The evaluation of prognostic factors in differentiated thyroid cancer

Ph.D. Thesis

Szabina Szujo M.D.

Doctoral School:
Clinical Medical Sciences

Doctoral Program:
Clinical aspects and pathobiochemistry of metabolic and endocrine diseases

Program leader and Supervisor:
Prof. Emese Mezosi MD, PhD

Ist Department of Internal Medicine
University of Pecs
2019

1. Introduction

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. Although the use of improved techniques leads to earlier and more accurate diagnosis, it may result in overdiagnosis and overtreatment; there is an urgent need to better distinguish the high-risk patients requiring therapy from those who do not need radioiodine after surgery, or may not need treatment at all. Patients with differentiated thyroid cancer (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. The conventional and effective treatment consists of surgical management followed by radioiodine (RAI) ablation of thyroid remnants and thyroid-stimulating hormone (TSH) suppressive therapy. Recently, the universal use of remnant ablation after surgery has been debated and mainly restricted to advanced disease. However, radioiodine 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 whole-body scan (WBS) or single photon emission computed tomography/computed tomography (SPECT/CT) may reveal previously undiagnosed tumor foci. Postoperative and follow-up management of patients with DTC highly depends on risk classification. Different risk stratification systems are used by the American Thyroid Association (ATA, 2009, 2015) and the European Thyroid Association (ETA, 2006). 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. 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 follicular thyroid cancers (FTC) 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.

2. 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 papillary thyroid cancer (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.

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

3.1 Patients and methods

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 (male and woman ratio was 74/306; median age at the time of diagnosis: 46 years {13-86 years}; median follow-up time: 55 months {0-144 months}). TSH, thyroglobulin (Tg) and thyroglobulin antibody (TgAb) were measured by electrochemiluminescence assays {Elecsys® TSH assay, Elecsys® TG II assay, Elecsys® anti-TG assay (Roche)}. Low risk patients younger than 45 years and whithout aggressive histology recieved 1100 MBq dose, while other patients received 3700 MBq dose RAI treatment. Statistical analysis was done with Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA, version 22.0).

3.2 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. 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). 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. 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. 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. In 2016, 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 1).

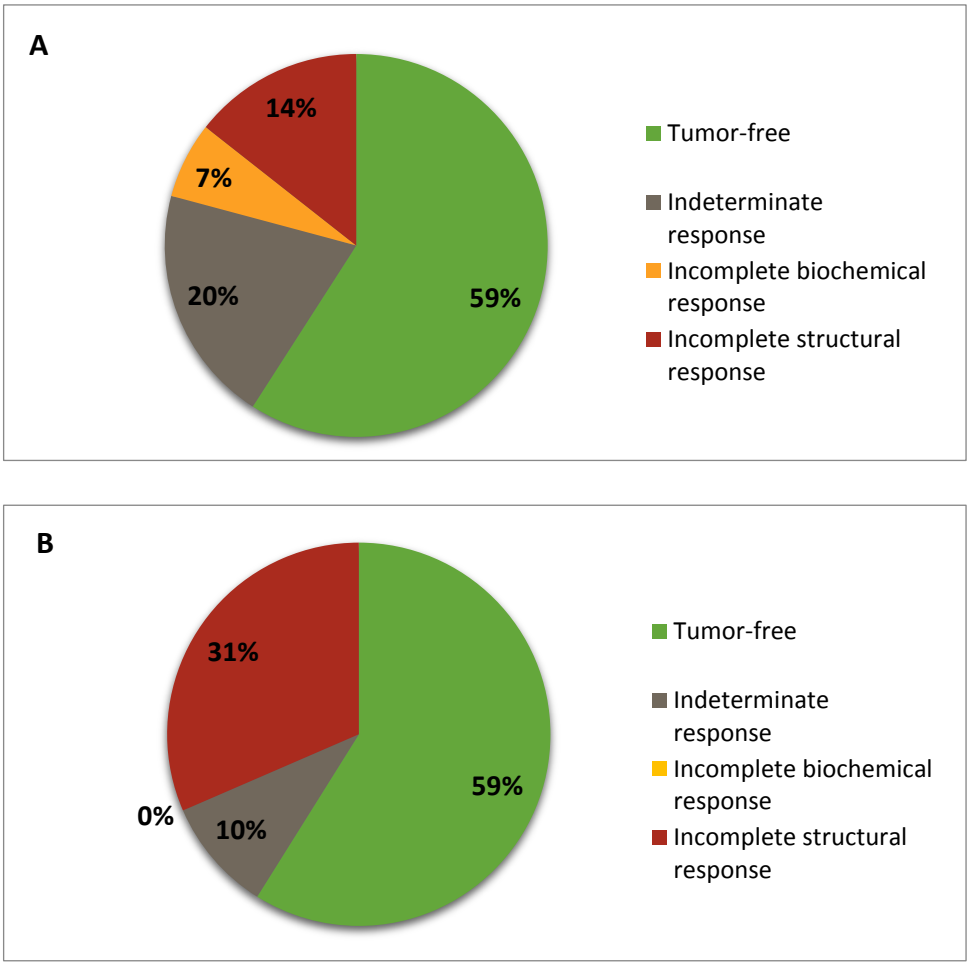

Figure 1 - Treatment results in papillary (A) and follicular (B) carcinoma in 2016

3.3 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. 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. 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%.

