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Ongoing risk stratification for differentiated thyroid cancer (DTC) — stimulated serum thyroglobulin (Tg) before radioiodine (RAI) ablation, the most potent risk factor of cancer recurrence in M0 patients

Ciągła stratyfikacja ryzyka w zróżnicowanym raku tarczycy (DTC) — stymulowane stężenie tyreoglobuliny (Tg) w surowicy, przed leczeniem uzupełniającym radiojodem (RAI), najważniejszym czynnikiem ryzyka nawrotu raka u pacjentów M0

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Abstract

Introduction: Adequate postoperative risk assessment currently constitutes the principle of DTC treatment and further management. The aim of the study — a retrospective assessment of risk factors influencing DTC relapse.

Material and methods: The study group consisted of 510 DTC staged pT1b-T4N0-N1M0, in whom total thyroidectomy and complementary radioiodine (RAI) treatment were carried out. In 71% papillary thyroid cancer was diagnosed, whereas in the remaining 29% — follicular thyroid carcinoma. Based on TNM classification from 1997, T1 feature was diagnosed in 11.6%, T2 in 35.1%, T3 in 8.4%, T4 in 9,4%, while in 35.5% — Tx. Lymph node metastases were present in 24.7% of cases. Median follow-up was 12.1 years (1.5–15.2).

Results: Age at DTC diagnosis, tumour diameter (T), lymph node metastases (N1), stimulated thyroglobulin, and RAI uptake in thyroid bed at qualification for RAI ablation significantly influenced freedom from progression time (FFP) in a multivariate analysis. When post-operative stimulated Tg was > 30 ng/mL the risk of relapse increased nearly six-fold, whereas the presence of N1 feature — four-fold. The total risk of relapse in the whole group was 12.55% while median FFP was 154.8 months. Five-year and 10-year FFP was 90.1% and 87.5%, respectively.

Conclusions: Postoperative stimulated thyroglobulin level was the most potent, independent risk factor influencing FFP in DTC patients. Age above 60 years, an initial DTC stage (T and N features), and low RAI uptake in thyroid bed (< 1%) were related to a higher risk of DTC relapse, whereas the investigated histopathological features were insignificant. **(Endokrynol Pol 2016; 67 (1): 2–11)**

Key words: *differentiated thyroid cancer; risk stratification; thyroglobulin; recurrence*

Streszczenie

Wstęp: Właściwa, pooperacyjna ocena ryzyka stanowi obecnie podstawę wyboru postępowania terapeutycznego i monitorowania chorych na zróżnicowanego raka tarczycy (DTC). Celem pracy była retrospektywna ocena czynników ryzyka nawrotu DTC.

Materiał i metody: Grupę badaną stanowiło 510 chorych z rozpoznaniem DTC w stadium pT1b-T4N0-N1M0, u których przeprowadzono całkowite wycięcie tarczycy i leczenie uzupełniające 131I. U 71% rozpoznano raka brodawkowatego, a u 29% raka pęcherzykowego tarczycy. Na podstawie klasyfikacji TNM z 1997 roku u 11,6% chorych rozpoznano cechę T1, u 35,1% — T2, u 8,4% — T3, u 9,4% — T4, a u 35,5% — Tx. Przerzuty do węzłów chłonnych (N1) były obecne u 24,7% przypadków. Mediana obserwacji wynosiła 12,1 lat (zakres 1,5–15,2).

Wyniki: Wiek w chwili rozpoznania, średnica guza (T), obecność przerzutów do węzłów chłonnych, stężenie tyreoglobuliny (Tg) stymulowanej i wychwyt 131I w loży tarczycy w scyntygrafii podczas kwalifikacji do leczenia uzupełniającego 131I znamiennie wpływały na czas do nawrotu DTC w analizie wieloczynnikowej. U chorych, u których pooperacyjne stymulowane stężenie Tg wynosiło > 30 ng/mL ryzyko nawrotu wzrastało blisko 6-krotnie. Zajęcie węzłów chłonnych wiązało się z 4-krotnym wzrostem ryzyka wznowy DTC. Ryzyko nawrotu w grupie badanej wynosiło 12,55%, mediana czasu do progresji — 154,8 miesięcy. Pięcioletni odsetek chorych bez nawrotu wynosił 90,1%, a 10-letni odpowiednio 87,5%.

