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RISK STRATIFICATION AND RADIOIODINE THERAPY RESPONSE IN DIFFERENTIATED THYROID CANCER: A SINGLE CENTER EXPERIENCE

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Differentiated thyroid cancer (DTC) is the predominant thyroid malignancy, the first-line therapy is surgery, followed by radioiodine (^{131}I) ablation therapy and L-thyroxine suppression therapy. The aim of this study was to evaluate clinical characteristics and the occurrence of radioiodine-refractory disease in patients with DTC treated with radioiodine therapy. This retrospective monocentric study included 312 patients diagnosed with DTC treated between 2017 and 2024. Radioiodine therapy was performed under TSH stimulation, according to the established clinical protocols. All patients had post-therapy whole-body scan (WBS), and control WBS 6-12 months after the therapy. Totally 65.1% of the patients received only one dose of radioiodine, while the others had to be treated more than once. On follow-up, 27 patients (8.7%) have developed radioiodine-refractory DTC (RAI-R). The histological subtype and the number of administered radioiodine doses did not differ statistically. Radioiodine-refractory DTC was significantly more frequent in patients older than 50 ($p=0.028$).

Key words: differentiated thyroid cancer, radioiodine-refractory DTC, thyroid cancer surgery, histopathology of thyroid cancer

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STRATIFIKACIJA RIZIKA I ODGOVOR NA RADIOJODNU TERAPIJU KOD DIFERENTOVANOG KARCINOMA ŠTITASTE ŽLEZDE: ISKUSTVO JEDNOG CENTRA

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Diferentovan tireoidni karcinom (DTK) je glavni oblik tireoidnih malignih bolesti i tretira se hirurški sa naknadnom radiojodnom (^{131}I) ablacionom terapijom i L-tiroksinskom supresionom terapijom. Cilj ove studije je bio da ispitaju kliničke karakteristike, kao i pojava radiojodne refraktorne bolesti (RAI) kod pacijenata tretiranih radiojodom. Retrospektivna studija je uključila 312 pacijenta sa diferentovanim tireoidnim karcinomom tretiranim u periodu od 2017. do 2024. godine. Radiojodna terapija je obavljana pod TSH stimulacijom prema utvrdjenim kliničkim protokolima. Svim pacijentima je posle terapije načinjen sken celog tela, sa kontrolom posle 6-12 meseci. Ukupno 65.1% pacijenata je primilo jednu dozu radiojoda, dok je kod ostalih aplikovano više doza. Praćenjem je ustanovljeno da je 27 pacijenata (8.7%) razvilo radiojodni refraktorni karcinom. Histološki subtip karcinoma i broj primljenih doza radiojoda se nije statistički razlikovao. Refraktorni tireoidni karcinom je bio značajno češći kod pacijenata starijih od 50 godina.

Ključne reči: diferentovani tireoidni karcinom, radiojodno refraktorni karcinom, hirurgija karcinoma tiroideje, histopatologija karcinoma tiroideje

Introduction

Thyroid cancer represents one of the most frequent endocrine malignant diseases, accounting for approximately 1-2% of all newly diagnosed cancers worldwide (1). Differentiated thyroid cancer (DTC) accounts for the majority of cases, and the 10-year survival rate is over 95% (2).

The global incidence of thyroid cancer has significantly increased over the last five decades (3). One of the principal reasons is probably a more accurate diagnosis of new cases of papillary thyroid cancer (4). Despite the rise in incidence, the mortality rate has remained relatively low due to the indolent nature of most of the DTC (5).

DTC is histologically divided into papillary (PTC), follicular (FTC), and Hurthle cell carcinoma (HTC), representing over 90% of all thyroid malignancies (6). DTC generally retains the ability to uptake iodine and synthesize thyroglobulin, which enables both diagnostic imaging and radioiodine-based therapy (7). In contrast, poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) that derive from thyroid follicular cells have shown progressive loss of normal structure and function, thus losing the ability to concentrate radioiodine and making it resistant to standard therapies (8). ATC is a very aggressive form with an average survival of only about 6 months (9).

Standard approach to treating patients with differentiated thyroid carcinoma is surgical thyroidectomy, followed by radioiodine (^{131}I) ablation therapy and lifetime L-thyroxine suppression therapy (10).

Radioiodine therapy plays a key role in reducing recurrent rates, and also in enabling sensitive follow-up using serum thyroglobulin and a diagnostic whole-body scan (WBS) (11).

Aim

The aim of this study was to evaluate clinical characteristics, histopathological subtypes, surgical approaches, therapeutic outcomes, and the occurrence of radioiodine-refractory disease in patients with DTC treated with radioiodine therapy at a single tertiary centre.

Material and methods

This retrospective study included 312 patients diagnosed with DTC (PTC, FTC or HTC) and treated at our institution, between the years 2017 and 2024.