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

4.1. Patients and methods

After their first radioiodine treatment, 323 consecutive DTC patients (181 at the University of Pecs and 142 at the University of Debrecen) were investigated (female and male ratio was 246/77; 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. Histology detected lymph node involvement in 95 cases, distant metastases were known in 12 patients. TgAb positivity was found in 88 patients. 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). 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. 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. TSH, Tg and TgAb were measured by electrochemiluminescence assays (University of Pecs: Elecsys® TSH assay, Elecsys® TG II assay, Elecsys® anti-TG assay [Roche}; University of Debrecen: LIAISON®-Tg {DiaSorin S.p.A}, DYNOtest anti-Tg {BRAHMS Diagnostica GmbH} and Elecsys® anti-TG assay{Roche}). Statistical analysis was done with Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA, version 22.0).

4.2. Results

No evidence of tumor was detected by SPECT/CT in 78.3% of cases. 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. 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%. 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. 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 1).

Table 1 - 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 2). 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 2 - 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**

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.

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 3.

Table 3 - 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 4.

Table 4 - 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 5).

Table 5 - 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 ($p<0.001$).

4.3. 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. 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. 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. The important diagnostic impact and the superiority of SPECT/CT over planar scintigraphy in cases of inconclusive lesions were also highlighted by others. 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.

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.

5. Experiences with new therapeutic options in differentiated thyroid cancer

5.1. Patients and methods

In the Ist Department of Internal Medicine, overall 21 patients with advanced, radioiodine refractory DTC were treated with sorafenib until March, 2018 (female to male ratio was 17/4, median age at the start of treatment was 67 {range 37 to 88} years, 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.

5.2. 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. 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. 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. 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 2.

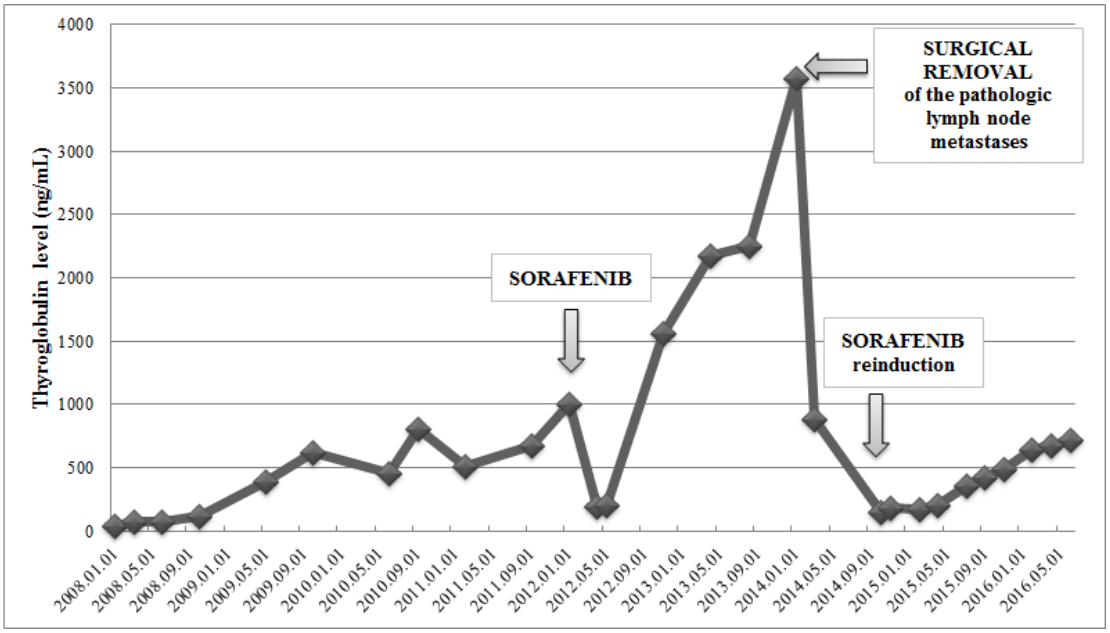

Figure 2 - Changes of thyroglobulin levels during the course of the disease.

5.3. 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. Nowadays other promising results were published with lenvatinib, sunitinib and selumetinib.

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.

6. 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.

7. List of publications

7.1 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. Szujo 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**

7.2 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**
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obesity and lipid parameters of the metabolic syndrome: a systematic review and meta-analysis. PSYCHONEUROENDOCRINOLOGY 95:(1) pp. 63-73. (2018) **IF: 4.731**

7.3 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

8. Acknowledgement

First of all, I would like to express my deepest gratitude to my mentor, Professor Emese

Mezosi, who gave me the love of endocrinology, suggested my PhD theme, provided all support and encouragement throughout my PhD work and even beyond that.

I am especially thankful to Professor Laszlo Bajnok for assisting my work with useful

ideas and new suggestions.

I would like to acknowledge the supports of Professor Endre V Nagy, Livia Sira, Zsuzsanna Valkusz, Krisztian Sepp, Ferenc Gyory their valuable help has greatly contributed to the result of this scientific work.

I would like to express my thanks to Erzsebet Schmidt, Zsuzsanna Szabo, Sarolta Szekeres, Professor Katalin Zambo and Sandor Barna, their valuable help in the nuclear medicine aspects of the scientific work was most appreciated.

I am also thankful to Peter Kenyeres for his contribution in the statistical aspects of my work.

I would like to express my special thanks to Zita Tarjanyi, Adrienn Litz, Kinga Totsimon, Dora Praksch, Dávid Kovács and Kornélia Fazekas Tapasztóné for their encouragement, stylistical help, and for the friendly lab community, too.

I am grateful for the encouragement of my immediate colleagues Orsolya Nemes, Beáta Bódis and Károly Rucz.

Last, but not least I thank all my family and my dear husband for their continuous support, patience and endurance during these past years.