Wnioski: Pooperacyjne stężenie Tg stymulowanej stanowiło najsilniejszy, niezależny czynnik rokowniczy wpływający na przeżycie bezobjawowe chorych na DTC. Wiek powyżej 60 lat, wyjściowe zaawansowanie (cechy T i N) oraz niski (< 1%) pooperacyjny wychwyt 131I w loży tarczycy wiązały się ze znamiennie wyższym ryzykiem nawrotu DTC, natomiast badane czynniki histopatologiczne nie miały istotnego znaczenia. **(Endokrynol Pol 2016; 67 (1): 2–11)**

Słowa kluczowe: *zróżnicowany rak tarczycy; stratyfikacja ryzyka; tyreoglobulina; nawrót*

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Introduction

The discussion about which prognostic factors are the most reliable to adequately assess the risk of relapse in differentiated thyroid cancers (DTC) is still ongoing. To date, age at diagnosis and distant metastases are considered as the most important risk factors. Among other factors that may influence both disease-free (DFS) and overall survival (OS) are male sex, histopathological features such as: follicular histotype, tumour diameter, extrathyroidal extension, angioinvasion, tumour grade, and lymph node involvement. However, the results of different analyses are distinct [1–9]. Some papers demonstrated that follicular thyroid cancer was related to poorer prognosis with reference to both DFS and OS than papillary subtype [1, 6–8, 10]. However, other reports did not demonstrate any differences in DFS and OS depending on histology [2, 9]. The importance of thyroid capsule infiltration, angioinvasion, and multifocality as prognostic factors was emphasised by numerous retrospective analyses that showed their negative impact on both OS [7, 8, 11–13] and DFS [8, 11, 12], but other papers questioned these data [9, 10, 14, 15]. Divergent opinions were one of the reasons to change this approach in the risk stratification in DTC patients. The new one is based on a continuous dynamic evaluation conducted throughout the whole follow-up, because a rigid risk assessment based only on histopathological findings and TNM classification does not reflect the real prognosis. Although, the importance of the TNM scale is still emphasised [16, 17], it is believed that clinical factors including serum thyroglobulin (Tg) concentration both stimulated and on l-thyroxine (LT4), therapeutic management, and the response to treatment administered should also be considered [18–23]. In 2010, Tuttle et al. proposed a new model of DTC risk assessment, called ongoing risk stratification. An initial stratification, according to the ATA criteria, was validated during the first two years of follow-up based on the assessment of treatment results [21]. This re-stratification reduced the likelihood of finding persistent or recurrent DTC in patients, demonstrating an excellent response to therapy despite the initial risk class (low, intermediate, or high). On the other hand, an incomplete response to initial therapy increased the probability of persistent structural disease or recurrence.

Thyroid diseases and particularly their treatments differ between distinct regions, because thyroid, as an endocrine gland, is very environment-dependent. Therefore, the present study analyses how to use the ongoing risk stratification under routine adjuvant radioiodine (RAI) administration, carried out in Central Europe. Thus, the aim to this study was to evaluate qualitatively the risk factors influencing DTC recurrence, considering Polish conditions, in DTC M0 patients treated equally according to the standardised algorithm in a single institution.

Material and methods

Patients

Medical records of 1212 DTC patients, admitted for the first time in M. Sklodowska-Curie Memorial Cancer Centre in Gliwice, Poland between 1994 and 1997, were retrospectively analysed. Twenty subjects diagnosed with non-DTC and 159 subjects with either further treatment carried out in other centre or follow-up shorter than one year were excluded. Finally, a population of 1033 patients was subjected to further analysis.

The study group was selected from among these 1033 subjects and consisted of 510 M0 DTC patients staged > pT1aN0 in whom total thyroidectomy was carried out within one year after DTC diagnosis and followed by complementary RAI treatment, performed within 24 months after surgery (Fig. 1). There were 409 women (80.2%) and 101 (19.8%) men. Mean age at cancer diagnosis was 42.2 years, median 43.3 years (range 8.4–77 years). In 362 (71%) papillary thyroid carcinoma was diagnosed, whereas in 148 (29%) — follicular thyroid cancer. Multifocal tumour growth was observed in 220 (43.1%) patients, thyroid capsule infiltration in 63 (12.4%), and vascular invasion in 72 (14.1%) cases. The mean tumour diameter was 25.2 mm, median 20 mm (range 1–100 mm). However, in 42.5% of cases the tumour diameter was not known. Based on the TNM classification (revised in 1997), 59 (11.6%) patients were classified as T1, 179 (35.1%) — as T2, 43 (8.4%) — as T3, and 48 (9, 4%) — as T4, whereas in the other 181 (35.5%) cases Tx was diagnosed. Lymph node metastases (N1) were present in 126 (24.7%) patients. Median follow-up was 12.1 years (range 1.5–15.2).

