTC is found more frequently in iodine-deficient areas whereas PTC is more common in areas receiving iodine prophylaxis [6, 14, 21-23].

Hormones may also affect the development of thyroid carcinoma. The thyroid gland is composed mainly of follicular cells that contain thyroglobulin (Tg), a receptor protein for iodine, and the synthesis of thyroid hormones depends on the availability of iodine and Tg [24]. Thyroid-stimulating hormone (TSH) is the major growth factor for thyroid cells and is involved in the regulation of thyroid hormones, thyroxine (T4) and triiodothyronine (T3), the maintenance of thyroid-specific gene expression, and glandular growth [14, 25]. TSH levels are particularly high during puberty and pregnancy [6, 14, 26] and iodine deficiency can also increase the levels of TSH [6]. Some evidence has suggested that patients with nodular thyroid disease have a higher concentration of TSH and therefore might have an increased risk of thyroid carcinoma, although the results are contradictory [27, 28]. DTC is more common in women, which assume the role of sex hormones in the development of thyroid cancer, however, the relationship between sex hormones and thyroid cancer remains unclear.

Genetic background and familial predisposition may also play a role in the development of thyroid cancer. Most PTCs and FTCs are sporadic, although familial tumours may account for 5% of all thyroid tumours [27, 29, 30]. Autosomal dominant genes involved in Gardner's syndrome, Cowden disease, and Carney complex, and autosomal recessive genes involved in Werner syndrome have been associated with non-medullary thyroid carcinoma [27, 31]. Although some evidence suggests a familial predisposition for DTC, this possibility should be given careful consideration because familial associations do not necessarily differentiate between inherited susceptibility caused by a single gene and the concurrence of multiple weak susceptibility genes [30].

Although the previously mentioned factors may play significant role in the etiology of DTC, the dramatic growth of incidence can not be explained by these. The role of chemical carcinogens is also should be considered [32].

In the pathogenesis of thyroid cancer several major signalling pathways and related molecular derangements play significant role. The effects of growth factors are realized through the signal pathways. They interact with membrane receptors belonging to the tyrosine kinase family. Activation of receptor genes increases the effect of growth factors, thus signaling increases. This group includes *met* oncogenes, *ret*/PTC oncogenes and *trk*. In the intracellular signaling disorders, the role of *ras* and b-*raf* oncogenes can be mentioned. B-raf600E mutation occurs in approximately 45% of PTCs. There is also a role for transcription factors, fusion genes. The mutation of the tumor suppressor p53 leads to inactivation and can be detected for example in the form of anaplastic disease. Activation of these pathways constitutes the primary oncogenic mechanism that promotes the development and progression of thyroid cancer. Many of these molecular alterations represent novel diagnostic and prognostic molecular markers and therapeutic targets for thyroid cancer, which provide unprecedented opportunities for further research and clinical development of novel treatment strategies for this cancer [33].

2.4. Clinical symptoms and diagnosis

In the previous history of the patient, the risk of malignancy is influenced by the following conditions: gender, age, localized radiotherapy for the cervical region, a family history of thyroid cancer, radioiodine (RAI) therapy, congenital genetic predisposition, iodine supply and etc. During physical examination thyroid cancer appears as a palpable and painless mass in the thyroid gland. In most cases, patients are asymptomatic, but in the case of large tumors they can complain cervical dyscomfort, dysphagia or hoarseness (palsy of the recurrent laryngeal nerve). The palpation findings may also have significance in the differential diagnosis, as there are many factors in the background of painful nodules, including acute, subacute thyroiditis, bleeding cyst. A malignant tumor can grow rapidly and maybe associated with cervical lymphnode enlargement. The metastatic potention of PTC is primarily

lymphogenic, while follicular carcinoma is haematogenic. The former occurs in the cervical and mediastinal lymph nodes, the most common distant metastases are in the lungs. The sights of distant metastases in FTC are the lungs and the bone. Sometimes the discovery of lymphnode metastases leads to the diagnosis of thyroid cancer. Bone metastases are characterized by pain, pathological fracture (underlying osteolytic processes) and lateral spinal cord compression. The bone metastases are most commonly found in the vertebrae, ribs and hip bone [34].

Different laboratory parameters such as TSH, T_4, T_3, thyroglobulin antibody (anti-Tg) and thyroperoxidase antibody (anti-TPO) provide useful information about the thyroid function and presence of thyroiditis. When monitoring laboratory parameters, thyroid hormones may be in the normal range unless there is a simultaneous thyroiditis. Serum Tg level before the operation has little importance in the diagnosis of thyroid cancer, except advanced metastatic disease. However, Tg and anti-Tg levels are fundamental to detect persistence or recurrence of the tumor during the follow-up investigations. The sensitivity of Tg can be increased by eliminating TSH suppression (levothyroxine withdrawn) or recombinant human TSH (rhTSH). The presence of circulating antithyroglobulin antibodies may cause false negative results, so parallel measurement of Tg and anti-Tg is required.

Fine needle aspiration biopsy (FNAB) is the best way to detect malignancy. According to recent studies, 70% of thyroid biopsies are benign, 5% malignant, 15% non-diagnostic, 10% unspecified or "suspicious".

There are many imaging studies that can provide valuable information to make a diagnosis, including cervical ultrasound (US), ^{99m}Tc pertechnetate, ^{99m}Tc-MIBI (technetium-99m methoxy-isobutyl-isonitrile) scintigraphy, CT (computed tomography), MRI (magnetic resonance imaging) and PET (positron emission tomography). Routine cervical US plays a major role in determining the size and location of tumor and cervical metastases. The

echosphere in the thyroid gland may indicate malignancy. PTCs are characterized by microcalcification, which is depicted as echogenous area [35]. Thyroid cancers are cold on thyroid scintigraphy with ^{99m}Tc pertechnetate, which can help to detect the location of the tumor, but this method otherwise has no role in the differential diagnosis, as more than 90% of thyroid nodules are cold on scintigraphy. The increased uptake of MIBI by thyroid nodules (which are cold on ^{99m}Tc pertechnetate scintigraphy) increased the risk of malignancy. CT and MRI are used during the staging investigations and play a key role in the localization of lung, bone and other metastases. Iodine accumulating metastases of thyroid cancer usually are negative on fluorodeoxyglucose-positron emission tomography (FDG-PET) scintigraphy: the increased FDG-uptake of metastases means the dedifferentation of the tumor and usually associated with the lack of iodine accumulating capability. PET/CT has no primary role in the diagnosis, however FDG positive thyroid nodules maybe incidental findings during PET imaging with other indications. The important role of PET/CT is to detect metastases in case of disproportionally high Tg level and without iodine accumulation on scintigraphy.

2.5. Treatment and follow-up

2.5.1 Surgery

Surgery is the primary mode of therapy for patients with DTC. The surgical approach depends on the extent of the disease. If the tumor diameter is less than 1 cm and there is no extrathyroidal extension or lymph node involvement, a thyroid lobectomy is preferred. According to the new American Thyroid Association (ATA) guideline, in case of 1-4 cm tumor without extrathyroidal extension and lymph node metastases, the initial surgical procedure can either be a total thyroidectomy or thyroid lobectomy. Total thyroidectomy would be chosen either based on patient preference, the presence of ultrasonographic abnormalities in the contralateral lobe (nodules, thyroiditis in the contralateral lobe, or

nonspecific lymphadenopathy that will make the follow-up difficult), or on a decision by the treatment team that radioiodine therapy may be beneficial either as adjuvant therapy or to facilitate follow-up. Total thyroidectomy is recommended if the primary tumor is ≥4 cm in diameter, there is extrathyroidal extension of tumor, or there are metastases to lymph nodes or distant sites. Preoperative US plays an important role in the evaluation of the central and lateral neck lymph nodes in order to plan the surgical procedure. For patients with clinical evidence of central or lateral node metastases, therapeutic regional lymph node dissection should be performed. Prophylactic central compartment lymph node dissection should be considered in case of advanced primary tumor (pT3 or pT4) or if the lateral neck lymph nodes are affected. Postoperative complications can be metabolic (eg, hypoparathyroidism) and anatomic (eg, laryngeal nerve damage) changes, although with an experienced surgeon these complications are rare [36].

2.5.2 Risk stratificaton

After surgery, the presence or absence of persistent disease and risk for recurrent disease should be assessed in order to determine the need for additional treatment, in particular radioiodine therapy. Typically, a serum TSH and a nonstimulated serum Tg are obtained approximately four to six weeks after thyroidectomy or lobectomy in order to better define the postoperative disease status. The optimal cutoff value for either a stimulated or nonstimulated postoperative Tg four to six weeks after surgery is not clearly established. Different risk stratification systems are used by the ATA (2009, 2015) and the European Thyroid Association (ETA, 2006) to estimate mortality and risk of recurrence. Risk stratification systems incorporate data from cancer related factors, clinical features, results of first whole-body scan (WBS) after radioiodine therapy and serum Tg level. The evaluation of response to initial therapy during the follow-up is especially important; risk categories may change during

the course of disease. The reclassification of patients based on post-radioiodine therapy imaging influences the management of the disease and the intensity of follow-up.

According to the ATA risk stratification system, patients can be categorized as (1) low risk, if there are no local or distant metastases, all macroscopic tumor has been removed, no tumor invasion of local regional tissues, no aggressive histology or vascular invasion, no RAI uptake outside the thyroid bed on the first posttreatment WBS are present; (2) intermediate risk, if there are microscopic invasion of the tumor into the perithyroidal tissue, or cervical lymph node metastases are present, or there is RAI uptake outside the thyroid bed on the first posttreatment WBS, or aggressive histology or vascular invasion, and (3) high risk, if there is macroscopic tumor invasion, or incomplete tumor resection, or distant metastases, or thyroglobulinemia out of proportion to what is seen on the posttreatment scan [36].

According to the ETA risk classification the risk is (1) very low if the tumor is unifocal T1 (≤1cm) N0M0 and there is no extension beyond the thyroid capsule; (2) low, if the tumor is T1 (>1cm) N0M0, or T2N0M0, or multifocal T1N0M0; (3) high if the tumor is any T3; any T4; any T with N1 or any M1 [1]. Postoperative management based on risk classification includes treatment with thyroid hormone suppressive therapy and radioiodine therapy, and it depends upon the risk of recurrence or persistent disease.

2.5.3 Pharmacotherapy

After thyroidectomy, whether or not radioiodine therapy is administered, L-thyroxin should start in most patients to prevent hypothyroidism and to minimize potential TSH stimulation of tumor growth. According to the ATA recommendations, initial thyroid hormone suppression therapy is based upon the risk of disease recurrence (Table 4).

Table 4 - Initial TSH target ranges based on ATA risk categories

	low risk	intermediate risk	high risk
after thyroidectomy with detectable seTg (with or without remnant ablation	0.1 - 0.5 mU/L	0.1 - 0.5 mU/L	<0.1 mU/L
after thyroidectomy with undetectable seTg (with or without remnant ablation) after lobectomy	0.5-2.0 mU/L		

Low risk patients who underwent lobectomy, thyroid hormone treatment may be unnecessary if a patient can maintain the TSH in this range [36].

During the long-term follow-up period, target TSH levels are based on response to therapy, further modified by comorbid conditions that increase the potential risks of prolonged TSH suppression (such as atrial fibrillation, older age and osteoporosis) (Figure 3).

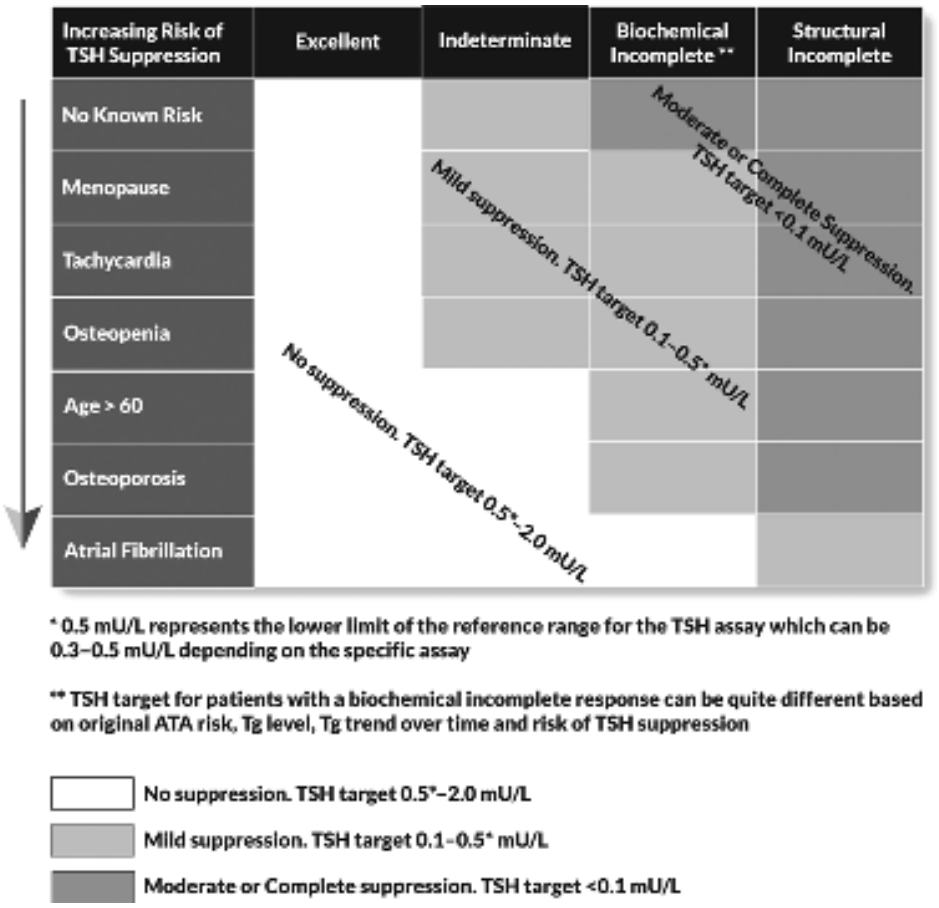


Figure 3 - TSH target levels for long-term thyroid hormone therapy [36]

The reduction of serum TSH levels to below the normal range may decrease morbidity and mortality in patients with DTC, although this theory has not been proven. There are controversial data; some studies suggested that greater TSH suppression was associated with improved progression-free survival, while some others did not find any difference between suppressive versus replacement therapy.

These findings, considering the risk of overly aggressive L-thyroxin therapy (including the potential for acceleration of bone loss, atrial fibrillation or cardiac dysfunctions), emphasize the importance of tailoring the L-thyroxin dose to the extent of the disease and the likelihood of recurrence.

