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Comparison of the usefulness of post-ablative and post-operative thyroglobulin concentration measuring in prognostic assessment of patients with differentiated thyroid cancer

Porównanie przydatności oznaczeń stężenia tyreoglobuliny poablacyjnej i tyreoglobuliny pooperacyjnej w ocenie rokowania chorych ze zróżnicowanym rakiem tarczycy

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Abstract

Introduction: Post-operative thyroglobulin (TgPO) is a recognised prognostic factor in patients following thyroidectomy due to differentiated thyroid cancer (DTC). However, its concentration is affected by thyroid remnants, which may diminish the prognostic value of TgPO. The aim of this paper is to assess the usefulness of stimulated post-ablative thyroglobulin (TgPA) measurements 6–9 months after ^{131}I therapy, as a prognostic factor, and its possible advantage over TgPO determination.

Material and methods: The study involved 577 DTC patients treated in the Holycross Cancer Centre in the years 2000–2013. Exclusion criteria were: patients with no recommendation for ^{131}I adjuvant therapy, positive thyroglobulin antibody titre, and initial distant metastases. On the basis of a ROC curve analysis, values of TgPO and TgPA concentrations were determined, which enable the most accurate identification of good prognosis. Calculating area under the curves (AUCs) allowed for comparison of the data.

Results: TgPO concentration ≤ 6.99 ng/mL, with 75.7% sensitivity and 94.7% specificity enables anticipation of remission of the disease. TgPA concentration ≤ 1.16 ng/mL under endogenous TSH stimulation with sensitivity of 91.1% and specificity of 94.7% allows anticipation of remission of the disease. TgPA concentration ≤ 1.24 ng/mL under rh TSH stimulation with sensitivity of 95.4% and specificity of 95.0% enables anticipation of remission of the disease.

Conclusions: No differences in clinical usefulness of the assessment of TgPO and stimulated TgPA concentrations as indicators of good prognosis were found. However, TgPA allows anticipation of remission of the disease with higher sensitivity. It also appears that TgPA may be of particular prognostic importance in baseline high-risk patients (pT3-T4/N1). A sufficiently low TgPA concentration, demonstrating good response to ^{131}I adjuvant therapy in these groups, is an indicator of improved prognosis. **(Endokrynol Pol 2015; 66 (6): 486–494)**

Key words: *differentiated thyroid cancer; thyroglobulin; prognostic factors; disease remission*

Streszczenie

Wstęp: Tyreoglobulina pooperacyjna (TgPO) jest uznanym czynnikiem rokowniczym u pacjentów po tyreoidektomii z powodu raka zróżnicowanego tarczycy (DTC). Na jej stężenie wpływa jednak ilość pozostawionej tkanki tarczycowej, co może obniżać jej wartość jako wskaźnika prognostycznego. Celem pracy jest ocena przydatności oznaczeń stymulowanej tyreoglobuliny poablacyjnej (TgPA), ocenianej 6–9 miesięcy po leczeniu ^{131}I, jako czynnika rokowniczego i jej ewentualna przewaga nad oznaczeniami TgPO.

Materiał i metody: Badaniem objęto 577 pacjentów z DTC leczonych w Świętokrzyskim Centrum Onkologii w latach 2000–2013. Wykluczono chorych niewymagających leczenia uzupełniającego ^{131}I, chorych z dodatnim mianem przeciwciał przeciw tyreoglobulinie oraz z przerzutami odległymi obecnymi w chwili rozpoznania. Na podstawie analizy krzywych ROC, ustalono wartości stężeń TgPO i TgPA, które pozwalają najlepiej przewidywać dobre rokowanie. Ocena wielkości pól pod krzywymi (AUCs) umożliwiła porównanie obu parametrów.

Wyniki: Remisję stwierdzono u 93,2 % chorych, brak remisji u 6,8 % badanych.

Stężenie TgPO ≤ 6,99 ng/ml z czułością 75,7% i swoistością 94,7 % pozwala przewidzieć remisję choroby. Stężenie TgPA ≤ 1,16 ng/ml na stymulacji endogennym TSH z czułością 91,1% i swoistością 94,7% pozwala przewidywać remisję choroby. Stężenie TgPA ≤ 1,24 ng/ml na stymulacji rhTSH z czułością 95,4% i swoistością 95,0% pozwala przewidywać remisję choroby.

Wnioski: Nie wykazano różnic w przydatności klinicznej oceny stężenia TgPO i stymulowanej TgPA jako wskaźnika dobrej prognozy. Jednak TgPA przy stężeniu ≤ 1,24ng/ml pozwala z większą czułością przewidzieć remisję choroby. Wydaje się również, że TgPA może mieć szczególne znaczenie rokownicze u pacjentów z wyjściowo wysokim ryzykiem (pT3-T4/N1). Odpowiednio niskie stężenie TgPA, świadczące o dobrej odpowiedzi na leczenie uzupełniające ^{131}I w tych grupach jest wskaźnikiem poprawy rokowania.

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Słowa kluczowe: *zróżnicowany rak tarczycy; tyreoglobulina; czynniki rokownicze; remisja*

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Introduction

Thyroglobulin (Tg) is a glycoprotein produced exclusively by the follicular cells of the thyroid. The follicular cells modified by the neoplastic process maintain the ability to produce thyroglobulin in most types of differentiated neoplasms [1].

Therefore, in patients following complete thyroidectomy and ^{131}I ablative treatment due to differentiated thyroid cancer (DTC), Tg is used as a neoplastic marker to monitor the disease [2–6].