The inclusion criteria comprised of histologically confirmed DTC, complete clinical, surgical, and pathological documentation and available follow-up data. Exclusion criteria included incomplete data or a lack of follow-up.

All patients underwent total thyroidectomy or lobo-isthmectomy followed by completion thyroidectomy prior to radioiodine ablation therapy. Radioiodine therapy was performed under TSH stimulation (TSH levels ≥ 30 μIU/ml were acceptable), according to the established clinical protocols – 3.7 GBq for ablation therapy and 5.5 GBq or 7.4 GBq for therapy doses of radioiodine. All patients had post-therapy WBS, another control WBS was performed 6-12 months after the therapy.

Crosstabulation between the histological subtype and the number of radioiodine doses (one vs. ≥2) and the associations between age groups (< 50 years and ≥ 50 years) and occurrence of RAI-R were analysed using the Pearson Chi-square test and, when needed, confirmed with Fisher's Exact test due to low expected counts in some cells. A p-value <0.05 was considered statistically significant.

Results

Of the total 312 patients, 240 were female (76.9%) and 72 were male (23.1%). Before the diagnosis, 40% of them presented with thyroid enlargement and dysphagia, 9.9% experienced fatigue and palpitations, and 8% reported typical hyperthyroidism symptoms. Approximately 30.1% of the patients were asymptomatic at initial presentation, while 8% had other nonspecific symptoms. The mean age of the patients was 51.4 ± 14.9 years.

A total of 203 (65.1%) patients received one dose of radioiodine, 68 (21.8%) patients had two, 30 (9.6%) patients had received three doses, five (1.6%) had four doses, two (0.6%) had five doses, one (0.3%) had six and three (1%) had seven doses. Figure 1. presents the age of the patients at the first ablative radioiodine treatment application.

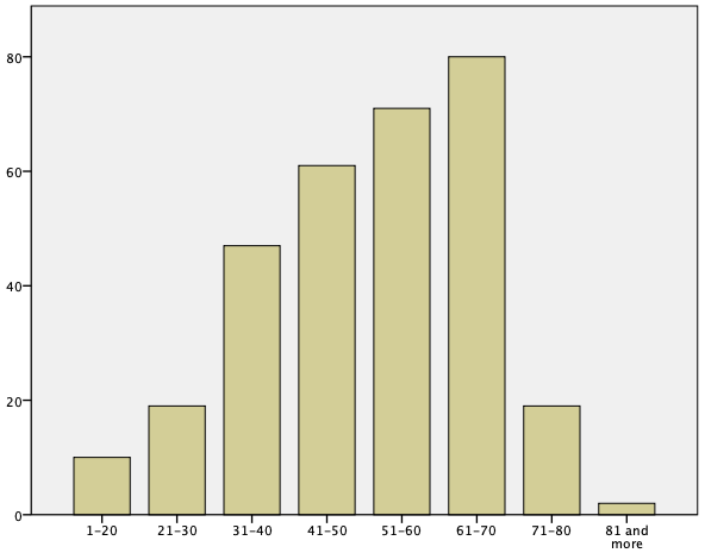

Figure 1. Age of the patients when receiving ablation therapy.

Regarding surgical treatment, 19.6% of the patients underwent lobectomy with subsequent completion thyroidectomy, 72.5% had total thyroidectomy, 5.8% total thyroidectomy with neck dissection, and 2.2% had lymph node extraction with later total thyroidectomy (Table 1.).

Histopathological results revealed 263 PTC, 25 FTC, 20 HTC, and 4 PDTC (Table 2.).

SURGERY	**Differentiated**		**Refractory**		**Total**	
	No	(%)	No	(%)	No	(%)
TT	210	93.3%	15	6.7%	225	72.1%
Lobectomy	55	90.2%	6	9.8%	61	19.6%
TT & ND	14	73.7%	5	26.3%	19	6.1%
LNE & later TT	6	85.7%	1	14.3%	7	2.2%
Total	**285**	**91.3%**	**27**	**8.7%**	**312**	**100%**

Table. 1. Differentiated and refractory thyroid carcinoma according to the surgical procedure.

TT=total thyrereoidectomy, ND=neck dissection, LNE=lymph node extraction

HISTOLOGICAL TYPE	Differentiated		Refractory		Total	
	No	(%)	No	(%)	No	(%)
Papillary	241	91.6%	22	8.4%	263	84.3%
Follicular	24	96.0%	1	4.0%	25	8.0%
Hurthle cell	18	90.0%	2	10.0%	20	6.4%
Poorly differentiated	2	50.0%	2	50.0%	4	1.0%
Total	**285**	**91.3%**	**27**	**8.7%**	**312**	**100%**

Table. 2. Differentiated and refractory thyroid carcinoma according to histological type.