The first postoperative assessment and RAI ablation

This diagnostics, preceded by a four-week LT4 withdrawal, was carried out to assess the radicalness of surgery and postoperative cancer stage. It included physical and histopathological examination, neck US, chest X-ray, whole-body scan (WBS) performed after administration of diagnostic RAI activity (2 mCi), Tg measurement, the assessment of postoperative complications (serum calcium concentration and laryngological evaluation), and others such as: bone scan, FNAB, CT scan, if necessary. RAI adjuvant treatment was carried out after 4–6 weeks of LT4 withdrawal (required TSH level ≥ 25 uIU/mL). The mean RAI activity was 66.7 mCi, median 60 mCi (range

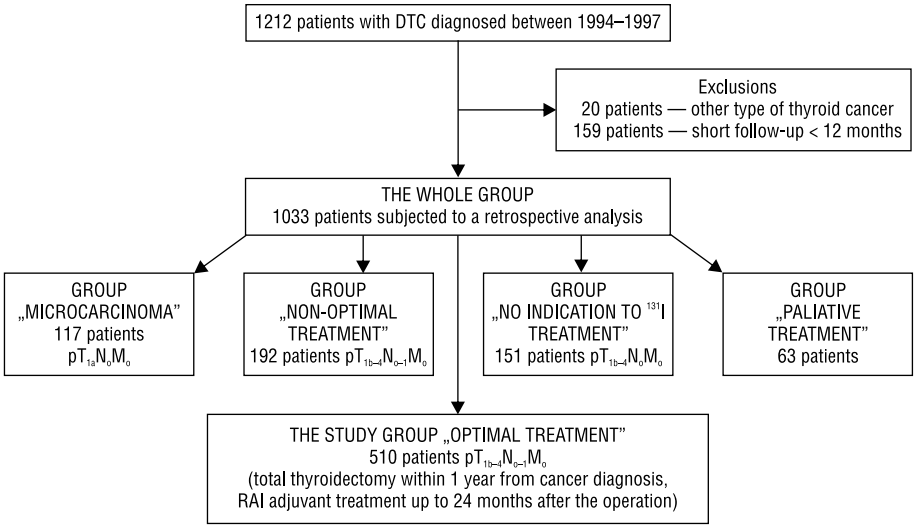

Figure 1. *Selection of the study group from the population of 1212 DTC patients*
Rycina 1. *Wybór grupy badanej spośród populacji 1212 chorych na DTC*

27.8–150 mCi). WBS was performed 72 hours following RAI administration.

Further follow-up and the evaluation of treatment outcomes

Further follow-up involved the assessment of serum TSH, Tg with Tg recovery, or Tg antibodies on LT4 and neck US every six months after RAI therapy. The first evaluation of treatment efficacy was performed 6–12 months following RAI ablation and included neck US, Tg measurement after LT4 withdrawal, diagnostic WBS, chest X-ray, and others, if necessary. Finally, the obtained results were classified as complete remission (negative WBS, stimulated serum Tg level ≤ 10 ng/mL at the absence of Tg antibodies, normal neck US, no distant metastases), persistent disease (the presence of local recurrence or distant metastases confirmed by neck US, pathological RAI uptake in WBS or in other imaging modalities and/or stimulated Tg level > 30 ng/mL), or doubtful remission (stimulated Tg between 10–30 ng/mL regardless of negative WBS and normal results of other examinations).

Tg assay

Between 1995 and 2003 serum Tg concentration was measured by immunofluorometric assay (Wallac-Delfia) with functional sensitivity of 1 ng/mL and analytic sensitivity of 0.2 ng/mL, whereas from 2003 this was done by Trace (Kryptor) method with functional sensitivity of 1 ng/mL and analytic sensitivity of 0.17 ng/mL. Both methods correlated with each other. The following cut-off values with sensitivity of 95% were used: 4 ng/mL on LT4 therapy and 30 ng/mL on LT4 withdrawal [24]. Tg recovery was measured to evaluate the interference by Tg antibodies (reference range 70–130%). Since 2008 the Tg antibody test has been performed.

Statistical analysis

Statistical analysis was based on the calculation of DFS and freedom-to-progression time (FFP). DFS was defined as the time from the complete disease remission after surgery to disease relapse, death, or last follow-up. In patients not fulfilling the criteria of complete remission DFS was coded as zero. FFP was defined as the time from first diagnostic or therapeutic RAI scan after surgery to disease relapse or progression.

Time-to-event data were analysed using Kaplan-Meier method and compared by log-rank, Breslow and Tarone-Ware tests; the highest p-value was reported. Quantitative variables were assessed for the association with time-to-event by Cox regression. P values below $p < 0.05$ were deemed statistically significant. Receiver operating characteristic curves were used to assess the diagnostic test parameters, sensitivity, specificity, positive and negative predictive value of test, and area under ROC curve were reported. Multivariate Cox regression was used, with stepwise backward feature elimination. Data mining with classification and regression trees (CART) was also carried out. Data were analysed using IBM SPSS Statistics ver. 22 (IBM Corp., Armonk, New York, USA) and JMP ver. 10.0 (SAS Corp, Cary, North Carolina, USA).

Results

The impact of different prognostic factors on the risk of cancer recurrence was evaluated on the basis of

univariate and multivariate analyses. The risk of relapse in the study group was 12.55%. Median FFP was 154.8 months (95% CI: 150.4–159.4 months). Five-year and 10-year recurrence-free survival were 90.1% and 87.5%, respectively. Due to the small number of deaths OS was not analysed.