2.5.4 Radioiodine therapy

After thyroidectomy, RAI treatment is administered to ablate residual normal thyroid tissue, provide adjuvant therapy of subclinical micrometastatic disease, and provide treatment of clinically apparent residual or metastatic thyroid cancer. The risk of recurrence or persistent disease determines whether RAI treatment is neccesary or not. RAI is routinely administered after total thyroidectomy in high-risk patients and in selected intermediate-risk patients, depending upon specific tumor characteristics (eg, microscopic invasion into the perithyroidal soft tissue, clinically significant lymph node metastases and etc.).

According the 2015 ATA guidelnie, in low-risk disease RAI therapy for remnant ablation is not routinely recommended. Previously, this practice was followed in the case of unifocal, <1 cm tumors without aggressive histology. However, 2015 ATA guideline considered the remnant ablation in all other tumor stages [36]. With the increasing incidence of low risk thyroid cancer, the probability of overtreatment became an important issue, although the proper selection of patients for remnant ablation is still questionable. Nowadays postoperative RAI ablation is suggested to selected intermediate-risk patients (microscopic invasion into the

perithyroidal soft tissue; clinically significant lymph node metastases, vascular invasion or aggressive histologic subtypes such as tall cell, columnar cell, insular, or poorly differentiated histologies). Previously the intermediate risk was a definitive indication for RAI therapy [1]. Postoperative RAI ablation is strongly recommended to patients with high-risk disease, including patients with distant metastases, macroscopic tumor invasion, and/or incomplete tumor resection with gross residual disease.

2.5.5 Patient follow-up

Follow-up strategies are based upon the patient's risk of recurrence and the reassessment of response to therapy at each follow-up visit. It is important to recognize that initial risk estimates may need to change as new data are accumulated during follow-up. The response to therapy is determined primarily with ultrasonography and measurements of serum Tg or anti-Tg antibody. According to the follow-up results, patients have excellent, biochemical incomplete, structural incomplete or indeterminate response (Table 5) [37, 38].

Table 5 – Evaluation of response to therapy

Excellent response	no clinical, biochemical or structural evidence of disease (on-thyroxin Tg<0,2 ng/ml, stimulated Tg<1 ng/ml)
Biochemical incomplete response	abnormal Tg (on-thyroxin Tg >1 ng/ml, stimulated Tg >10 ng/ml) or rising anti-Tg antibody levels in the absence of localizable disease
Structural incomplete response	persistent or newly identified loco-regional or distant metastases
Indeterminate response	nonspecific biochemical findings without structural evidence of disease (on-thyroxin Tg: 0,2-1 ng/ml, stimulated Tg: 1-10 ng/ml, anti-Tg positivity with stable or declining antibody titer)

Reclassification allows to tailor ongoing management recommendations to the current clinical status. In the first year after thyroidectomy or lobectomy, neck ultrasound, TSH and on-thyroxine seTg levels help the detection of possible persistent or recurrent disease [36, 39]. In

this period seTSH and on-thyroxine Tg level is generally measured every three to six months, with ultrasound at 6- to 12-month intervals depending on initial risk assessment (Table 6).

Table 6 - Follow-up during the first year after thyroid surgery [36]

	Risk of recurrence		
	Low	*Intermediate*	*High*
Non-stimulated Tg	4-6 weeks 3-6 months 9-12 months	4-6 weeks 3-6 months 9-12 months	4-6 weeks 3-6 months 9-12 months
Neck ultrasound	At 6-12 months	At 6-12 months	At 6-12 months
Diagnostic WBS	Usually not indicated	Case-specific	Case specific
MRI, CT	Not indicated	Not indicated	If Tg elevated or high clinical suspicion
FDG-PET	Not indicated	Not indicated	If Tg > 10 ng/ml
SeTSH target	0.1-0.5 ng/mL (non-stimulated Tg detectable) 0.5-2.0 ng/mL (non-stimulated Tg undetectable	0.1-0.5 ng/mL	<0.1 ng/mL

ATA high-risk and low/intermediate-risk patients who have a structural or biochemical incomplete response to therapy during the first year of follow-up require further evaluation to identify residual disease, with consideration for additional therapies. If residual disease in cervical lymph nodes can be suspected by physical examination or ultrasound, it should be confirmed by FNAB and surgical resection should be considered. Diagnostic whole-body radioiodine scanning and single-photon emission computed tomography (SPECT/CT) have a great role in the follow-up of high-risk patients. SeTg levels are important for monitoring persistent or recurrent disease after initial therapy (Table 6). In case of high-risk patients with persistent positive anti-Tg antibodies, imaging in addition to neck US (including neck and chest CT and/or PET-CT) may be warranted to detect structural disease.

Ongoing follow-up (neck US, serum Tg) is based on the assessment of the individual patient's response to therapy during the first one to two years of follow-up (Table 7). Most recurrences of differentiated thyroid cancer occur within the first five years after initial treatment, but

recurrences may occur many years or even decades later [40], particularly in patients with PTC.

Table 7 – Management of patients during ongoing follow-up based on response to therapy [36]

	Response to therapy			
	Excellent	*Biochemical incomplete*	*Structural incomplete*	*Indeterminate*
Non-stimulated Tg	Every one to two years	Every six months	Every six months	6 to 12 months
Stimulated Tg	Not needed	May be repeated at two to three-year intervals if needed to establish an excellent response to therapy	Not needed	May be repeated at two to three-year intervals if needed to establish an excellent response to therapy
Neck ultrasound	Consider at three to five-year intervals	Yearly for five years	Yearly for five years	6 to 12-month intervals for five years
Diagnostic WBS	Not indicated	Not usually done*	To evaluate RAI avidity of structural disease	Not usually done*
MRI, CT	Not indicated	Not indicated*	6 to 12-month intervals depending on rate of progression	Not indicated*
FDG-PET	Not indicated	Not indicated*	To identify additional sites of disease and for prognostic purposes	Not indicated*
Serum TSH	0.5 to 2.0 mU/L	0.1 to 0.5 mU/L	<0.1 mU/L	0.1 to 0.5 mU/L

* Consider if nonstimulated Tg is greater than 10 ng/mL or Tg is rising.

Recurrent or persistent disease in the neck may be detected by clinical examination, rising seTg, but US is the most sensitive technique for localization [41, 42]. In this stage of disease therapeutic solution can be RAI therapy, if the tumor has not lost its iodine absorption ability yet. In advanced disease other options should be considered e.g. systemic chemotherapy (kinase inhibitors), external radiotherapy, percutaneous ethanol injection of cervical nodal metastases, radiofrequency ablation of cervical, osseous, and pulmonary metastases or palliative embolization of bone metastases. Surgery may be considered for patients with single distant metastases.

3. Aims

In the last few years the new European and American clinical guidelines have led to significant changes in the routine management of DTC.

Our aims were the following:

1) to analyze how cure and survival rates have been changed in a Hungarian cohort of patient managed according to the new guidelines.
2) to determine and analyze the incidence rate of FTC and PTC, histological subtypes, surgical management, and the application of RAI treatment and external beam radiation in the therapeutic practice.
3) to evaluate the impact of post-RAI therapy SPECT/CT on early risk stratification in DTC.
4) to evaulate our own experiences with a thyrosine kinase inhibitor, sorafenib in RAI-refractory, locally advanced or metastatic thyroid cancer.

4. The prevalence, management and prognosis of differentiated thyroid cancer in a large cohort of Hungarian patients

4.1 Patients and methods

4.1.1 Characteristics of the patients

In the Ist Department of Internal Medicine, Divison of Endocrinology and Metabolic Disorders, 380 patients with DTC were treated between January 01, 2005 and May 01, 2016. Patient data is summarized in Table 8. The gender ratio was 74 male and 306 women, which proportion corresponds to the literature data. The median age of patients at diagnosis was 46 years (13-86 years), while the median follow-up time was 55 months (0-144 months). Response to therapy was available in 337 cases. The PTC and FTC ratio was 79%/21%. Among PTCs the most frequently occurring histologic subtype was the classic variant (75%), the follicular variant (19%), sclerosing variant (3%), tall cell variant (1%), trabecular variant (1%), anaplastic and solid tumors (0.5-0.5%) could be observed in a smaller proportion. The only anaplastic carcinoma was a dedifferentiated tumor from papillary carcinoma. In FTCs, classical variant was diagnosed in 76% of cases, while Hürthle cell variant in 19%, insular variant in 4% and trabecular variant in 1% were found. Considering the 45-year age cut-off, 64%, 10%, 9% and 17% of patients, while with the 55-year age cut-off 74%, 7%, 6% and 13% of patients were classified into the I, II, III and IV clinical stage groups, respectively. The initial anti-Tg values were available in 355 patients; anti-Tg positivity was found in 27% of patients.

Table 8 - Patient's data (n=380)

Characteristics	n (%)
Age (years)	
Median (range)	46 (13-86)
Gender	
Female	306 (80)
Male	74 (20)
Histology	
Papillary (PTC)	301 (79)
Classical	226 (75)
Follicular	57 (19)
Sclerotising	9 (3)
Tall cell	4 (1)
Trabecular	3 (1)
Anaplastic	1 (0,5)
Solid	1 (0,5)
Follicular (FTC)	79 (21)
Classical	60 (76)
Hürthle cell	15 (19)
Insular	3 (4)
Trabecular	1 (1)
T stage	
T1	154 (41)
T2	96 (25)
T3	93 (24)
T4	32 (10)
N stage	
N0	263 (70)
N1	117 (30)
M stage	
M0	357 (94)
M1	23 (6)
pTNM stage (cut-off 45years/55 years)	
I	243 (64) / 282 (74)
II	40 (10) / 25 (7)
III	34 (9) / 21 (6)
IV	63 (17) / 52 (13)
Tg antibody	
Positive	104 (27)
Negative	251 (66)
No data	25 (7)

4.1.2 Laboratory assessments

TSH was measured by an electrochemiluminescence assay (Elecsys® TSH assay, Roche, measuring range: 0.005-100 mU/L, normal range: 0.27-4.2 mU/L), while Tg and TgAb were measured by Elecsys® TG II assay (Roche, measuring range of 0.04 - 500 ng/mL) and Elecsys® anti-TG assay (Roche, measuring range of 10.0-4000 IU/mL, normal range <40 IU/mL), respectively.

Anti-Tg determination was routinely performed at the beginning of patient care and in a parallel way with the determination of stimulated thyroglobulin before radioiodine treatment. Subsequently, only anti-Tg positive patients were followed by antibody determination.

4.1.3 Radioiodine treatment

Based on the surgical and pathological status of the tumor, patients were classified into different risk groups in accordance with the European guidelines [1]. In order to obtain the appropriate ablation, two different preparation methods were available: thyroid hormone withdrawal or rhTSH. Low risk patients younger than 45 years and whithout aggressive histology recieved 1100 MBq dose, while other patients received 3700 MBq dose RAI treatment.

4.1.4 Management of patients

Long-term care for DTC patients is really important because of the high recurrence risk. The frequency of follow-up visits depends on the risk group of patient. The European guideline (2006) distinguishes very low, low and high risk groups, while the American (2009, 2015) guidelines defines low, intermediate and high risk groups [1, 36, 43]. Patients were regularly followed with cervical US, Tg, TSH and if necessary, anti-Tg level determination. The anti-Tg positivity is a major problem during follow-up because Tg can not be used in monitoring of disease activity. When the anti-Tg titer does not decrease or increase, recurrent disease is

suspected. The therapeutic response was evaluated in accordance to the new American guidelines. Patients belong to the tumor-free group if they have a negative cervical US, a <0.2 ng/ml on-thyroxin or <1 ng/ml stimulated Tg value and negative anti-Tg titer. Patients are also considered tumor-free, if they have negative radiological findings and anti-Tg titer became negative. Indeterminate response was established with negative imaging findings, with 0.2-1 ng/ml on-thyroxine and 1-10 ng/ml stimulated Tg value, and if anti-Tg titer was not change or decreased. Incomplete biochemical response was found if on-thyroxin Tg was >1 ng/ml, stimulated Tg level was >10 ng/ml or anti-Tg was rising, although at the same time morphological abnormalities were not detected. Structural disease was reported if tumor tissue was detected by radiological examinations and in the vast majority of cases increased Tg or anti-Tg antibody titer was measured.

4.2 Results

In our study, we retrospectively analyzed the data of 380 patients with DTC who were treated at the PTE KK Ist Department of Internal Medicine between 01 Jan, 2005 and 01 May, 2016. The incidence rate of FTC with a worse prognosis was 21%. Patients with PTC were significantly younger and were diagnosed in earlier tumor stage than FTC patients (Figures 4 and 5).