The majority of the patients had achieved complete remission after the first dose of radioiodine (Figure 2.). However, 27 patients (8.7%) have developed radioiodine-refractory DTC (RAI-R) over time (Figure 3.). Female patients represented 74.1% of the refractory group.

No statistically significant association was observed between the histological subtype and the number of administered radioiodine doses ($\chi 2 = 5.53$, df = 3, $p = 0.14$; Fisher's Exact test, $p = 0.13$) (Table 3.).

HISTOLOGICAL TYPE	One dose		>1 dose		Total		p
	No	(%)	No	(%)	No	(%)	
Papillary	167	64.0%	94	36.0%	261	83.7%	
Follicular	20	83.3%	4	16.7%	24	7.7%	
Hurthle cell	12	52.2%	11	47.8%	23	7.4%	
Poorly differentiated	3	75.0%	1	25.0%	4	1.3%	0.14
Total	**202**	**64.7%**	**110**	**35.3%**	**312**	**100%**	

Table. 3. Histological type of thyroid carcinoma and the number of doses of radioiodine.

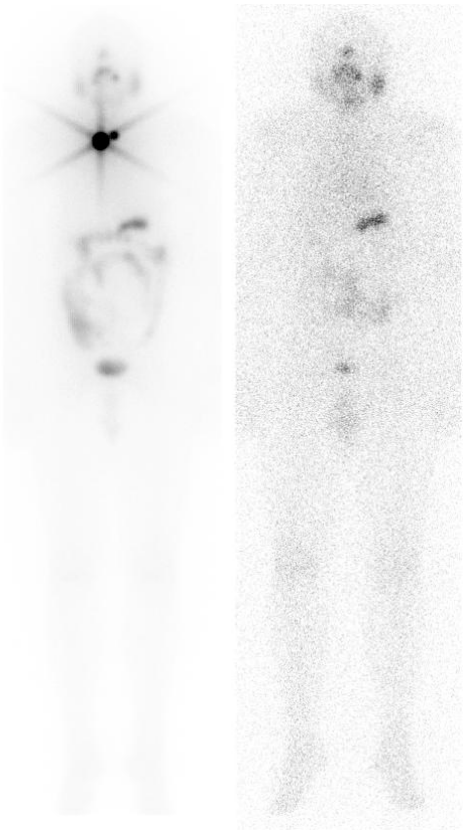

Figure 2. Male, 56 years, papillary thyroid cancer, pT1. Posttherapy scintigram after ablation therapy with ^{131}I-NaI, and control scintigram 6 months after the ablation. Thyroglobulin < 0.04 ng/ml. Complete remission.

Figure 3. Female, 52 years, follicular thyroid cancer, Posttherapy scintigram after ablation therapy with ^{131}I-NaI , and posttherapy scintigram after sixth therapy dose. Thyroglobulin >500 ng/ml. Radioiodine refractory carcinoma.

We also tested association between the age and RAI-R (Table 4). Patients were divided into two age groups: <50 years and ≥50 years. In the age group <50 years 6 out of 130 patients (4.6%) have developed RAI-R, while in the ≥50 years age group RAI-R was registered in 21 out of 182 patients (11.5%). Chi-square test shows statistically significant correlation between the age group and the occurrence of RAI-R (p=0.028).

AGE GROUP	**Differentiated**		**Refractory**		**Total**		**p**
	No	(%)	No	(%)	No	(%)	
<50	124	95.4%	6	4.6%	130	41.7%	
≥50	161	88.5%	21	11.5%	182	58.3%	0.028*
Total	**285**	**91.3%**	**27**	**8.7%**	**312**	**100%**	

Table. 4. The distribution of differentiated and refractory thyroid carcinoma according to the age groups of patients. *Statistically significant at $p<0.05$

Discussion

The demographic characteristics of the patients in our study, including clear female predominance and median age are comparable to the well-established epidemiological trends of DTC (12). Numerous population-based studies confirm that thyroid cancer occurs three to five times more often in women, likely due to hormonal, genetic, and environmental factors (13).

The majority of the patients were diagnosed with PTC (over 80%), which is consistent with global data, indicating that PTC represents the most frequent subtype of thyroid cancer, and is also in accordance with its recognized tendency to increase in incidence due to improved detection techniques, such as high-resolution ultrasonography (14).

The majority of DTC in high-developed countries is diagnosed incidentally, often during imaging studies for unrelated reasons, which reflects good preventive care and regular systemic health check-ups (≈50-60% incidental detection rates) (14). In contrast, in our study group, the most common sign was thyroid enlargement, suggesting limited screening practices and lower public awareness of thyroid disease. These findings underscore the importance of strengthening preventive strategies, most importantly regular thyroid ultrasonography, and thus improving early referral pathways and consequently reducing the burden of advanced disease at presentation.