Univariate analyses

Age at diagnosis, sex, thyroid capsule infiltration, multifocal tumour growth, tumour size, lymph node metastases, stimulated Tg level, and RAI thyroid remnant uptake, evaluated before adjuvant RAI treatment were found to be statistically significant in univariate analyses. The detailed results are summarised in Table I.

Multivariate regression analysis

Stimulated Tg level, measured before complementary RAI treatment, was the most important, independent risk factor in the multivariate Cox regression analysis for FFP (Fig. 2). The values > 30 ng/mL increased the risk of any cancer recurrence nearly six-fold (p = 0.000). Lower Tg values, ranged between 10 and 30 ng/mL also markedly increased the risk of relapse by nearly three times (p = 0.017), while low stimulated Tg level, both < 1 ng/mL and 1–10 ng/mL, were related to favourable outcomes.

N1 feature was another independent poor prognostic factor associated with a nearly four-fold increase in the risk of any cancer relapse comparing to N0 and Nx subjects (p = 0.000).

Tumour size and age at DTC diagnosis were independently related to a higher relative risk of DTC relapse, nearly three times in the case of T3 or T4 tumour (p = 0.000) and 2.5 times when DTC was diagnosed after the age of 60 years (p = 0.008).

RAI thyroid remnant uptake before RAI ablation was also an independent risk factor in the multivariate analysis for FFP. Similarly to the univariate analysis, the lowest percentage of RAI uptake was associated with poorer prognosis and showed a 2.5-fold increase in the risk of DTC recurrence (p = 0.007).

Neither sex nor multifocal tumour growth and thyroid capsule infiltration were associated with a higher relative risk of cancer recurrence.

Association analysis

Age at diagnosis, tumour diameter, lymph node metastases, stimulated Tg level, and RAI thyroid remnant uptake, evaluated before adjuvant RAI treatment, were statistically significant in both univariate and multivariate analyses. However, other factors like sex, thyroid capsule infiltration, and multifocal tumour growth were significant in univariate analy-

Table I. *Results of univariate analyses performed in a group of 510 M0 DTC patients*

Tabela I. *Wyniki analiz jednoczynnikowych przeprowadzonych w grupie 510 chorych na DTC, bez przerzutów odległych (M0)*

Prognostic factor	10-year FFP (%)	p
Age (years)		
< 21	86.3	p = 0.05
21–40	87.8	
40–50	95.2	
50–60	90.3	
> 60	81.4	
Sex		
Females	91.9	p < 0.001
Males	77.8	
Histopathological features		
Histopathological subtype		
Papillary thyroid cancer	87.9	ns
Follicular thyroid cancer	92.3	
Thyroid capsule infiltration		
Absent	90.8	p < 0.01
Present	77.5	
Multifocal tumour growth		
Absent	91.2	p < 0.01
Present	86.4	
Vascular invasion		
Absent	90.1	ns
Present	83.4	
T feature		
T1	94.9	p < 0.0001
T2	93.6	
T3	74.8	
T4	73.7	
Tx	90.4	
Lymph node metastases (N feature)		
N0	95.5	p < 0.0001
N1	72.7	
Nx	93.5	
Clinical factors		
Stimulated serum Tg level before complementary RAI treatment		
< 1ng/mL	94.2	p < 0.0001
1–10 ng/mL	92.6	
10–30 ng/mL	89.6	
> 30 ng/mL	60.2	
RAI uptake in thyroid bed before complementary RAI treatment		
< 1%	80.5	p = 0.01
1–5%	91.1	
> 5%	90.1	

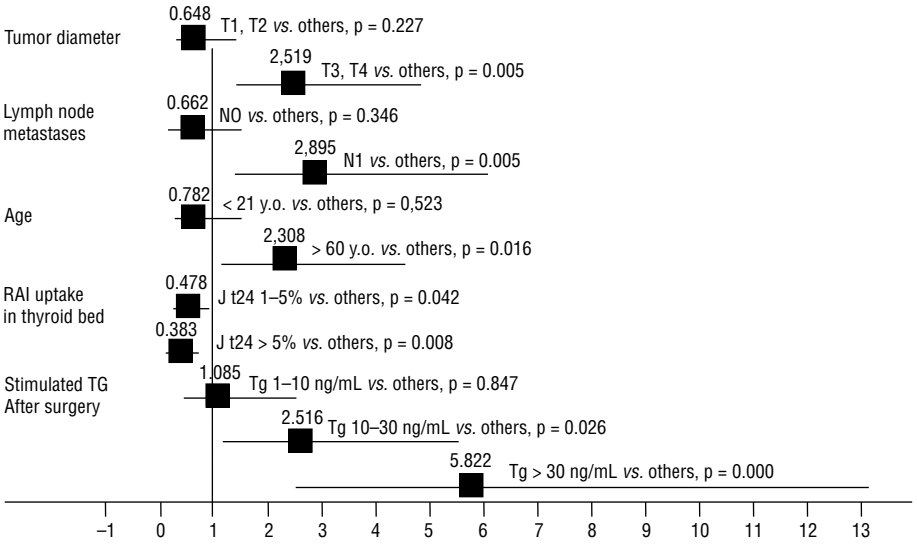

Figure 2. *Results of Cox multivariate regression analysis. Stimulated serum Tg level > 30 ng/mL before RAI ablation was the most potent independent prognostic factor of cancer recurrence*