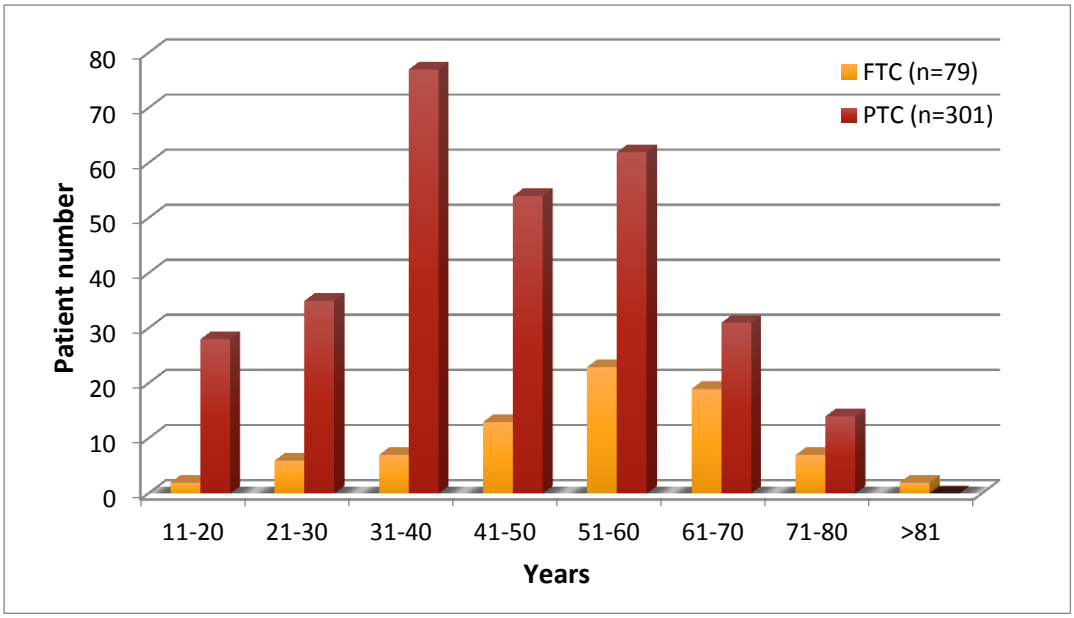


Figure 4 - The age distribution of patients at diagnosis

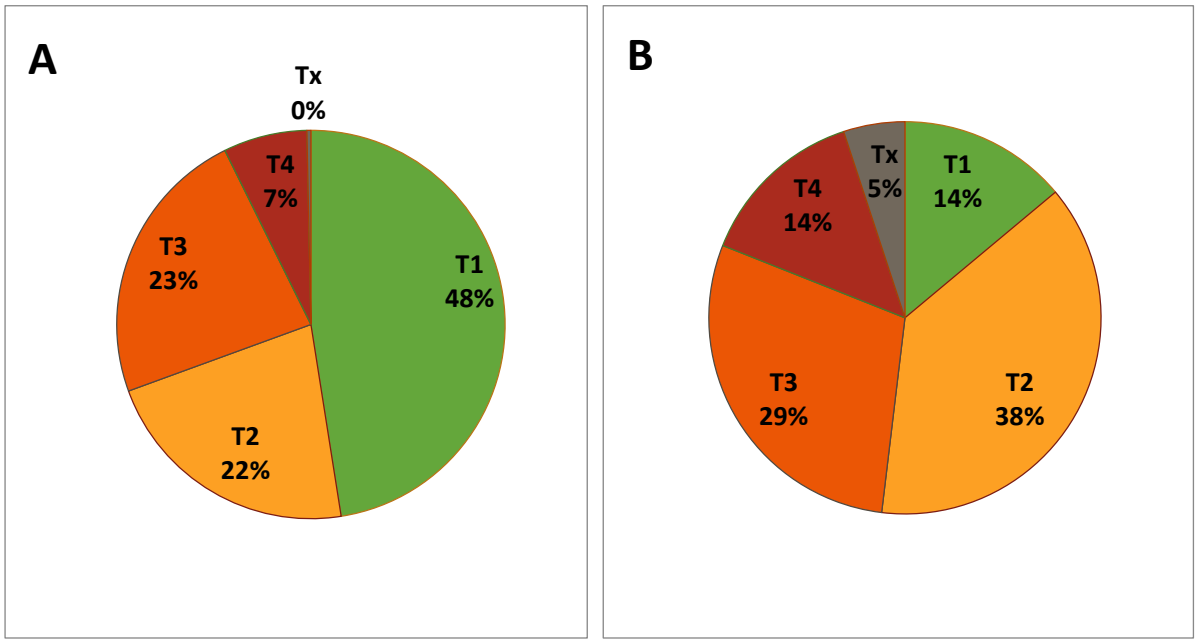


Figure 5 - The distribution of tumor stages in papillary (A) and follicular (B) carcinoma

In PTC, lymph node metastases were found in 35%, distant metastases in 4% of cases, while in FTC this ratio was 15% (N1) and 14% (M1) (Figure 6.)

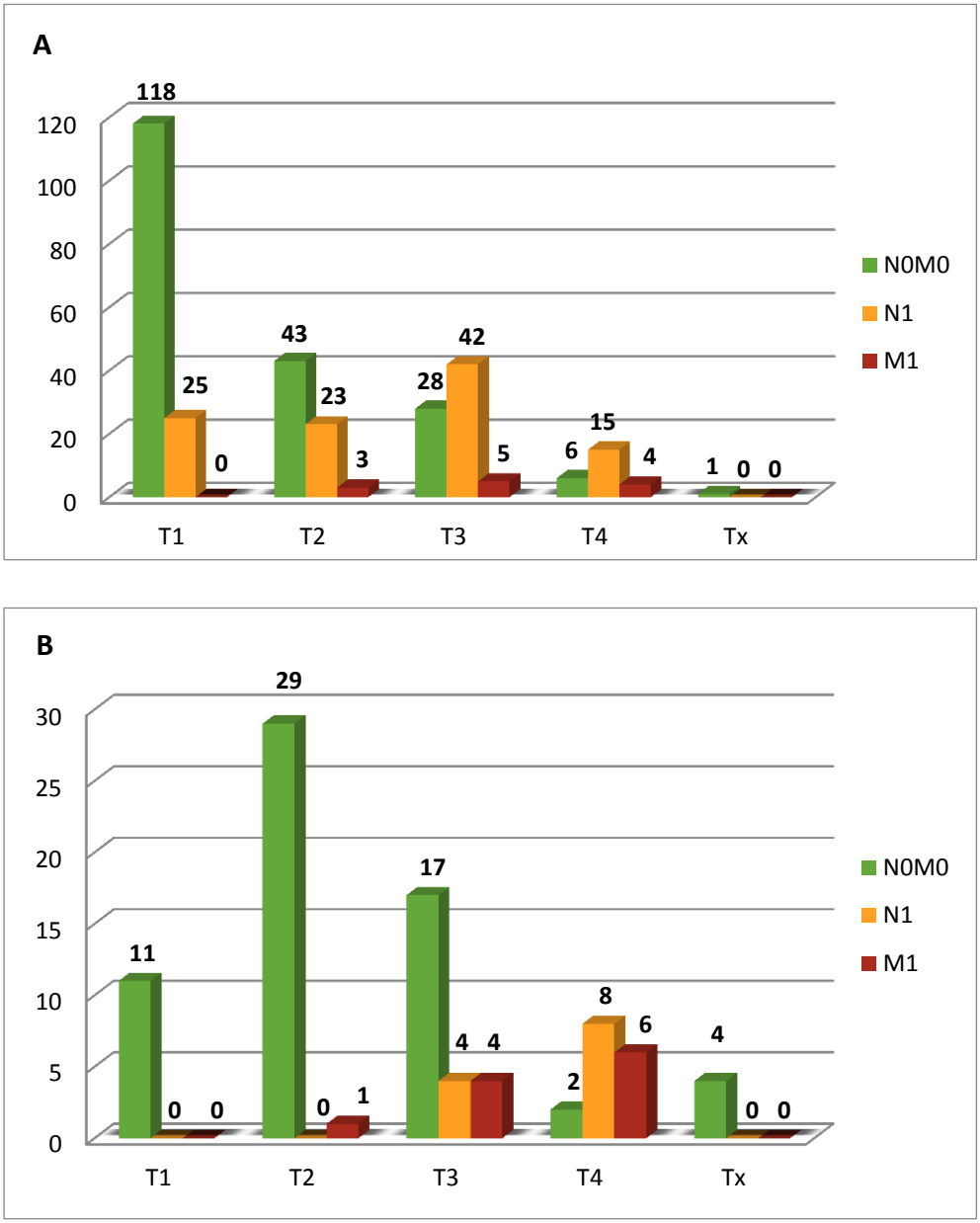
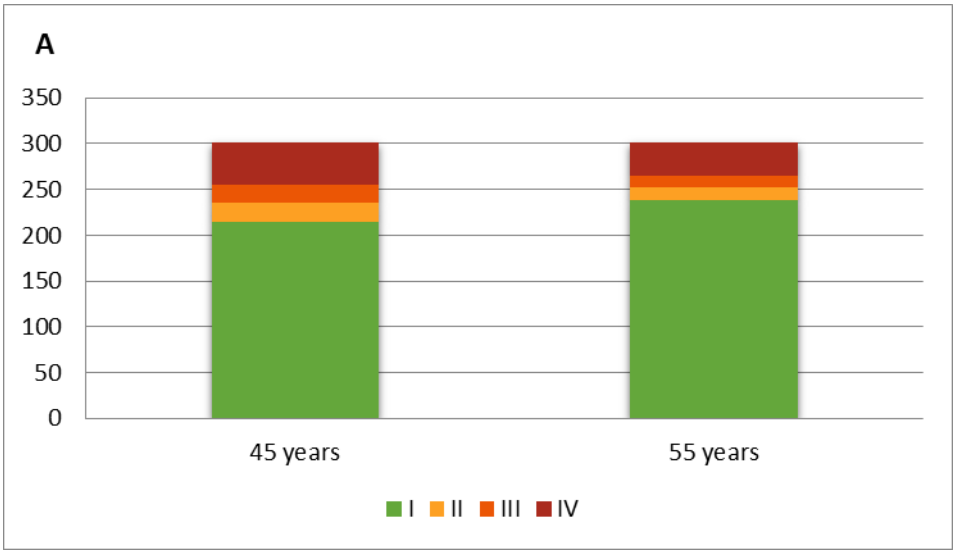


Figure 6 - The occurrence of lymph node status and distant metastasis in papillary (A) and follicular (B) carcinomas

According to literature data, lymph node metastases were more frequently found in PTC, while distant metastasis was relatively rare. In our patient population, the FTC with size < 2

cm did not cause lymph node or distant metastases, wich finding correlated to the literature data, but from T2 tumor stage the incidence of distant metastasis was progressively increased. Patients were also evaluated according to the new clinical staging system, which was introduced in January, 2018 [4]. Considering that the prognosis of older patients is significantly worse, previously patients under the age of 45 with distant metastasis were classified only at clinical stage II. Now the age limit is increased to 55 years, thus a significant proportion of patients re classified into a lower clinical stage group (Figure 7)



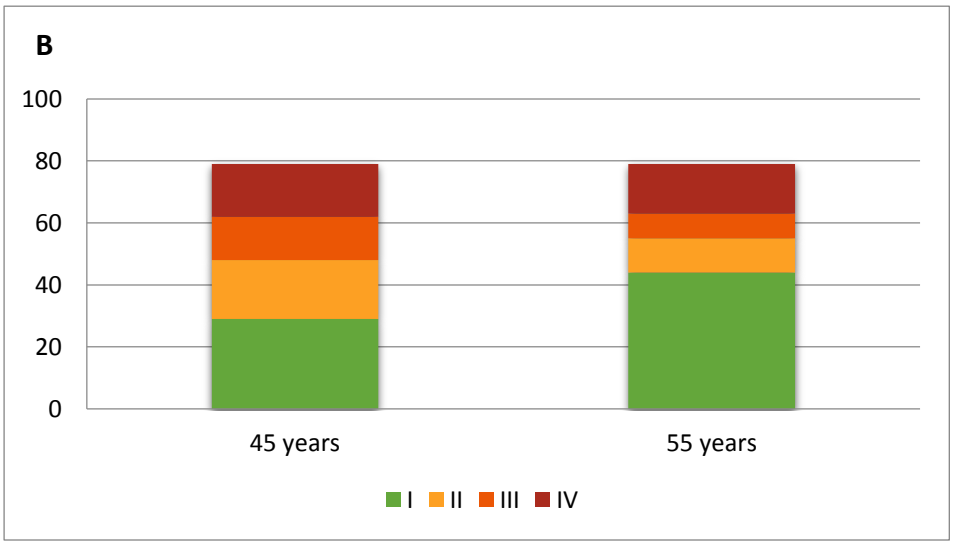


Figure 7 - Clinical stages depending on the age limit in papillary (A) and follicular (B) carcinomas

Surgery was performed in 625 cases. Surgical intervention was not performed in only one patient, who had inoperable distant metastasis. One surgery in 191, two in 150, three in 24 and more than 3 was performed in case of 14 patients. RAI treatment was performed in 542 cases; PTC patients had an average of 1.3, while FTC patients received an average 1.8 RAI treatments. External radiotherapy was needed in case of 27 patients (17 papillary, 10 follicular carcinomas), because of inoperable disease infiltrating the trachea and oesophagus (9), inoperable local recurrence (5), extensive mediastinal lymph node metastases (5), hilar lymph node metastases (2), bone metastases (4) and cerebral metastases (2). In decision-making about external radiotherapy, it was important that the tumor did not take up RAI (primary oncocytaer carcinomas) or despite of repeated RAI treatments the disease progressed. Sorafenib (Nexavar) treatment was used in case of 17 patients, during data evaluation, partial remission or stable disease was found in 6 cases, in 4 patients due to the shortness of the follow-up time therapeutic response was not measurable, 7 patients died. In one case successful reinduction was reached with sorafenib [42]. In 2016, in PTC 59% of the follow-up patients (n = 264) were tumor-free, indeterminate response in 20%, incomplete biochemical response in 7% and incomplete structural response in 14% of cases was found. Unfortunately, 6 patients died. In FTC, 59% of patients (n = 73) were tumor-free, indeterminate response in 10%, residual disease in 31% were diagnosed and the disease-specific mortality was 10% (Figure 8).

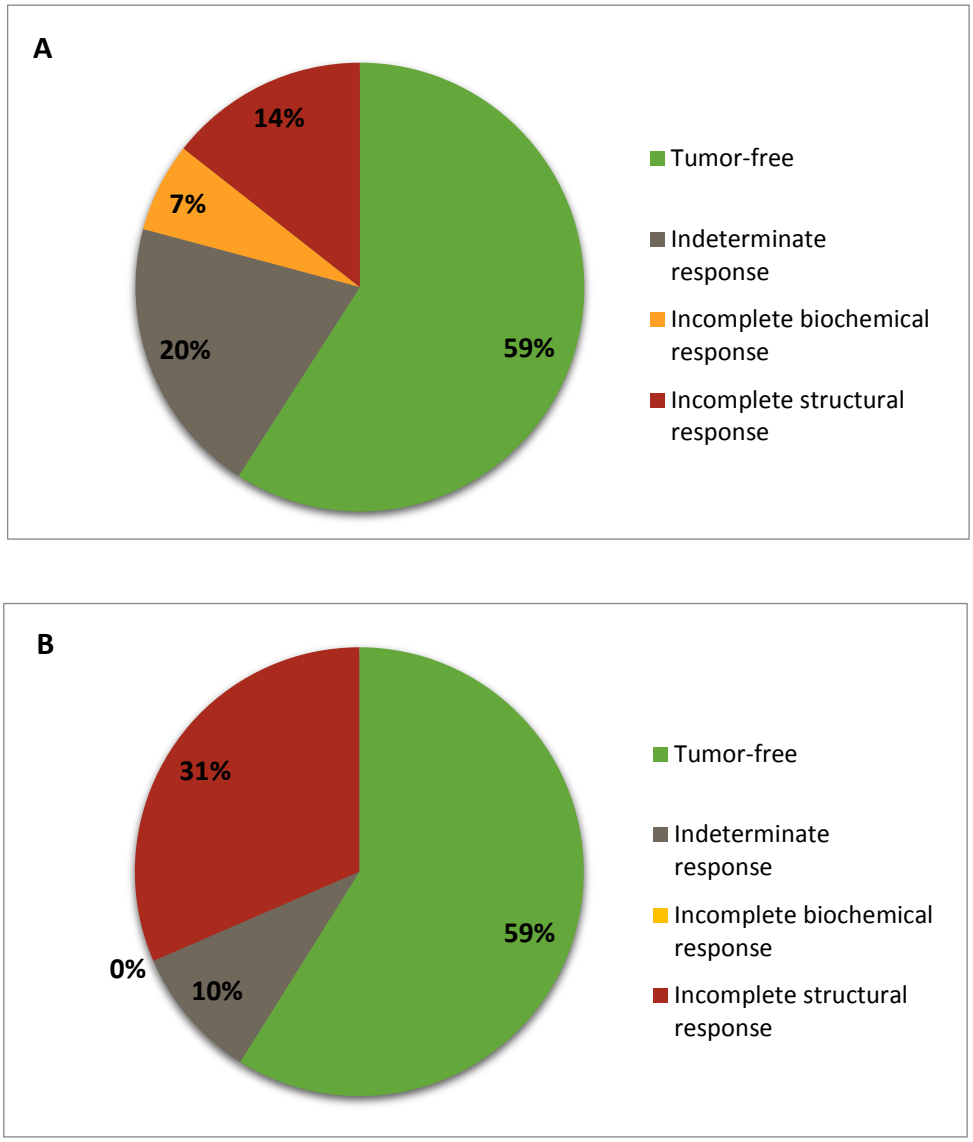


Figure 8 - Treatment results in papillary (A) and follicular (B) carcinoma in 2016