With this study, we have reaffirmed that radioiodine therapy is the cornerstone in the management of patients with DTC demonstrating a high remission rate following a single radioiodine dose, and it also highlights the effectiveness of the combined surgical and radioiodine approach (15, 16). Similar outcomes have been reported in previous studies highlighting that adequate thyroidectomy followed by ^{131}I ablation ensures optimal disease control and facilitates accurate long-term follow-up through thyroglobulin monitoring and diagnostic whole-body scintigraphy (17). A meta-analysis showed successful RAI-R ablation in 72% of intermediate risk patients, and in 52% of the patients with high risk. The recurrence

rate in such groups of patients with successful ablation was only 2% (18). Our results similarly demonstrate that the patients requiring multiple doses generally presented with advanced disease or distant metastases, aligning with findings from other studies that demonstrate disease stage as the main determinant of the number of therapeutic doses required (19). This further emphasizes that adequate initial staging and risk stratification are essential for tailoring radioiodine therapy and assessing the need for repeated administration.

The choice of surgical approach to thyroid carcinoma remains a matter of ongoing debate (20). Hemithyroidectomy may be sufficient for small, low-risk papillary carcinomas, with the advantage of avoiding lifelong hormone replacement therapy (21). However, this approach has several limitations. Apart from the potential risk of residual tumor, and subsequent need for total thyroidectomy, hemithyroidectomy has some other disadvantages. Namely, after hemithyroidectomy, thyroglobulin (Tg) in serum, and whole-body ^{131}I scan are of limited value in detection of tumor recurrence. Tg is recognized as a highly sensitive marker for recurrent or persistent thyroid cancer, but mainly in patients who have undergone total thyroidectomy followed by radioiodine ablation (22).

Approximately 9% of our patients developed radioiodine-refractory DTC, comparable to the 5-15% range reported in other studies (23). There was a clear predominance in patients older than 50 years, which aligns with previous observations that older age reflects biologically more aggressive tumors with a higher propensity for dedifferentiation and loss of radioiodine uptake (24). This is believed to be due to the higher prevalence of telomerase reverse transcriptase (TERT) promoter mutations in older patients, which further contributes to reduced sodium/iodide symporter (NIS) expression and impaired responsiveness to radioiodine (25).

Although histological subtype did not reach statistical significance as a predictor of repeated radioiodine treatment in our study group, there is existing evidence that HTC and PDTC often require more radioiodine doses (26). Tumors of Hurthle cell origin often exhibit lower iodine avidity, and PDTC is characterized by the loss of follicular cell function. In both cases, there is frequently increased metabolic activity of Fluorodeoxyglucose Positron Emission Tomography/Computed tomography (FDG PET-CT) (27).

The development of RAI-R is a significant therapeutic challenge. Identified risk factors for the development of RAI-R include aggressive histological subtypes (tall cell, diffuse sclerosing or

hobnail variants of PTA, follicular and poorly differentiated carcinoma), extrathyroidal extension, and molecular alterations such as TERT promoter and B-Raf proto-oncogene, serine/threonine kinase (BRAF)^{V600E} mutations (28). Patients with RAI-R have only 10–20 % 10-years overall survival, and treatment options in these group of patients is limited (29). Currently available systemic therapies such as multikinase inhibitors (sorafenib, lenvatinib) have shown meaningful progression-free survival, but long-term administration is required, and they are also associated with substantial toxicity, and even sometimes with allergic reactions (30). Novel therapies such as redifferentiation techniques (e.g. mitogen-activated protein kinase (MEK) and BRAF inhibitors) which aim to restore NIS expression and renew radioiodine uptake in patients with RAI-R have shown promising results, thus potentially making RAI-R patients eligible for radioiodine therapy again (31).

Functional imaging techniques continue to play a crucial role in disease management. Single Photon Emission Computed Tomography/Computed Tomography (SPECT-CT) is a useful tool in detecting residual disease with CT portion for better anatomical localization of iodine-avid lesions and FDG PET-CT in identifying metabolically active radioiodine-refractory lesions, with high FDG uptake correlating with more aggressive biological behavior and reduced survival (32).

The findings in our study underscore the importance of a multidisciplinary approach to the management of DTC that incorporates clinical, pathological, molecular, and imaging data to optimize treatment selection and follow-up.

Conclusion

Differentiated thyroid carcinoma (DTC) predominantly affected female patients (76.9%) with thyroid enlargement as the main symptom at initial evaluation.

Totally 65.1% received a single radioiodine dose, while the others had to be treated with more doses, up to seven doses in some patients.

Total thyroidectomy was the main surgical treatment. Histopathologically, papillary carcinoma was confirmed in 83.3%.

Overall, 27 patients (8.7%) have developed radioiodine-refractory DTC (RAI-R). There was no significant association between the histological subtype and the number of administered radioiodine doses. Radioiodine-refractory DTC was significantly more frequent in patients over 50 years of age.

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