Rycina 2. *Wyniki wieloczynnikowej analizy regresji Coxa. Stymulowane stężenie Tg w surowicy > 30 ng/ml przed leczeniem uzupełniającym radiojodem stanowi najsilniejszy, niezależny czynnik prognostyczny dla nawrotu raka*

ses only. Therefore, further evaluation concerned the features that showed the strongest association with variables significant in the univariate analysis. Thyroid capsule infiltration demonstrated a positive association with the more advanced initial cancer stage, N1 feature, high stimulated Tg level, younger age at DTC onset, and low RAI thyroid remnant uptake before RAI ablation (Table II). Multifocality was observed significantly more often in the case of younger age, N1 feature, high stimulated Tg level, and low RAI thyroid remnant uptake. However, no impact of tumour diameter was noticed (Table III). Male sex was associated with younger age, advanced cancer stage (T3, T4, and N1), and high stimulated Tg level, while no relationship with RAI remnant uptake was observed (Table IV).

Summary of the obtained results by the classification and regression trees method

The most important, independent prognostic factor influencing FFP in the whole group was stimulated serum Tg concentration measured before RAI ablation. The risk of cancer relapse in patients with Tg level > 30 ng/mL was 50.9%, compared to 8.1% in the subgroup with Tg level < 30 ng/mL. Considering the subjects with Tg level < 30 ng/mL only, lymph node metastases showed the strongest impact on the risk of DTC recurrence — 18.7% in the N1 subgroup and 5.5% in N0 and Nx subjects. In the N0 group the most potent prognostic factor was tumour diameter. If the primary tumour was bigger than 2 cm the recurrence rate was 7%, whereas for tumours smaller than 2 cm it was 3.3%

Table II. ***Correlation between the presence of thyroid capsule infiltration and other significant independent risk factors selected on the basis of multivariate analysis for FFP***

Tabela II. ***Korelacja między obecnością nacieku torebki tarczycy a innymi istotnymi, niezależnymi czynnikami ryzyka wpływającymi na czas do progresji (FFP), wybranymi na podstawie analizy wieloczynnikowej***

		Thyroid capsule infiltration		p
		Present	Absent	
Age	< 21	14 (23.3%)	46 (76.7%)	p < 0.04
	21–60	42 (11.2%)	334 (88.8%)	
	> 60	7 (9.5%)	67 (90.5%)	
T	T_{1-2}	10 (4.2%)	228 (95.8%)	p < 0.000
	T_x	6 (3.3%)	175 (96.7%)	
	T_{3-4}	47 (51.6%)	44 (48.4%)	
N	N_0	21 (9.5%)	199 (90.5%)	p < 0.001
	N_x	16 (9.8%)	148 (90.2%)	
	N_1	26 (20.6)	100 (79.4%)	
Tg	< 1 ng/mL	23 (12.2)%	165 (87.8%)	p < 0.01
	1–10 ng/mL	13 (8.1%)	147 (91.9%)	
	10–30 ng/mL	18 (15.8%)	96 (84.2%)	
	> 30 ng/ml	9 (18.8%)	39 (81.2%)	
T_{24}	< 1%	16 (18.6%)	70 (81.4%)	p = 0.02
	1–5%	20 (10.6%)	168 (89.4%)	
	> 5%	24 (10.5%)	205 (89.5%)	

only. Only when small tumours were considered did a histopathological feature such as multifocality become an important risk factor (Fig. 3).

Table III. *Correlation between the presence of multifocal tumour growth and other significant independent risk factors selected on the basis of multivariate analysis for FFP*

Tabela III. *Korelacja między wieloogniskowym wzrostem nowotworu a innymi istotnymi, niezależnymi czynnikami ryzyka wpływającymi na (FFP), wybranymi na podstawie analizy wieloczynnikowej*

		Multifocal tumour growth		p
		Present	Absent	
Age	< 21	37 (61.7%)	23 (38.3%)	p < 0.001
	21–60	153 (40.7%)	223 (59.3%)	
	> 60	30 (40.5%)	44 (59.5%)	
T	$T_{1–2}$	110 (46.2%)	128 (53.8%)	ns
	T_x	70 (38.7%)	111 (61.3%)	
	$T_{3–4}$	40 (44.0%)	51 (56.0%)	
N	N_0	77 (35.0%)	143 (65.0%)	p < 0.000
	N_x	66 (40.2%)	98 (59.8%)	
	N_1	77 (61.1%)	49 (38.9%)	
Tg	< 1 ng/mL	84 (44.7)%	104 (55.3%)	p < 0.001
	1–10 ng/mL	55 (34.4%)	105 (65.6%)	
	10–30 ng/mL	53 (46.5%)	61 (53.5%)	
	> 30 ng/mL	28 (58.3%)	20 (51.7%)	
T_{24}	< 1%	50 (58.1%)	36 (41.9%)	p < 0.001
	1–5%	72 (38.3%)	116 (61.7%)	
	> 5%	93 (40.6%)	136 (59.4%)	