4.3 Discussion

Since 2005, a high number of patients with DTC have been managed in the PTE-KK Ist Department of Internal Medicine, Endocrinology Division. Among the universities, our institute was the first, where high dose radioiodine treatment was available. In our work, we have summarized the experiences of 11 years of care for DTC patients. The proportion of PTC and FTC indicates that the region is still considered to have iodine deficiency, as the expected incidence of FTCs is higher. In the areas with iodine deficiency, the occurrence of

DTCs with worse prognosis should be expected [45, 46]. According to the literature data, the PTC is mostly occurred in the 3rd and 4th decades, but there were also many patients who were diagnosed in their early twenties. The FTCs were mostly diagnosed in the 5th and 6th decades. The distribution of histological subtypes was usually consistent with the literature data. The earlier stage T in PTC can be attributed to several factors. On the one hand, a significant amount of T1 stage tumors were diagnosed incidentally during performing surgery with other indications. On the other hand, PTC gives early lymph node metastases, so in many cases the lymph node metastases draw the attention to the primary tumor. The frequency of lymph node metastases was increased with the tumor size and stage, but lymph node involvement has already diagnosed in 8% of T1 stage PTCs. In contrast, in the T1 stage FTC, neither lymph node metastasis nor distant metastasis were found, therefore in case of <2 cm FTC an excellent prognosis can be exptected. In the FTC, 14% of patients were diagnosed with distant metastases, which is strongly affected the options of treatment. While in PTC the micronodular pulmonary metastases gave a good response to RAI treatment, in FTC the long-term prognosis of distant metastases much less favorable, only the temporary stabilization of the disease can be expected. In the literature, a better prognosis of patients younger than 45 years has been published. Nowadays as a novelty, the 55-yearage cut-off value is suggested. In our study, the clinical stage of patients was determinated according to both 45- and 55-year cut-off values. With the increase of age cut-off, a significant proportion of patients are classified to lower risk group, which leads to the reduction of treatment agressivity. In the Hungarian literature, our data can be compared regarding to the severity of disease with the research of Győry et al. [45, 46]. Although a direct comparison is difficult because of the change in the terminology of therapeutic response, but we can conclude that the chance of remission in DTC has not improved substantially over the past two decades, especially in the

case of advanced stage FTC, where the prognosis is poor. The metastases become refractory to RAI over time.

Among our patients, cases with late diagnosis and advanced tumor stage occurred in a relatively large number. It is important to emphasize the high ratio of FTC, which is also a factor determining the prognosis. It seems that the problem in the region is not the recognition of too many early stages microcarcinoma, but the delay of diagnosis. Even today, the chance of curing tumors with advanced stage, especially in the RAI-refractory cases is little. In the future, sorafenib treatment may probably contribute to improving the survival of the metastatic DTC. This fact does not doubt the reduction of treatment radicality in early disease stage.

In summary, in our country, DTC showing an increasing incidence has a good prognosis, however, 31% of FTC and 14% of PTC patients could not reach tumor-free stage. During the median 55-month follow-up time the disease-specific mortality in FTC was 10%, while in PTC was 2%.

5. The impact of post-radioiodine therapy SPECT/CT on early risk stratification in differentiated thyroid cancer

5.1. Introduction

Patients with DTC usually have a favorable prognosis with high cure rates; however, lifelong follow-up is required as potentially curable local recurrences and distant metastases may occur even decades later [1, 36, 43]. The conventional and effective treatment consists of surgical management followed by RAI ablation of thyroid remnants and TSH suppressive therapy [1, 43]. Recently, the universal use of remnant ablation after surgery has been debated and mainly restricted to advanced disease [36]. However, RAI therapy has additional benefits, e.g. the destruction of undetected residual tumor foci and the ablation of normal thyroid tissue which facilitates the detection of recurrent disease during follow up. The information obtained through the posttherapeutic ^{131}I-WBS or SPECT/CT may reveal previously undiagnosed tumor foci [47-50]. Planar WBS is routinely performed after radioiodine treatment; however, SPECT/CT is proven to be more accurate in the evaluation of residual disease [51-53]. Hybrid systems − integrating a SPECT camera with a CT scanner in one gantry − have been in use since 2001, and in the last 5 years the application of SPECT/CT imaging system is gaining more importance [55]. In comparison to WBS, SPECT/CT adds simultaneous 3D anatomic mapping to functional imaging [56]. The recognition of artifacts is easier and metastatic foci without radioiodine uptake are also detected [57]. SPECT/CT significantly ameliorates the diagnosis and staging, and differentiates between benign and malignant foci of radioiodine accumulation [58]. Postoperative and follow-up management of patients with DTC highly depends on risk classification. Different risk stratification systems are used by the ATA (2009, 2015) and the ETA (2006). Risk stratification systems incorporate data from cancer related factors, clinical features, results of first WBS after radioiodine therapy and serum Tg level. The evaluation of response to initial therapy during the follow-up is especially

important; risk categories may change during the course of disease. The reclassification of patients based on post-radioiodine therapy imaging influences the management of the disease and the intensity of follow-up [59].

5.2. Patients and methods

5.2.1 Characteristics of the patients

After their first radioiodine treatment, 323 consecutive DTC patients (181 at the University of Pecs and 142 at the University of Debrecen) were investigated. Demographic data are summarized in Table 9. The female to male ratio was 246 to 77. The median age at diagnosis was 46 (range 13 to 86) years. All patients were diagnosed with DTC; papillary and follicular histotypes were identified in 249 and 74 cases, respectively. Among the PTCs, classical papillary variant was the most common subtype (75.1%), while the incidence rate of follicular (20.9%), sclerosing (2.4%) and tall cell variants (1.6%) was lower. Of the FTCs, classical variant was the most common (81.1%); Hürthle-cell, trabecular and insular variants were diagnosed in 16.2% 1.3% and 1.3% of cases, respectively. Histology detected lymph node involvement in 95 cases, distant metastases were known in 12 patients. TgAb positivity was found in 88 patients.

Table 9 - Patients' demographics (n=323)

Characteristics	**n (%)**
Age (years)	
Median (range)	46 (13-86)
Gender	
Female	246 (76.2)
Male	77 (23.8)
Tumor histology	
Papillary (PTC)	249 (77.1)
Classical	187 (75.1)
Follicular	52 (20.9)
Sclerosing	6 (2.4)
Tall cell	4 (1.6)
Follicular (FTC)	74 (22.9)
Classical	60 (81.1)
Hürthle cell	12 (16.2)
Trabecular	1 (1.3)
Insular	1 (1.3)
T stage	
Tx	2 (0.4)
T1	143 (44.3)
T2	79 (24.5)
T3	78 (24.3)
T4	21 (6.5)
N stage	
N0	228 (70.6)
N1	95 (29.4)
M stage	
M0	311 (96.3
M1	12 (3.7)
pTNM staging	
I	219 (67.8)
II	28 (8.7)
III	36 (11.1)
IV	40 (12.4)
TgAb	
Negative	235 (72.8)
Positive	88 (27.2)

The study protocol was approved by the Institutional Ethics Committees of the University of Pecs and the University of Debrecen.

5.2.2 Radioiodine ablation

Based on the surgical and pathological status of the tumor, patients were classified into risk groups according to the European consensus guideline [1]. Patients with low risk for recurrence, younger than 45 years and without aggressive histology were treated with 1100 MBq, while other patients received 3700 MBq doses. In order to reach effective thyroid ablation, two methods of preparation were available: thyroid hormone withdrawal or administration of recombinant human thyrotropin (rhTSH, 34 patients). Total body retention and external radiation dose were measured before discharge of the patient.

5.2.3 Post-radioiodine therapy imaging with WBS and SPECT/CT

Both planar WBS and SPECT/CT from the neck and chest were carried out in all patients 4-6 days after oral administration of 1100-3700 MBq radioiodine. Additional SPECT/CT scans of the abdomen and pelvis were acquired if suspicious isotope accumulations were detected on the WBS. The WBS examination consisted of anterior and posterior whole-body images acquired at 6 cm/min using a DHV SPECT/CT equipment (Mediso, Budapest, Hungary). The SPECT/CT unit consisted of dual head SPECT, 50 sec/frame, 64 frames, and a low dose, 16 slices spiral CT, 120 KeV, 50 mAs [60]. The examination was carried out with HEGP collimator. Evaluation of WBS and SPECT/CT images were performed by two independent nuclear medicine specialists and a radiologist; in case of dissent opinion, consensus was achieved. The CERTOP 01-13044/6/11-07755 Quality Management System was applied, which satisfied the requirements of the Hungarian Health Care Standards Guide (MEES) 1.0. Identical protocols were used at both university centers.

5.2.4 Risk classification systems and SPECT/CT based upgrading and downgrading rules

The risks of recurrence were calculated separately according to both the ATA 2009 and ETA 2006 guidelines. The risk of recurrence was reevaluated based on SPECT/CT results. Patients without RAI uptake outside the thyroid bed, except those with aggressive histology, were downgraded, while those with detected tumor foci were upgraded according to the ATA classification. The SPECT/CT results served as a basis for separating patients into two groups: those with or without residual tumor. Serum Tg, TgAb, neck US and other imaging modalities were used during reclassification of patients at 9-12 months after the RAI treatment. No evidence of tumor was established with negative neck US, on-thyroxine Tg<0.2 ng/ml or stimulated Tg<2.0 ng/ml, negative TgAb or significant decrease in TgAb titer. Incomplete biochemical response was determined if Tg was measurable or TgAb titer did not decrease without morphological abnormality. Structural disease was diagnosed with positive imaging findings.

5.2.5 Laboratory assessments

TSH was measured by an electrochemiluminescence assay (Elecsys® TSH assay, Roche, measuring range: 0.005-100 μIU/mL).

For the University of Pecs patients, Tg and TgAb were measured by Elecsys® TG II assay (Roche, measuring range of 0.04 - 500 ng/mL) and Elecsys® anti-TG assay (Roche, measuring range of 10.0-4000IU/ml), respectively.

For the University of Debrecen patients, Tg was measured by chemiluminescent immunoassay (LIAISON®-Tg, DiaSorin S.p.A., Saluggia, Italy; measuring range: 0.2-1000 ng/ml). Before December 1, 2014 concentrations of TgAb were measured by radioimmunoassay (DYNOtest anti-Tg, BRAHMS Diagnostica GmbH, Hennigsdorf,

Germany; measuring range: 20-2000 U/ml); from December 1, 2014 the Elecsys® anti-TG assay (Roche, measuring range: 10.0-4000 IU/ml) was used.

5.2.6 Data analysis

Statistical analysis was done with Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA, version 22.0). Normality of distribution of data was tested by Kolmogorov-Smirnov test. Non-normally distributed parameters were presented as median and ranges. The diagnostic value of risk classification systems to predict the recurrence of tumor at one-year and at the end of follow-up was calculated according to Galen. It was based on true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results: sensitivity: TP/TP+FN, specificity: TN/TN+FP, positive predictive value (PPV): TP/TP+FP, negative predictive value (NPV): TN/(TN+FN) and diagnostic accuracy: (TP+TN)/(TP+TN+FP+FN). The agreement between risk stratification systems was calculated with Cohen's *kappa* coefficient. The diagnostic value of different risk classification systems were compared by McNemar test. For comparison to other systems, ATA intermediate and high risk categories were handled together. To identify the determinants of disease outcome, binary logistic regression analysis using backward method was performed. We considered $p < 0.05$ to be significant for all analyses.

5.3. Results

5.3.1 SPECT/CT after the first ^{131}I treatment

No evidence of tumor was detected by SPECT/CT in 78.3% of cases (Table 10). Local residual tumor was observed in 6 patients (1.8%), lymph node metastases were detected in 61 cases (18.8%), lung and bone metastases were found in 13 (4.0%) and 5 (1.5%) patients, respectively.

Table 10 - The distribution of metastases according to SPECT/CT results in the original ATA risk categories (n=323)

	ATA - low risk (138 patients)	***ATA - intermediate risk (159 patients)***	***ATA - high risk (26 patients)***	***TOTAL***
No evidence of tumor	125	122	6	***253***
Lymph node metastases	10	35	16	***61***
Lung metastases	2	3	8	***13***
Bone metastases	1	1	3	***5***
Other metastases	0	1	0	***1***

In the ATA low risk category (n=138), 91% of patients were tumor-free; lymph node, lung and bone metastases were detected in 10, 2 and 1 cases, respectively. In the ATA intermediate category (n=159), no evidence of tumor was established in 75%. Lymph node, lung, bone and other metastases were diagnosed in 35, 3, 1 and 1 cases. Posttherapeutic SPECT/CT detected residual disease in every forth patient. ATA high risk patients (n=26) were tumor-free only in 18%. Typical images of a patient with lymph node and pulmonary metastases are shown in Figure 9. Non-radioiodine avid lesions with suspected malignancy were detected in 8 cases (2.5%); these cases were further investigated by PET/CT, CT with contrast material or MRI.