Table IV. *Correlation between sex and other significant independent risk factors selected on the basis of multivariate analysis for FFP*

Tabela IV. *Korelacja między płcią a innymi istotnymi, niezależnymi czynnikami ryzyka wpływającymi na (FFP), wybranymi na podstawie analizy wieloczynnikowej*

		Sex		p
		Female	Male	
Age	< 21	36 (60.0%)	24 (40.0%)	p < 0.000
	21–60	317 (84.3%)	59 (15.7%)	
	> 60	56 (75.7%)	18 (24.3%)	
T	$T_{1–2}$	202 (84.9%)	36 (15.1%)	p < 0.000
	T_x	147 (81.2%)	34 (18.8%)	
	$T_{3–4}$	60 (65.9%)	31 (34.1%)	
N	N_0	189 (85.9%)	31 (14.1%)	p < 0.000
	N_x	142 (86.6%)	22 (13.4%)	
	N_1	78 (61.9%)	48 (38.1%)	
Tg	< 1 ng/mL	161 (85.6%)	27 (14.4%)	p < 0.000
	1–10 ng/mL	132 (82.5%)	28 (17.5%)	
	10–30 ng/mL	85 (74.6%)	29 (25.4%)	
	> 30 ng/ ml	31 (64.6%)	17 (35.4%)	
T_{24}	< 1%	64 (74.4%)	22 (25.6%)	ns
	1–5%	156 (83.0%)	32 (17.0%)	
	> 5%	183 (79.9%)	46 (20.1%)	

New model of risk stratification

In a further step we tried to create our own prognostic system, based on independent risk factors, selected by multivariate analysis, such as: tumour diameter (T3 and T4 feature), lymph node metastases (N1 feature), stimulated serum Tg concentration, and RAI remnant uptake before RAI ablation (Table V). Next, the patients from the study group were stratified on the basis ofthe aforementioned system (Table VI). Subjects who scored 0 points were characterised by the lowest 10-year risk of DTC relapse — 2.6% only, whereas in patients who received 9–15 points it was 54.5% (p < 0.001) (Fig. 4).

Discussion

The present study, including 510 M0 DTC patients who underwent total thyroidectomy and complementary RAI treatment, identified a lot of significant prognostic factors influencing the risk of cancer relapse. The importance of primary tumour advancement and lymph node metastases, as previously reported [2, 6, 13, 25, 26], was confirmed. Bimodal dependence between the age of DTC diagnosis and recurrence risk, a well-known DTC feature, was also observed. According to the univariate analyses the highest percentage of recurrent DTC concerned the youngest and the eldest subjects. Interestingly, in the multivariate analysis, this recurrence risk was independent of cancer stage only in the subgroup > 60 years of age, while in young patients < 21 years of age it was directly related to more advanced disease and it was not an independent factor. The most potent prognostic factor was stimulated Tg level measured before RAI ablation, significantly increasing recurrence risk if its value was > 10 ng/mL. Surprisingly, low RAI thyroid remnant uptake (< 1%) was identified as a poor prognostic factor in DTC patients after radical surgical approach.

Our findings, confirming the importance of clinical data, are strongly concordant with a new approach to risk stratification, considering not only an initial DTC stage but also clinical features and the response to treatment administered [21–23]. Tuttle et al. [21] first stratified patients according to ATA risk groups (low, intermediate, or high). Next, on the basis of clinical data, obtained during the first two years of follow-up (suppressed or stimulated Tg level, imaging studies) and response to initial treatment (excellent, acceptable, or incomplete) the patients were re-stratified. Persistent DTC or relapse was observed in the low-, intermediate-, and high-risk group in 3%, 21%, and 68% of patients,

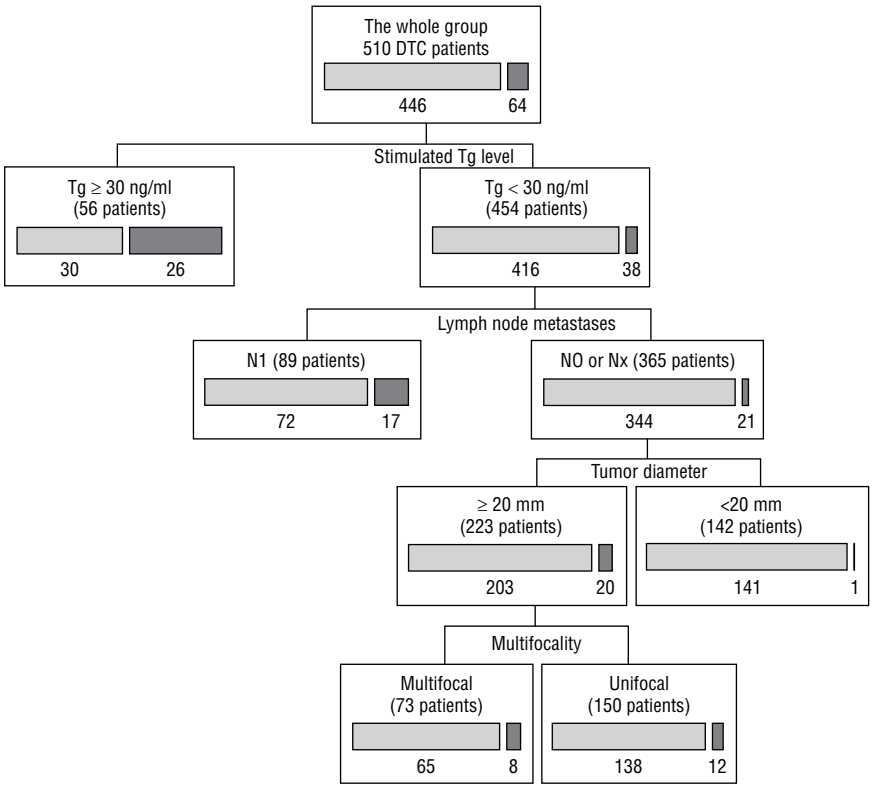

Figure 3. *Summary of the multivariate analysis performed with the use of classification and regression trees*

Rycina 3. *Podsumowanie analizy wieloczynnikowej przeprowadzone przy użyciu metody drzew klasyfikacji i regresji*

Table V. ***Risk factors used to create our own prognostic system based on the results of multivariate analysis***

Tabela V. ***Czynniki ryzyka wykorzystane przy tworzeniu własnego systemu prognostycznego na podstawie wyników analizy wieloczynnikowej***

Stimulated Tg > 30 ng/mL	6 points
Stimulated Tg 10–30 ng/mL	3 points
N1 feature	4 points
T3–T4 feature	3 points
131I remnant uptake < 1%	2 points

respectively. Re-stratification reduced the likelihood of persistent or recurrent DTC in patients with an excellent response to initial therapy up to 2% in the low-risk, 2% in the intermediate-risk, and 14% in the high-risk group, while in subjects with incomplete response it increased the likelihood of persistent or recurrent disease to 13%, 41%, and 79% in low-, intermediate-, and high-risk groups, respectively [21]. Similar results were reported by Castagna et al. [22], who evaluated the predictive value of delayed risk stratification (DRS) performed 8–12 months after initial treatment [22].

Table VI. ***Stratification of the risk of DTC relapse according to our own prognostic system based on the results of multivariate analysis***

Tabela VI. ***Stratyfikacja ryzyka nawrotu DTC według własnego systemu prognostycznego na podstawie wyników analizy wieloczynnikowej***

Points scored according to the prognostic system	Risk group	Number of patients	Number of events	The mean time to relapse	The median time to relapse	The percentage of patients without DTC relapse after 10-year follow-up
0	Very low	213	5	171		97.4%
1–4	Low	169	17	161		89.3%
5–8	Intermediate	78	15	140		81.4%
9–15	High	50	27	76	36	45.5%

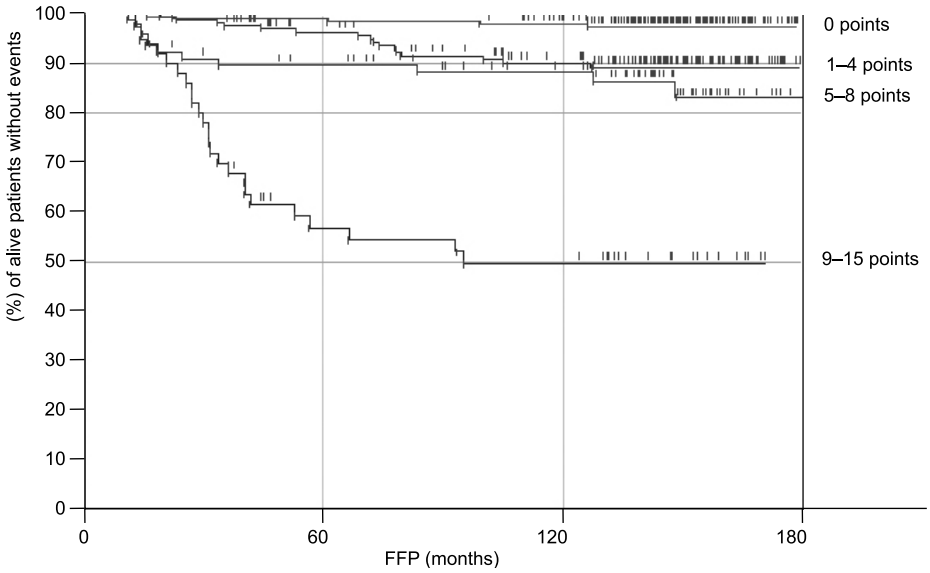

Figure 4. *The comparison between subgroups selected according to our own prognostic system that was based on the results of a multivariate analysis. Patients scoring 9–15 points were characterised by the poorest DTC prognosis*