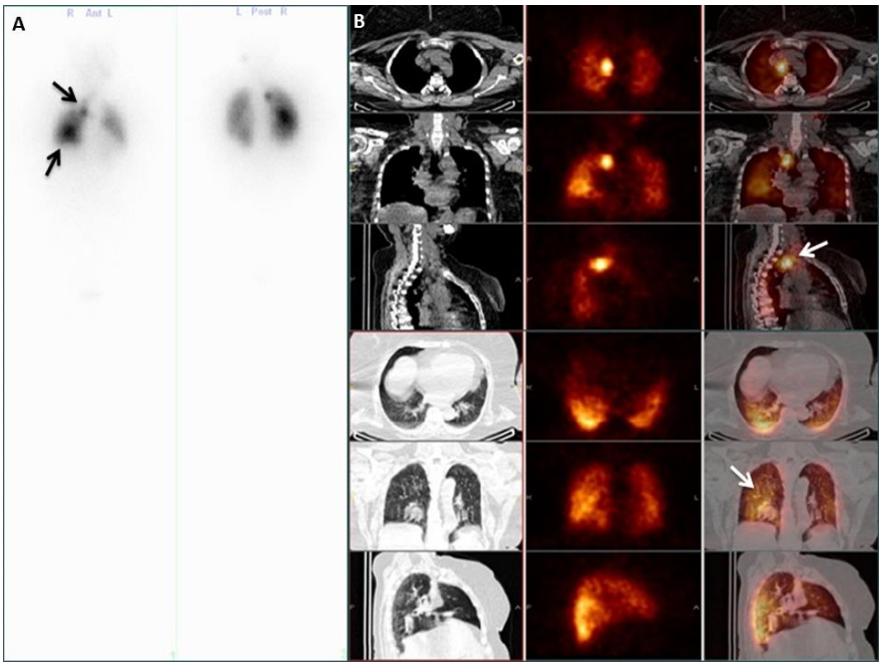


Figure 9 - Anterior and posterior whole body scan (A) and SPECT/CT (B) images of a papillary cancer patient with lymph node and pulmonary metastases (arrows)

5.3.2 Changes in risk classification and clinical stage based on SPECT/CT

The ATA risk stratification includes the WBS based RAI uptake outside the thyroid bed. In the present series, based on SPECT/CT results, patients with detectable residual disease were upgraded: the presence of lymph node metastases classified the patients to the intermediate risk, while incomplete tumor resection or distant metastases classified them to high risk of recurrence category. Patients without RAI uptake outside the thyroid bed previously categorized having intermediate or high risk were downgraded to low risk category except those with aggressive histology (Table 11).

Table 11 - Changes in ATA risk classification based on SPECT/CT results

		Before SPECT/CT			
		low	*intermediate*	*high*	***TOTAL***
After SPECT/CT	*low*	124	83	5	**212**
	intermediate	11	70	7	**88**
	high	3	6	14	**23**
	TOTAL	**138**	**159**	**26**	**323**

Twenty patients were upgraded, while 95 patients downgraded, thus, the risk categories changed in 115 (35.6%) of cases. The risk distribution of the patients according to the ATA system before and after SPECT/CT differed significantly ($p < 0.001$), the Cohen's *kappa* coefficient was 0.386, expressing a moderate agreement. The last ATA guideline does not recommend RAI ablation in the low risk category and the RAI therapy should be considered in the intermediate risk category. Without RAI treatment 103 (34.7%) patients would have been misclassified in the low and intermediate categories.

Changes in clinical staging were not so profound (Cohen's *kappa*: 0.894), since the stage of young patients did not change even if they had lymph node metastases (Table 12). However,

18 patients were upgraded, and 14 of them were classified to stage IV category, increasing the number of patients in stage IV by 25.9% ($p < 0.001$).

Table 12 - Changes in ATA risk classification and clinical stages based on SPECT/CT results

		Before SPECT/CT				
		I	*II*	*III*	*IV*	***TOTAL***
After SPECT/CT	*I*	208	0	0	0	**208**
	II	1	26	0	0	**27**
	III	3	0	31	0	**34**
	IV	7	2	5	40	**54**
	TOTAL	**219**	**28**	**36**	**40**	**323**

5.3.3 Follow-up

Follow-up data were available in 315 cases; the median follow-up time was 37 months (range: 9-98 months). One patient died within one year and seven patients were lost for follow-up. Patients with confirmed residual tumor were treated by repeated surgery, RAI, irradiation or sorafenib in 23, 57, 9 and 6 cases, respectively, depending on the extension of the disease, type of tumor tissue and RAI resistance. Serum Tg, TgAb, neck US and other imaging modalities were used during long-term follow up. No evidence of tumor was found at 9-12 months after the RAI treatment in 251 (79.7%) cases. Incomplete biochemical response was detected in 20 cases (6.3%), residual tumor was evident in 44 patients (13.9%). Eighty-five percent of patients were tumor-free at the end of follow-up period. The incomplete biochemical response decreased to 2.5% (8 cases) while 12.1% (38 cases) of patients suffered from persistent thyroid cancer, seven of them died due to this disease.

5.3.4 Comparison of the diagnostic value of the currently used risk stratification systems and SPECT/CT

Sensitivity, specificity, PPV, NPV and diagnostic accuracy of risk classification systems and SPECT/CT based on follow-up data at 9-12 months after RAI therapy are presented in Table 13.

Table 13 - Comparison of the diagnostic value of the currently used risk stratification systems and SPECT/CT at one-year after RAI treatment

	Sensitivity	***Specificity***	***PPV***	***NPV***	***Diagnostic accuracy***
ATA	76.6	47.4	27.1	88.8	53.3
ETA	70.3	62.2	32.1	89.1	63.8
ATA after SPECT/CT	65.6	73.3	38.5	89.3	71.7
SPECT/CT	***60.9****	***88.0*****	56.5	89.8	***82.5*****

Positive predictive value (PPV), negative predictive value (NPV), Risk stratification of American Thyroid Association (ATA), Risk stratification of European Thyroid Association (ETA), Risk stratification of American Thyroid Association after SPECT/CT (ATA after SPECT/CT) and SPECT/CT alone (SPECT/CT).

* Sensitivity of SPECT/CT compared to the ATA classification was significantly lower (p=0.021)
** Specificity of SPECT/CT was significantly higher than any other classification (p<0.001)
*** Diagnostic accuracy of SPECT/CT was significantly better than any other classification (p<0.001)

All methods had acceptable sensitivity and NPV to predict the presence of DTC; however, the sensitivity of SPECT/CT compared to the ATA system was significantly lower (61% to 77%, p=0.021). The ATA classification had the lowest specificity (47%) and diagnostic accuracy (53%) compared to the other systems tested (p <0.001). The modification of ATA classification based on SPECT/CT findings significantly improved the specificity (73%) and diagnostic accuracy (72%) of this method (both p<0.001). The results of SPECT/CT alone, without any other data, had the highest specificity (88%) and diagnostic accuracy (83%, p <0.001). The usefulness of risk classification systems and SPECT/CT to predict the presence of thyroid cancer at the end of follow-up is shown on Table 14.

Table 14 - Comparison of the diagnostic value of the currently used risk stratification systems and SPECT/CT at the end of follow-up (median 37 months, n=315)

	Sensitivity	***Specificity***	***PPV***	***NPV***	***Diagnostic accuracy***
ATA	80.4	46.5	20.4	93.3	51.4
ETA	73.9	60.6	24.3	93.1	62.5
ATA after SPECT/CT	78.3	72.9	33.0	95.1	73.7
SPECT/CT	71.7	***86.6*****	47.8	94.7	***84.4******
Risk at 1 year	***100****	***93.3*****	71.9	100	***94.3******

Positive predictive value (PPV), negative predictive value (NPV), Risk stratification of American Thyroid Association (ATA), Risk stratification of European Thyroid Association (ETA), Risk stratification of American Thyroid Association after SPECT/CT (ATA after SPECT/CT) and SPECT/CT alone (SPECT/CT).

* No significant differences in sensitivities were found except in case of one-year reclassification ($p<0.01$)
** Specificities of the individual parameters differed significantly, the one-year reclassification had the highest value ($p<0.01$). The specificity of SPECT/CT was also significantly better than the values of the ATA and ETA risk classifications ($p<0.001$).
*** Diagnostic accuracy of one-year reclassification was excellent but not significantly better than that of SPECT/CT ($p=0.59$). Both method provided better prediction than ATA, ETA and ATA after SPECT/CT classifications ($p<0.01$).

The reclassification of patients at one year was included in the analysis. No significant differences in sensitivities were found except in case of reclassification at one year, which was 100%. Specificity of the individual parameters differed significantly, the highest value was also found in case of one-year reclassification (93%, $p <0.01$). Reclassification of patients at one year resulted in excellent diagnostic accuracy (94%). The specificity and the diagnostic accuracy of SPECT/CT alone were also high (87% and 84%), being significantly better ($p<0.01$) than the values of the ATA and ETA risk stratification systems (ATA: 47% and 51%, ETA: 61% and 63%, respectively). The completion of ATA classification by SPECT/CT results provided better specificity (73%) and diagnostic accuracy (74%) than the ATA classification ($p<0.001$). The diagnostic accuracy provided by the SPECT/CT to predict the presence or relapse of DTC at the end of follow-up was similar to the result of the one-year reclassification ($p=0.59$). However, SPECT/CT results are obtained one year earlier. Diagnostic accuracies of different risk stratifications according to disease stages were also calculated (Table 15).

Table 15 - Comparison of the diagnostic accuracy of the currently used risk stratification systems, SPECT/CT and one-year data at the end of follow-up (median 37 months, n=315) in different disease stages

	Stage I	***Stage II***	***Stage III***	***Stage IV***
ATA risk	57.5	50.0	22.9	44.7
ETA risk	71.5	82.1	11.4	44.7
ATA after SPECT/CT	75.2	67.9	74.3	68.4
SPECT/CT	***84.6***	***89.3***	***94.3***	***71.1***
Risk at 1 year	93.0	96.4	97.1	97.4

Risk stratification of American Thyroid Association (ATA risk), Risk stratification of European Thyroid Association (ETA risk), Risk stratification of American Thyroid Association after SPECT/CT (ATA after SPECT/CT) and SPECT/CT alone (SPECT/CT).

The diagnostic accuracies of SPECT/CT at the end of follow-up in stage I, II, III and IV were 84.6%, 89.3%, 94.3% and 71.1%, respectively; these values were significantly higher than the diagnostic values of ATA and ETA risk stratifications in every stage.

The role of SPECT/CT in predicting the disease outcome was further investigated by binary logistic regression analysis; age, TNM stage, clinical staging, histology, ATA, ETA risk classification and SPECT/CT were included to the model. The age, T, M stage and the SPECT/CT result proved to be the independent predictors of the outcome at one year. These determining factors were completed by ETA risk at the end of follow-up. SPECT/CT results were the strongest predictors in both models ($p<0.001$).

5.4. Discussion

The postoperative management of DTC is based on the risk stratification of patients. However, different risk classification systems are used in the US, in Europe, and in other parts of the world [1, 43]. The risk classification mainly rests on the pathological results and surgical findings. The ATA risk classification contains the results of WBS after RAI; however, performing WBS is not obligatory. In the last few years several articles have been published evaluating the advantages of additional SPECT/CT over WBS alone in the management of DTC patients [49, 55]. Investigating 148 consecutive patients, SPECT/CT

significantly reduced the number of equivocal findings on WBS and simultaneously was more accurate in the characterization of focal iodine accumulation in one fifth of patients [61]. The important diagnostic impact and the superiority of SPECT/CT over planar scintigraphy in cases of inconclusive lesions were also highlighted by others [62-68]. Despite of the obvious advantages of the hybrid imaging method, it is not a routine procedure in the world.

In this study, the role of SPECT/CT was evaluated in early risk classification of patients with DTC and in prediction of long-term prognosis compared to the risk of relapse determined by ATA and ETA risk classifications. To our best knowledge, so far our study has had the largest number of DTC patients with the longest follow-up time investigated by SPECT/CT. Moreover, this is the first study where the diagnostic value of combined imaging with additional SPECT/CT to predict the long-term outcome of DTC was compared to the usefulness of ATA and ETA risk stratifications.

Residual tumor was detected by post-radioiodine SPECT/CT in 22% of patients and this was unexpected in the majority of cases. The results of SPECT/CT basically modified the management in a considerable ratio of patients. The information about the lack of residual disease was equally important. The ratio of reclassified cases by SPECT/CT was high (36%). The majority of reclassifications moved the patients towards lower risk categories. This reclassification influences the treatment and follow-up e.g. the TSH target values and the frequency of follow-up visits. The detection of non-RAI avid lesions by SPECT/CT has also crucial importance as the loss of RAI accumulating capability means that this tumor will be resistant to RAI treatment and other treatment options are required e.g. irradiation or sorafenib treatment.

In prognostic models of disease outcome evaluated by binary logistic regression analysis, age, T, M stage and SPECT/CT results were found as independent predictors; The result of

SPECT/CT was the strongest determining factor both at one-year evaluation and at the end of follow-up.

We tested two different applications of the post-radioiodine therapy SPECT/CT. Using the ATA risk categories, a large proportion of patients had to be reclassified based on the SPECT/CT results. Further, when post-radioiodine therapy SPECT/CT was used as the sole predictor of outcome, its specificity and diagnostic accuracy was significantly higher than any of the other currently used risk stratification systems. Using the SPECT/CT results alone, its sensitivity in predicting residual disease at one-year was lower than that of the ATA classification without SPECT/CT data; however, this difference disappeared by the end of follow-up. The lower sensitivity may be explained by the fact that very small metastatic foci are below the detection limit of SPECT/CT.

The response to the initial therapy is essential in determining long-term outcome. It has also been proven in our investigation that reclassification of patients at one-year based on the residual disease has the highest sensitivity, specificity and diagnostic accuracy predicting long-term outcome.

It is worth to mention that the ratio of FTC (with potentially poor prognosis) was relatively high in our patients' cohorts, probably due to marginal iodine deficiency in Hungary. The ratio of TgAb positive patients was also higher than expected [69, 70]. In TgAb positive cases, Tg cannot be used as a tumor marker for the follow-up. Therefore, the role of imaging methods in the TgAb positive patient population is even more important.

In our study, the residual disease was responsible for the biochemically or structurally incomplete response in the vast majority of patients and not a relapsing tumor was detected. It is possible that previous methods e.g. earlier Tg assays were not enough sensitive to detect the

residual disease, however the follow-up time in this study is not enough long to withdraw final conclusion.

5.5. Conclusions

In conclusion, SPECT/CT after RAI treatment is a useful tool in the early classification of DTC patients and largely influences treatment strategy. ATA and ETA risk classification systems are sensitive and have high NPVs, but are less specific when compared to post-RAI therapy SPECT/CT. Due to its better diagnostic accuracy, post-RAI therapy SPECT/CT can greatly facilitate staging, risk classification and management of DTC. We suggest that post-radioiodine therapy SPECT/CT should be included in the risk classification of patients with DTC.

6. Experiences with new therapeutic options in differentiated thyroid cancer

6.1 Introduction

Iodine-refractory, locally advanced or metastatic DTC usually have a poor prognosis in comparison to other thyroid cancer types as conventionally used therapeutic strategies may be less effective in these cases. Oncocytic FTCs have reduced capacity to uptake radioactive iodine and therefore less responsive to radioactive iodine therapy. In recent years, tyrosine kinase inhibitors (TKI) have been brought new opportunities for the management of thyroid cancers. Sorafenib (Nexavar®) was the first TKI approved for the treatment of iodine-refractory, locally advanced or metastatic DTC [71]. Through the inhibition of tyrosine kinases and RAF serine/threonine kinases, sorafenib has a great impact on tumor cell proliferation and angiogenesis [72]. Based on previous data, sorafenib proved to be a potent systematic therapy. Orally administered sorafenib in 400 mg twice daily dose may slow the progression of disease in the majority of cases and it may significantly prolong median progression-free survival [71, 73-76]. Unfortunately, sorafenib shows a remarkable toxicity and can cause severe side effects, the most common are hand-foot skin reaction, diarrhea, and alopecia, and therefore dose reduction or discontinuation of treatment may be required in some cases.

6.2 Own experiences with sorafenib treatment

In the Ist Department of Internal Medicine, overall 21 patients with advanced, radioiodine refractory DTC were treated with sorafenib until March, 2018. The female to male ratio was 17 to 4. The median age at the start of treatment was 67 (range 37 to 88) years. The median follow-up time between the diagnosis and the start of sorafenib treatment was 8 (0-21) years. According to the histology results, classical follicular carcinoma was diagnosed in 10, oncocytic variant in 5 and papillary carcinoma in 6 cases. Metastases have already found at

the time of diagnosis in 6 patients. Patients had an average of 2.4 (1-8) surgeries, 3.7 (1-10) RAI treatments; external radiotherapy was performed in 12 cases. The median sorafenib treatment time was 15 months. Therapeutic response was partial remission or stable disease in 14 (66%), progression in 3 and not measurable because of the short follow-up period in 4 cases. The outcome at the time of evaluation is the following: 8 patients were on treatment and had a stable disease, progression was found in 4 cases without sorafenib, therapy was changed to another TKI inhibitor in 1 case and 8 patients were died.

6.3 Succesful reinduction with sorafenib

We report a 68-year-old woman. Past medical history was not a factor and there was no family history of thyroid cancer either, although close relatives had various malignant diseases. In 2001, FNAB of the thyroid raised the suspicion of cytological malignancy. The patient was referred to a thyroid surgeon and bilateral subtotal thyroid resection was carried out. Histological examination confirmed the diagnosis of oncocytic follicular carcinoma of the thyroid; the tumor was in dimension of 3.5 cm without any lymph node involvement (pT2a, Nx, Mx). In 2006 October, a total thyroidectomy and neck exploration were performed due to local recurrence and lymph node metastases. Pathologic findings in thyroid gland are showed in Figure 10.

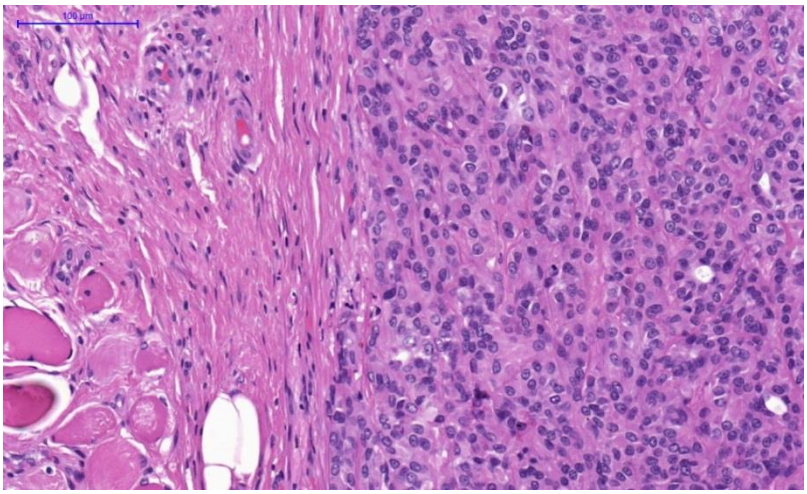


Figure 10 - Hematoxylin and eosin (HE) staining of oncocytic follicular thyroid cancer; the image was magnified 20 times. Oncocytic cells showing abundant eosinophilic granular cytoplasm and prominent nucleoli.

Furthermore, the patient received an irradiation therapy to the neck with 49.8 Gy cumulative dose. CT scans of the chest were done but no positive findings were noted. After one year patient was presented complaining a small growing mass on the right side of her neck. During US examination a hypoechoic nodule (measuring 10x5 mm) was detected arising from the right residual thyroid tissue; while elevated Tg 42.1 ng/mL (normal range: 1.4-78.0 ng/mL) and anti-Tg 124.1 IU/ml (normal range: <40 IU/ml) levels were presented. Due to these findings, patient received high-dose (3700 MBq) RAI therapy with rTSH. Posttherapeutic ^{131}I SPECT/CT was done with no positive findings. Three months later, in the background of further rise of the tumor markers, abnormal isotope accumulation on the right side of the thyroid cartilage was identified on PET/CT. At the end of 2008 patient received the second high-dose (3700 MBq) RAI treatment, SPECT/CT results were negative. In 2009 October Tg level was 616,8 ng/mL, and pulmonary metastases were observed during the second PET/CT examination (Figure 11).

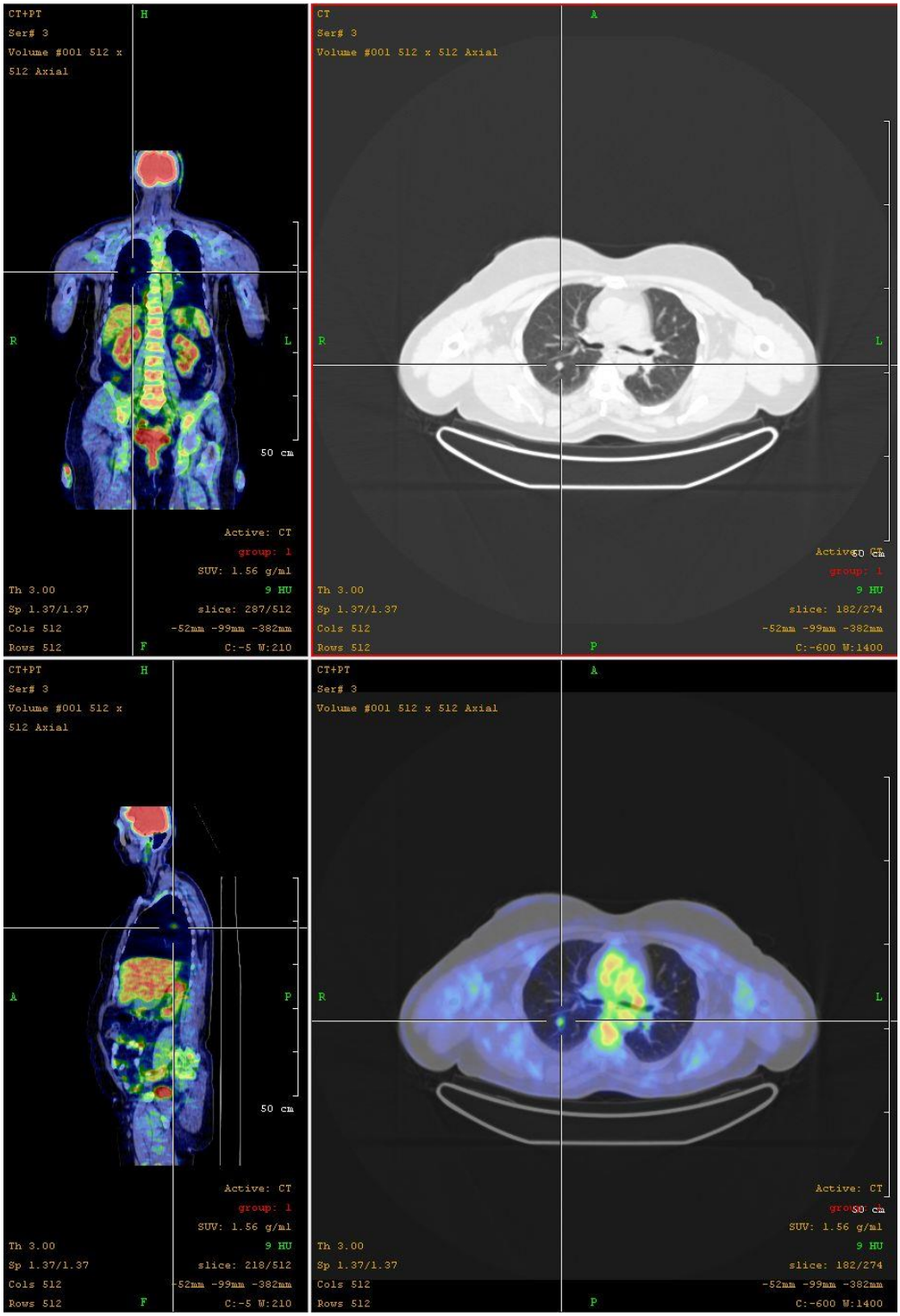


Figure 11 - PET/CT showed a pulmonary metastasis with 9 mm diameter in the sixth segment of the right pulmonary lobe.

Furthermore a 6 mm lesion was found in the ninth segment of the left pulmonary lobe, which could not be clearly characterized, while the size of the previously identified mass with abnormal accumulation on the right side of the thyroid cartilage was not changed. According

to decision of the oncoteam, patient received the second irradiation therapy with 50 Gy cumulative dose to the known pulmonary metastasis. Slow but continuous progression with recent bilateral pulmonary metastases led to the third high-dose (3700 MBq) RAI treatment. SPECT examination did not show abnormal isotope accumulation, but the previously identified bilateral pulmonary metastases could be identified on the CT pictures. In 2012, with extremely elevated Tg level, >1000.0 ng/mL, some nodes with approximately one cm size were palpable on the left side of the larynx and in front of the sternocleidomastoideus muscle. US and FNAB examinations confirmed the malignancy (Figure 12).

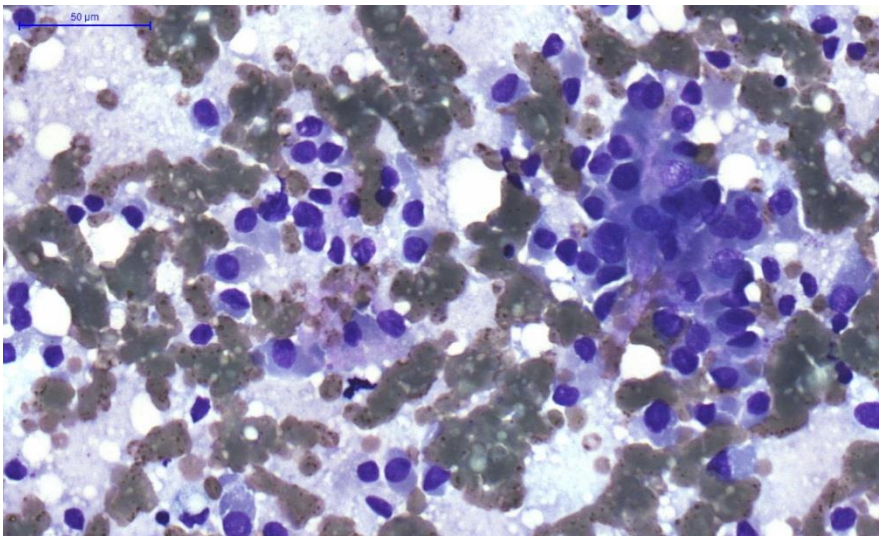


Figure 12 - Giemsa staining of cytological specimen from fine-needle aspiration of metastatic cervical lymph node; the image was magnified 40 times.

A lymph node metastasis with 8 mm was found on the left side of the neck, while a lymph node conglomerate with 16 mm was identified on the right side of the thyroid cartilage. In 2012 February, due to lymph node and radioiodine-refractory pulmonary metastasis, sorafenib treatment was started with 2x400 mg daily dose. Initially a remarkable reduce in Tg levels was observed and neck/chest CT showed a stable disease (radiologic response to sorafenib was classified according to the Response Evaluation Criteria In Solid Tumors system criteria, RECIST). Various side effects of sorafenib treatment appeared, such as moderate hand-foot

syndrome, diarrhea, weight loss (8 kg within 3 months) and alopecia. Symptoms could be relieved successfully with dose reduction (to 2x200 mg daily) for ten days and supportive medical treatment. During the next twenty months, Tg levels showed a significant increase, from 190.9 ng/mL to 2170.0 ng/mL, while imaging techniques did not show any change in the state of disease. Then in 2013 October, physical examination revealed palpable nodules with approximately 1-1.5 cm diameter on both side of the neck. FNAB results confirmed the lymph node metastases of the primary disease. Sorafenib treatment was stopped due to the progression. At the beginning of 2014, surgical removal of the pathologic lymph node metastases was performed (Tg level decreased from 3570 ng/mL to 882 ng/mL) and then sorafenib therapy was restarted in 2014 July in 2x400 mg dose. No other treatment was used after sorafenib reintroduction. In 2016 June, at the end of follow-up the patient was in stable condition with sorafenib (Tg 713.9 ng/mL). Changes of thyroglobulin levels during the course of the disease are presented on Figure 13.