Rycina 4. *Porównanie podgrup wybranych według własnego systemu prognostycznego, na podstawie wyników analizy wieloczynnikowej. Pacjenci, którzy zdobyli 9–15 punktów zostali scharakteryzowani jako pacjenci z najgorszym rokowaniem*

High stimulated Tg level above 30 ng/mL, evaluated before RAI ablation, was the most potent, independent prognostic factor in the analysed group regarding the risk of DTC relapse. Similarly, the prognostic value of Tg measurements was demonstrated in numerous studies [18, 23, 27–35]. In 2012 Webb et al. published the results of meta-analysis involving nearly 4000 DTC patients and evaluating the utility of serum Tg measurement performed at the time of RAI remnant ablation [36]. The authors clearly demonstrated that preablation Tg concentration was a negative predictor of persistent or recurrent disease. Subjects with a postoperative, preablation Tg value < 10 ng/mL showed a 6% likelihood of persistent DTC. In contrast to the high negative predictive value the positive predictive value of preablation Tg > 10 ng/mL was rather poor, at only 47% [36]. According to the study by Hussain et al. both preablation-stimulated Tg (sTg) level and stimulated Tg/TSH (sTg/TSH) ratio were significantly associated with ablation outcome. The following cut-off values for stimulated Tg of 18 ng/mL and for sTg/TSH of 0.35 allowed the prediction of successful and unsuccessful ablation with a sensitivity of 76.7% and 81.4% and specificity of 79.1 and 81.5%, respectively. Simultaneously, no significant dependence between ablation outcome and other risk factors such as: age, gender, tumour size, capsular invasion, lymph node and distant metastases, and ETA risk group was noticed [37]. Ronga et al. demonstrated that the first Tg measurement, carried out after total thyroidectomy may result in early diagnosis of metastatic disease, in spite of the presence of thyroid remnants, regardless of TSH value and WBS. The proposed Tg cut-off value calculated on the basis of the ROC curve was 69.7 ng/mL [28]. While, according to another study published in 2014, the optimal cut-off for the preablative, stimulated Tg level to predict persistent DTC was 28 ng/mL [29]. A similar preablative Tg cut-off, with a value of 27.5 ug/L, proposed by Heemsta et al. showed a sensitivity of 87.9% and specificity of 90.3%. When this cut-off level was decreased up to 2 ug/L the sensitivity increased to 93.9% whereas specificity fell to 45% with a positive predictive value 62% and 23%, respectively, and similar negative predictive value [27]. On the other hand, Nascimento et al. analysed a group of 242 patients with undetectable stimulated serum Tg at the time of RAI ablation. Persistent disease was diagnosed in eight cases (3%), all with initial lymph node metastases [38]. These results, convergent with our own data, confirmed that lymph node metastases constitute a strong independent risk factor.

Moreover, Malandrino et al. emphasised also the role of serum Tg assessment, measured on LT4 therapy (basal Tg) in 425 patients who underwent total thyroidectomy and RAI ablation. Based on ROC curve the optimal basal Tg value, characterised by the best combination of sensitivity and specificity, was 0.15 ng/mL (sensitivity 87%, specificity 91%, PPV 47.8%, and NPV 98.6%). The risk of DTC relapse in low-risk subjects with basal Tg level < 0.15 ng/mL was 1% and it was low even in patients primarily classified as intermediate and high-risk — 2.7% only. However, in subjects with basal Tg level above 0.15 ng/mL the recurrence rate was

much higher — from 12.5% for the low-risk group to 72% for the high-risk group. The authors concluded that this simple Tg measurement may be sufficient to assess the risk-adapted management in DTC [23]. Also a French group demonstrated that ultrasensitive serum Tg assessment in patients on LT4 therapy was useful for DTC follow-up in patients without anti-Tg antibodies, who underwent total thyroidectomy only without RAI ablation [39]. However, we do not share this statement as according to our data more than 50% of relapses were detected by neck ultrasound [40]. Similarly, Giovanella et al., on the basis on meta-analysis published in 2014, emphasised the high NPV of basal Tg and believed that because of the low PPV it was insufficient for DTC monitoring [41].

Conclusions

Postoperative stimulated Tg level was the most potent, independent risk factor influencing FFP in DTC patients. Age above 60 years, an initial DTC stage (T and N features), and low RAI uptake in thyroid bed (< 1%) were related to a higher risk of DTC relapse, whereas the investigated histopathological features were insignificant.

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