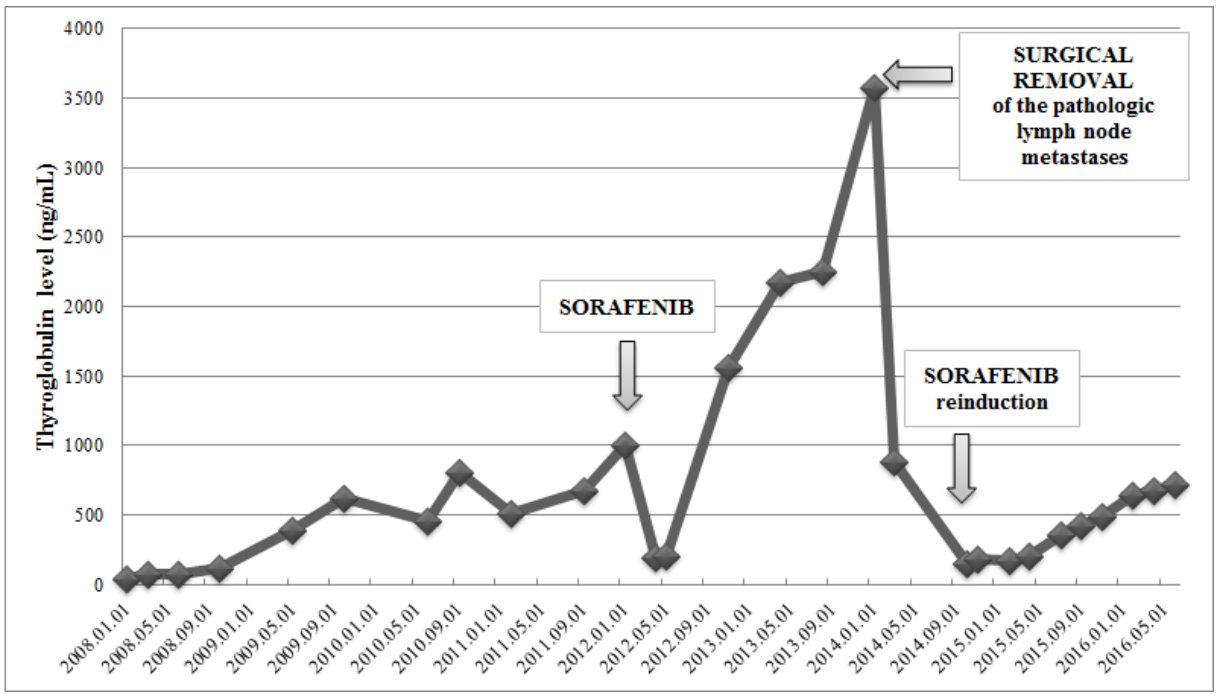


Figure 13 - Changes of thyroglobulin levels during the course of the disease.

6.4 Discussion

It was known from earlier clinical data that sorafenib is an effective therapeutic option for iodine-refractory, locally advanced or metastatic DTC. Appropriate starting dose is questionable, many clinicians try to use a smaller than 800 mg starting dose to eliminate or reduce the appearance of adverse effects, and it seems that reduced daily dose is not influence negatively the efficacy of sorafenib, although according some findings reduced starting doses not necessarily lead to better tolerability [77]. Nowadays other promising results were published with lenvatinib, sunitinib and selumetinib [78-80].

We presented a patient suffering from oncocytic FTC with 15 years of disease duration. Radioiodine-resistance and PET positivity indicated the poor prognosis of the tumor. The patient had two thyroid operations and received three high-dose radioiodine treatments and two irradiation therapies. Despite of the conventional treatment options, disease showed progression from time to time. She was one of the first patients in Hungary receiving sorafenib therapy. Therapeutic response to sorafenib treatment was really good, although several side effects developed like hand-foot syndrome, diarrhea, weight loss and alopecia. After 20 months of treatment, progression was detected in the cervical lymph node metastases but not in the pulmonary metastases. After the surgical removal of metastatic lymph nodes, the sorafenib therapy was continued and has been effective to stabilize the disease until today. Tg level was more sensitive predictor of disease recurrence than imaging techniques.

In conclusion, sorafenib is an effective option for iodine-refractory, locally advanced or metastatic DTC. Adverse effects are mostly manageable and well-tolerated. Clinicians should carefully evaluate the use of systematic sorafenib treatment with the consideration of individual basis.

7. Summary of new scientific results

1) Clinical data of 380 DTC patients treated between 01 Jan 2005 and 01 May 2016 at the Ist Dept. of Internal Medicine, University of Pecs were analyzed and a general good prognosis was found. However, 31% of FTC and 14% of PTC patients could not reach tumor-free stage. During the median 55-month follow-up time the disease-specific mortality in FTC was 10%, while in PTC was 2%. The problem in the region is not the recognition of too many early stages microcarcinoma, but the delay of diagnosis.
2) The incidence rate of PTC/FTC was 79/21%. The distribution of histological subtypes was similar to literature data. In PTC, lymph node metastases were found in 35%, distant metastases in 4% of cases, while in FTC this ratio was 15% (N1) and 14% (M1). Surgery was performed in overall 625 cases. One surgery in 191, two in 150, three in 24 and more than 3 was performed in case of 14 patients. Radioiodine treatment was done in 542 cases; PTC patients had an average of 1.3, while FTC patients received an average 1.8 RAI treatments. External radiotherapy was needed in case of 27 patients (17 papillary, 10 follicular carcinomas).
3) Residual tumor was detected by SPECT/CT in 21.7% of patients. The original ATA risk stratification was changed by the results of SPECT/CT in 115 (35.6%) of cases. Sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of ATA and ETA risk classification systems and SPECT/CT were evaluated. The results of SPECT/CT alone, without any other data, had the highest specificity and diagnostic accuracy, with similar sensitivity to other methods. SPECT/CT results were the strongest predictors of outcome in models which contain age, TNM stage, clinical staging, histology, ATA, ETA risk classification and SPECT/CT (binary logistic regression analysis).

SPECT/CT after radioiodine treatment is a useful tool in the early classification of DTC patients and its use should be included in the management of patients with DTC.

4) Sorafenib was used for the treatment of RAI-refractory, locally advanced or metastatic thyroid cancer in 21 cases in our clinic. Partial remission or stable disease was reached in 14 patients (66%) with a median 15-month treatment time, and treatment is ongoing in 8 cases. A successful reintroduction of treatment was done in 1 patient.

8. References

1. Furio Pacini, Martin Schlumberger, Henning Dralle, Rossella Elisei, Johannes W. A. Smit, Wilmar Wiersinga and the European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. European Journal of Endocrinology 2006, 154;787-803
2. Sherman SI. Thyroid carcinoma. Lancet. 2003;361:501–511.
3. Bychkov, A. World Health Organization (WHO) classification. PathologyOutlines.com website. http://www.pathologyoutlines.com/topic/thyroidwho.html. Accessed July 14th, 2018.
4. Tuttle M, Morris LF, Haugen B, Shah J, Sosa JA, Rohren E, Subramaniam RM, Hunt JL, Perrier ND 2017 Thyroid-Differentiated and Anaplastic Carcinoma (Chapter 73). In: Amin MB, Edge SB, Greene F, Byrd D, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley J, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR, (eds) AJCC Cancer Staging Manual. 8th ed. Springer International Publishing, New York City.
5. Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid. 2013; 23: 885-91. doi: 10.1089/thy.2013.0045.
6. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013; 2013: 965212. doi: 10.1155/2013/965212.
7. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, Negri E. Thyroid cancer mortality and incidence: a global overview. Int J Cancer. 2015; 136: 2187-95. doi: 10.1002/ijc.29251.
8. Brito JP, Al Nofal A, Montori VM, Hay ID, Morris JC. The Impact of Subclinical Disease and Mechanism of Detection on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Olmsted County, Minnesota During 1935 Through 2012. Thyroid. 2015; 25: 999-1007. doi: 10.1089/thy.2014.0594.
9. Morris LG, Tuttle RM, Davies L. Changing Trends in the Incidence of Thyroid Cancer in the United States. JAMA Otolaryngol Head Neck Surg. 2016; 142: 709-11. doi: 10.1001/jamaoto.2016.0230.
10. https://seer.cancer.gov/statfacts/html/thyro.html, accessed in 04/OCT/2017
11. Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. Curr Opin Endocrinol Diabetes Obes. 2017 Oct;24(5):332-336.
12. European Network of Cancer Registries: Thyroid cancer factsheets. 2017, January https://www.encr.eu/factsheets, accessed 23/JUL/2018
13. http://www.onkol.hu/hu/nemzeti_rakregiszter, accessed in 04/OCT/2017
14. IARC (2004). Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press.
15. Moysich KB, Menezes RJ, Michalek AM (2002). Chernobyl-related ionising radiation exposure and cancer risk: an epidemiological review. Lancet Oncol. 3(5):269–79. http://dx.doi.org/10.1016/S1470-2045(02)00727-1 PMID:12067803
16. Mahoney MC, Lawvere S, Falkner KL, Averkin YI, Ostapenko VA, Michalek AM, et al. (2004). Thyroid cancer incidence trends in Belarus: examining the impact of Chernobyl. Int J Epidemiol. 33(5):1025–33. http://dx.doi.org/10.1093/ije/dyh201 PMID:15166190
17. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. (1995). Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res. 141(3):259–77. http://dx.doi.org/10.2307/3579003 PMID:7871153

18. Duntas LH, Doumas C (2009). The 'rings of fire' and thyroid cancer. Hormones (Athens). 8(4):249–53. http://dx.doi.org/10.14310/horm.2002.1242 PMID:20045797
19. Malandrino P, Scollo C, Marturano I, Russo M, Tavarelli M, Attard M, et al. (2013). Descriptive epidemiology of human thyroid cancer: experience from a regional registry and the "volcanic factor". Front Endocrinol (Lausanne). 4:65. http://dx.doi.org/10.3389/fendo.2013.00065 PMID:23761783
20. Harach HR, Ceballos GA (2008). Thyroid cancer, thyroiditis and dietary iodine: a review based on the Salta, Argentina model. Endocr Pathol. 19(4):209–20. http://dx.doi.org/10.1007/s12022-008-9038-y PMID:18696273
21. Sehestedt T, Knudsen N, Perrild H, Johansen C (2006). Iodine intake and incidence of thyroid cancer in Denmark. Clin Endocrinol (Oxf). 65(2):229–33. http://dx.doi.org/10.1111/j.1365-2265.2006.02580.x PMID:16886965
22. Blomberg M, Feldt-Rasmussen U, Andersen KK, Kjaer SK (2012). Thyroid cancer in Denmark 1943–2008, before and after iodine supplementation. Int J Cancer. 131(10):2360–6. http://dx.doi.org/10.1002/ijc.27497 PMID:22337133
23. Harach HR, Galíndez M, Campero M, Ceballos GA (2013). Undifferentiated (anaplastic) thyroid carcinoma and iodine intake in Salta, Argentina. Endocr Pathol. 24(3):125–31. http://dx.doi.org/10.1007/s12022-013-9248-9 PMID:23666798
24. Rinaldi S, Plummer M, Biessy C, Tsilidis KK, Østergaard JN, Overvad K, et al. (2014). Thyroid-stimulating hormone, thyroglobulin, and thyroid hormones and risk of differentiated thyroid carcinoma: the EPIC study. J Natl Cancer Inst. 106(6):dju097.
25. McLeod DSA, Watters KF, Carpenter AD, Ladenson PW, Cooper DS, Ding EL (2012). Thyrotropin and thyroid cancer diagnosis: a systematic review and dose–response meta-analysis. J Clin Endocrinol Metab. 97(8):2682–92.
26. Negri E, Dal Maso L, Ron E, La Vecchia C, Mark SD, Preston-Martin S, et al. (1999). A pooled analysis of case–control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control. 10(2):143–55.
27. Stewart BW, Wild CP, editors. (2014). World cancer report 2014. Lyon: International Agency for Research on Cancer.
28. Papaleontiou M, Haymart MR (2014). New insights in risk stratification of differentiated thyroid cancer. Curr Opin Oncol. 26(1):1–7.
29. Nosé V (2011). Familial thyroid cancer: a review. Mod Pathol. 24(S2):S19–33. http://dx.doi.org/10.1038/modpathol.2010.147 PMID:21455198
30. Malchoff CD, Malchoff DM (2006). Familial nonmedullary thyroid carcinoma. Cancer Control. 13(2):106–10. PMID:16735984
31. Bonora E, Tallini G, Romeo G (2010). Genetic predisposition to familial nonmedullary thyroid cancer: an update of molecular findings and state-of-the-art studies. J Oncol. 2010:385206.
32. Malaguarnera R Vella V, Pellegriti G, Belfiore A: Editorial: Clinical and Molecular Epidemiology of Thyroid Cancer of Follicular Origin. Front Endocrinol (Lausanne). 2018; 9: 67.
33. Xing M: Molecular pathogenesis and mechanisms of thyroid cancer. Nat Rev Cancer. 2013 Mar; 13(3): 184–199.
34. Muresan M. M., P. Oliver, J. Leclére, F. Sirveaux, L. Brunaud, M. Klein, R. Zarnegar and G. Weryha. Bone metastases from differentiated thyroid carcinoma; Endocrine-Related Cancer 2008; 15:37-49
35. Caleo O, Maurea S, Klain M, Salvatore B, Storto G, Mancini M, Pace L and Salvatore M. Postsurgical diagnostic evaluation of patients with differentiated thyroid carcinoma: comparison of ultrasound, iodine-131 scintigraphy and PET with fluorine-18 fluorodeoxyglucose. Abstr. Radiol Med 2008, Med;113(2):278-88

36. 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, et al.: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016; 26: 1-133.
37. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, Brokhin M, Omry G, Fagin JA, Shaha A. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20(12):1341. Epub 2010 Oct 29.
38. Vaisman F, Shaha A, Fish S, Michael Tuttle R: Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. Clin Endocrinol (Oxf). 2011;75(1):112.
39. Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, Braunstein GD, Lee S, Davies TF, Arafah BM, Ladenson PW, Pinchera A: A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab. 2003;88(4):1433.
40. Shaha AR, Loree TR, Shah JP: Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. Surgery. 1995;118(6):1131.
41. Torlontano M, Crocetti U, Augello G, D'Aloiso L, Bonfitto N, Varraso A, Dicembrino F, Modoni S, Frusciante V, Di Giorgio A, Bruno R, Filetti S, Trischitta V: Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole-body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid microcarcinoma who have not undergone radioiodine therapy. J Clin Endocrinol Metab. 2006;91(1):60. Epub 2005 Oct 11.
42. Frasoldati A, Pesenti M, Gallo M, Caroggio A, Salvo D, Valcavi R: Diagnosis of neck recurrences in patients with differentiated thyroid carcinoma. Cancer. 2003;97(1):90.
43. American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19: 1167-214. doi: 10.1089/thy.2009.0110.
44. Szujó S, Farkas R, Illényi L, et al. Successful reinduction therapy by sorafenib in oncocytic follicular thyroid cancer: a case report. JSM Chem. 2016; 4: 1028.
45. Gyory F, Lukacs G, Nagy EV, et al. Differentiated thyroid carcinoma: prognostic factors. [Differenciált pajzsmirigyrák: prognosztikai faktorok.] Magy Seb. 2001; 54: 69–74. [Hungarian]
46. Gyory F, Balazs G, Nagy EV, et al. Differentiated thyroid cancer and outcome in iodine deficiency. Eur J Surg Oncol. 2004; 30:325–331.
47. Oh JR, Byun BH, Hong SP, Chong A, Kim J, Yoo SW, Kang SR, Kim DY, Song HC, Bom HS, Min JJ. Comparison of (1)(3)(1)I whole-body imaging, (1)(3)(1)I SPECT/CT, and (1)(8)F-FDG PET/CT in the detection of metastatic thyroid cancer. Eur J Nucl Med Mol Imaging. 2011; 38: 1459-68. doi: 10.1007/s00259-011-1809-x.
48. Ota N, Kato K, Iwano S, Ito S, Abe S, Fujita N, Yamashiro K, Yamamoto S, Naganawa S. Comparison of (1)(8)F-fluoride PET/CT, (1)(8)F-FDG PET/CT and bone scintigraphy (planar and SPECT) in detection of bone metastases of differentiated thyroid cancer: a pilot study. Br J Radiol. 2014; 87: 20130444. doi: 10.1259/bjr.20130444.

49. Barwick T, Murray I, Megadmi H, Drake WM, Plowman PN, Akker SA, Chew SL, Grossman AB, Avril N. Single photon emission computed tomography (SPECT)/computed tomography using Iodine-123 in patients with differentiated thyroid cancer: additional value over whole body planar imaging and SPECT. Eur J Endocrinol. 2010; 162: 1131-9. doi: 10.1530/EJE-09-1023.
50. Schmidt D, Linke R, Uder M, Kuwert T. Five months' follow-up of patients with and without iodine-positive lymph node metastases of thyroid carcinoma as disclosed by (131)I-SPECT/CT at the first radioablation. Eur J Nucl Med Mol Imaging. 2010; 37: 699-705. doi: 10.1007/s00259-009-1299-2.
51. Kohlfuerst S, Igerc I, Lobnig M, Gallowitsch HJ, Gomez-Segovia I, Matschnig S, Mayr J, Mikosch P, Beheshti M, Lind P. Posttherapeutic (131)I SPECT-CT offers high diagnostic accuracy when the findings on conventional planar imaging are inconclusive and allows a tailored patient treatment regimen. Eur J Nucl Med Mol Imaging. 2009; 36: 886-93. doi: 10.1007/s00259-008-1044-2.
52. Utsunomiya D, Shiraishi S, Imuta M, Tomiguchi S, Kawanaka K, Morishita S, Awai K, Yamashita Y. Added value of SPECT/CT fusion in assessing suspected bone metastasis: comparison with scintigraphy alone and nonfused scintigraphy and CT. Radiology. 2006; 238: 264-71. doi: 10.1148/radiol.2373041358.
53. Wakabayashi H, Nakajima K, Fukuoka M, Inaki A, Nakamura A, Kayano D, Kinuya S. Double-phase (131)I whole body scan and (131)I SPECT-CT images in patients with differentiated thyroid cancer: their effectiveness for accurate identification. Ann Nucl Med. 2011; 25: 609-15. doi: 10.1007/s12149-011-0513-z.
54. Wang H, Fu HL, Li JN, Zou RJ, Gu ZH, Wu JC. The role of single-photon emission computed tomography/computed tomography for precise localization of metastases in patients with differentiated thyroid cancer. Clin Imaging. 2009; 33: 49-54. doi: 10.1016/j.clinimag.2008.06.024.
55. Xue YL, Qiu ZL, Song HJ, Luo QY. Value of (1)(3)(1)I SPECT/CT for the evaluation of differentiated thyroid cancer: a systematic review of the literature. Eur J Nucl Med Mol Imaging. 2013; 40: 768-78. doi: 10.1007/s00259-012-2310-x.
56. Zambo K SE, Szabo Zs, Sarkadi M, Dérczy K, Szekeres S. News and new opportunities for clinical applications of SPECT/CT. [Hun]. Magyar Onkológia. 2015; 59: 17-24. doi:
57. Barwick TD, Dhawan RT, Lewington V. Role of SPECT/CT in differentiated thyroid cancer. Nucl Med Commun. 2012; 33: 787-98. doi: 10.1097/MNM.0b013e3283550257.
58. Spanu A, Solinas ME, Chessa F, Sanna D, Nuvoli S, Madeddu G. 131I SPECT/CT in the follow-up of differentiated thyroid carcinoma: incremental value versus planar imaging. J Nucl Med. 2009; 50: 184-90. doi: 10.2967/jnumed.108.056572.
59. Cano-Palomares A, Castells I, Capel I, Bella MR, Barcons S, Serrano A, Guirao X, Rigla M. Response to initial therapy of differentiated thyroid cancer predicts the long-term outcome better than classical risk stratification systems. Int J Endocrinol. 2014; 2014: 591285. doi: 10.1155/2014/591285.
60. Sarkadi M ZK, Schmidt E, Szabo Zs, Szekeres S. SPECT/CT in diagnosis and therapeutic follow-up of thyroid cancer. [Hun]. IME. 2010; 9: 23-7
61. Grewal RK, Tuttle RM, Fox J, Borkar S, Chou JF, Gonen M, Strauss HW, Larson SM, Schoder H. The effect of posttherapy 131I SPECT/CT on risk classification and management of patients with differentiated thyroid cancer. J Nucl Med. 2010; 51: 1361-7. doi: 10.2967/jnumed.110.075960.
62. Kohlfurst S. The role of nuclear medicine in differentiated thyroid cancer. Wien Med Wochenschr. 2012; 162: 407-15. doi: 10.1007/s10354-012-0129-5.
63. Avram AM, Esfandiari NH, Wong KK. Preablation 131-I scans with SPECT/CT contribute to thyroid cancer risk stratification and 131-I therapy planning. J Clin Endocrinol Metab. 2015; 100: 1895-902. doi: 10.1210/jc.2014-4043.

64. Shen CT, Wei WJ, Qiu ZL, Song HJ, Luo QY. Value of post-therapeutic (131)I scintigraphy in stimulated serum thyroglobulin-negative patients with metastatic differentiated thyroid carcinoma. Endocrine. 2016; 51: 283-90. doi: 10.1007/s12020-015-0660-4.
65. Chen L, Luo Q, Shen Y, Yu Y, Yuan Z, Lu H, Zhu R. Incremental value of 131I SPECT/CT in the management of patients with differentiated thyroid carcinoma. J Nucl Med. 2008; 49: 1952-7. doi: 10.2967/jnumed.108.052399.
66. Yamamoto Y, Nishiyama Y, Monden T, Matsumura Y, Satoh K, Ohkawa M. Clinical usefulness of fusion of 131I SPECT and CT images in patients with differentiated thyroid carcinoma. J Nucl Med. 2003; 44: 1905-10. doi:
67. Wong KK, Zarzhevsky N, Cahill JM, Frey KA, Avram AM. Hybrid SPECT-CT and PET-CT imaging of differentiated thyroid carcinoma. Br J Radiol. 2009; 82: 860-76. doi: 10.1259/bjr/25645894.
68. Wong KK, Sisson JC, Koral KF, Frey KA, Avram AM. Staging of differentiated thyroid carcinoma using diagnostic 131I SPECT/CT. AJR Am J Roentgenol. 2010; 195: 730-6. doi: 10.2214/AJR.09.3458.
69. Ciappuccini R, Heutte N, Trzepla G, Rame JP, Vaur D, Aide N, Bardet S. Postablation (131)I scintigraphy with neck and thorax SPECT-CT and stimulated serum thyroglobulin level predict the outcome of patients with differentiated thyroid cancer. Eur J Endocrinol. 2011; 164: 961-9. doi: 10.1530/EJE-11-0156.
70. Ciappuccini R, Hardouin J, Heutte N, Vaur D, Quak E, Rame JP, Blanchard D, de Raucourt D, Bardet S. Stimulated thyroglobulin level at ablation in differentiated thyroid cancer: the impact of treatment preparation modalities and tumor burden. Eur J Endocrinol. 2014; 171: 247-52. doi: 10.1530/EJE-14-0192.
71. Marotta V, Sciammarella C, Vitale M, Colao A, Faggiano A. The evolving field of kinase inhibitors in thyroid cancer. Crit Rev Oncol Hematol. 2015; 93(1): 60-73.
72. Blair HA, Plosker GL. Sorafenib: a review of its use in patients with radioactive iodine-refractory, metastatic differentiated thyroid carcinoma. Target Oncol. 2015; 10(1): 171-8.
73. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014; 384(9940): 319-28.
74. McFarland DC, Misiukiewicz KJ. Sorafenib in radioactive iodine-refractory well-differentiated metastatic thyroid cancer. Onco Targets Ther. 2014; 7: 1291-9.
75. Pitoia F. Response to sorafenib treatment in advanced metastatic thyroid cancer. Arq Bras Endocrinol Metabol. 2014; 58(1): 37-41.
76. Gallo M, Michelon F, Castiglione A, Felicetti F, Viansone AA, Nervo A, et al. Sorafenib treatment of radioiodine-refractory advanced thyroid cancer in daily clinical practice: a cohort study from a single center. Endocrine. 2015; 49(3):726-34.
77. Dadu R, Waguespack SG, Sherman SI, Hu MI, Busaidy NL, Jimenez C, et al. Efficacy and tolerability of different starting doses of sorafenib in patients with differentiated thyroid cancer. Oncologist. 2014; 19(5): 477-82.
78. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015; 372:621-630.
79. Marotta V, Di Somma C, Rubino M, Sciammarella C, Modica R, Camera L, et al. Second-line sunitinib as a feasible approach for iodine-refractory differentiated thyroid cancer after the failure of first-line sorafenib. Endocrine. 2015; 49(3):854-8.
80. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N. Engl. J. Med. 2013; 368: 623–632.

9. List of figures and tables

10. List of publications

10.1 Publications related to the thesis

1. Szujo Sz, Farkas R, Illenyi L, Kalman E, Schmidt E, Mangel L, Mezosi E: Successful Reinduction Therapy by Sorafenib in Oncocytic Follicular Thyroid Cancer: a Case Report. JSM CHEMISTRY 4:(3) Paper 1028. 4 p. (2016)
2. Szujo Sz, Sira L, Bajnok L, Bodis B, Gyory F, Nemes O, Rucz K, Kenyeres P, Valkusz Z, Sepp K, Schmidt E, Szabo Z, Szekeres S, Zambo K, Barna S, Nagy EV, Mezosi E: The impact of post-radioiodine therapy SPECT/CT on early risk stratification in differentiated thyroid cancer; a bi-institutional study. ONCOTARGET 8:(45) pp. 79825-79834. (2017) **IF: 5.168, Q1**
3. Szujó Sz, Bajnok L, Bodis B, Nemes O, Rucz K, Mezosi E: A differenciált pajzsmirigyrákban szenvedő betegek gyógyulási esélyei. Egy hazai centrum tapasztalatai. ORVOSI HETILAP 159:(22) pp. 878-884. (2018) **IF: 0.322**

10.2 Publications not related to the thesis

1. Gáspár B, Bódis B, Nemes O, Szujó Sz, Bajnok L, Mezősi E: A hyponatraemia előfordulása és okai egy belgyógyászati-endokrinológiai osztály kétéves beteganyagában. MAGYAR BELORVOSI ARCHIVUM 67:(6) pp. 399-405. (2014)
2. Nemes, N Kovacs, Sz Szujo, B Bodis, L Bajnok, A Buki, T Doczi, E Czeiter, E Mezosi: Can early clinical parameters predict post-traumatic pituitary dysfunction in severe traumatic brain injury? ACTA NEUROCHIRURGICA 158:(12) pp. 2347-2353. (2016) **IF: 1.881**
3. Tenk J, Mátrai P, Hegyi P, Rostás I, Garami A, Szabó I, Hartmann P, Pétervári E, Czopf L, Hussain A, Simon M, Szujó Sz, Balaskó M: Perceived stress correlates with visceral

obesity and lipid parameters of the metabolic syndrome: a systematic review and meta-analysis. PSYCHONEUROENDOCRINOLOGY 95:(1) pp. 63-73. (2018) **IF: 4.731**

10.3 Presentations and posters related to the thesis

1. Szujó Sz, Bajnok L, Bódis B, Rucz K, Mezősi E: A differenciált pajzsmirigy carcinomás betegek gondozása. MEAT XXV. Kongresszusza, Pécs, 2014. június 05-07.
2. Szujó Sz, Bajnok L, Bódis B, Nemes O, Rucz K, Mezősi E: Az első hazai tapasztalatok a Nexavar kezeléssel differenciált pajzsmirigyrákban. Magyar Belgyógyász Társaság Dunántúli Szekciójának LVIII. Vándorgyűlés, Kaposvár, 2015. június 18-20
3. Mezosi E, Szujo Sz: Predictive value of single-photon emission computed tomography/computed tomography after radioiodine therapy in differentiated thyroid cancer. "Individualized management of well-differentiated thyroid cancer" conference, Athén, 2015. december 5.
4. Szujó Sz, Bajnok L, Bódis B, Győry F, Nemes O, Rucz K, Kenyeres P, Valkusz Zs, Sepp K, Schmidt E, Szabó Zs, Szekeres S, Zámbó K, Mezősi E: Az első radiojód kezelés után végzett, SPECT/CT-vel kiegészített izotóp vizsgálat prediktív értéke differenciált pajzsmirigyrákban. MEAT 26. Kongresszusa, 2016.05.05-07.- (Góth Endre díj - a Kongresszus legjobb klinikai tárgyú előadásáért)
5. Sz Szujo, E Schmidt, Zs Szabo, S Szekeres, K Zambo, E Mezosi: Predictive value of SPECT/CT after radioiodine therapy in differentiated thyroid cancer. ECE, Munich, Germany, 2016.május 28-31.
6. Szujó Sz: Tapasztalatok Nexavar kezeléssel a differenciált pajzsmirigy carcinomás betegeknél XXII. PECH 2015.10.02-03.

7. Sz Szujo, L Sira, L Bajnok, B Bodis, F Gyory, O Nemes, K Rucz, P Kenyeres, Zs Valkusz, K Sepp, E Schmidt, Zs Szabo, S Szekeres, K Zambo, S Barna, EV Nagy, E Mezosi: The impact of post-radioiodine therapy SPECT/CT on risk stratification in differentiated thyroid cancer; a bi-institutional study. ECE, Lisbon, Portugal, 2017. május 20-23.
8. Szujó Sz: A radiojód terápiát követő SPECT/CT vizsgálat korai rizikó klasszifikációban betöltött szerepe differenciált pajzsmirigyrákban. Magyar Belgyógyász Társaság Dunántúli Szekciójának LIX. Vándorgyűlése, 2017. június 15-17.
9. Szujó Sz, Mezősi E: Nyelvgyöki áttét papillaris pajzsmirigyrákban. XXIV. PECH 2017.10.06-07.
10. Sz Szujo, E Mezosi: Lingual metastasis of papillary thyroid carcinoma? 22nd Postgraduate Course in Clinical Endocrinology 2018. február 22-25. - Nodular thyroid - thyroid cancer kategóriában díjazott előadás

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