Differentiated thyroid cancer (DTC) is a neoplasm characterised by good prognosis. Approximately 80% of patients recover after the first treatment. However, around 15% of patients are affected by local recurrence of the disease, and in 5–10% distant metastases occur. Most recurrences of the disease take place within the first five years; however, recurrences were also observed as late as after 45 years [7, 8]. Such reports necessitate life-long oncological monitoring of DTC patients.

Prognostic factors are still being sought that would enable the identification of patients with high risk of disease recurrence, allowing personalisation of the method of DTC management according to the patient's risk group.

Recently, numerous publications have appeared indicating the usefulness of the assessment of thyroglobulin concentration following thyroid surgery (TgPO) as a prognostic marker. Makarewicz et al., using an analysis of 247 patients, demonstrated that TgPO > 38.1 ng/mL is strongly correlated with the presence of distant metastases (sensitivity — 0.57; specificity — 0.96) [9]. The studies by Piccardo et al. established that in high-risk patients TgPO concentrations > 50 μ/L had the highest positive predictive value (PPV) — 97% for the presence of persistent disease, compared to factors such as age, feature T, N, G, or histological type of cancer [10]. The cut-off point for TgPO concentration, indicating favourable prognosis, has not been arbitrarily established. It is believed that in patients with lower TgPO concentration the probability of persistent or recurring disease is reduced. It has been concluded in a few studies that TgPO concentrations < 10 ng/mL indicate good prognosis. Polachek et al. decided, based on observations of 420 patients, that this TgPO concentration has a negative predictive value (NPV) of 89% for persistent disease, with sensitivity and specificity of 73% [11]. The same cut-off point for TgPO concentration, which enables one to anticipate a remission, has been determined by Piccardo et al. in low-risk [12] and high-risk [10] patients. In a two-year observation of 169 low-risk patients, they established that NPV for a recurrence of the disease was 100% with TgPO concentration < 10 ng/mL and undetectable Tg concentration during the suppressive treatment [12]. In a group of 243 high-risk patients, NPV was 93% with TgPO concentration of <10 μg/L [10]. Heemstra et al. advocate that TgPO concentrations < 27.5 μg/L enable anticipation of a favourable course of the disease (sensitivity — 87.9%, specificity — 90.3%; PPV for remission — 98%) [13]. A study by Kim et al. demonstrated that patients with TgPO concentrations > 5.22 ng/mL are burdened with a higher risk of recurrence of the disease [14]. Klubo-Gwiezdzinska et al. claimed TgPO < 5 ng/mL to have NPV = 100% in a study of 91 patients [15].

TgPO concentration values are affected by the presence of thyroid tissue remaining after surgery. It is estimated that 1 g of thyroid tissue causes an increase in Tg concentration of approximately 1 μg/L with normal TSH concentration, and by approximately 0.5 μg/L during TSH suppression. The fact may reduce the prognostic usefulness of TgPO [16].

It seems that the assessment of Tg concentration following ablative ^{131}I treatment (TgPA) may demonstrate greater prognostic value. The aim of the work was to assess the usefulness of measuring Tg concentration under exogenous or endogenous TSH stimulation as a prognostic factor, and its possible advantage over the TgPO determination.

Material and methods

The study involved 1200 DTC patients treated in the Holycross Cancer Centre in the years 2000–2013. Patients with distant metastases at the diagnosis and those who did not require ^{131}I adjuvant therapy were excluded from the study. Out of the remaining 661 patients, 85 were excluded due to the presence of thyroglobulin antibodies.

Eventually, the study involved 577 patients: 491 (85%) females and 86 (15%) males. The age median at the diagnosis was the same for both sexes, at 53 years (minimum–maximum age for women was 17–80 years, for men it was 23–76 years).

The dominant histological type was papillary carcinoma: 531 cases (92%), then follicular carcinoma — 33 cases (5.7%), insular carcinoma — 7 cases (1.2%), and oxyphil carcinoma — 6 cases (1%).

All patients underwent complete thyroidectomy with the intent to remove the central cervical compartment lymph nodes, and later they received adjuvant ^{131}I treatment with 1100–3700 MBq activity, repeated according to indications.

Patients having pT1N0/Nx and pT2N0 stage were assigned for low 131-I activity (patients with Nx feature were considered as low-risk on the basis of undetectable

Table I. *Characteristics of patients with remission and without remission*

Tabela I. *Charakterystyka pacjentów z remisją i chorobą przetrwałą*

Clinical factor	Patients in remission (n = 538)	Patients without remission (n = 39)	P value
Age (years) at the disease onset Median (Q_1–Q_3)	52 (42–60)	61 (50–69)	**0.0021** for Mann-Whitney test
Sex:			
Female	466 (87%)	25 (64%)	**0.0003** for chi-square test
Male	72 (13%)	14 (36%)	
T1	275 (51%)	8 (21%)	**0.0005** for chi-square test[1]
T2	74 (14%)	3 (8%)	
T3	140 (26%)	22 (56%)	
T4	25 (5%)	4 (10%)	
Tx	24 (4%)	2 (5%)	
N0	125 (23%)	5 (13%)	**0.0001** for chi-square test[1]
N1	59 (11%)	14 (36%)	
Nx	354 (66%)	20 (51%)	
TgPO [ng/mL] Median (Q_1–Q_3)	2.0 (0–148	29.8 (4.29–300)	**0.0001** for Mann-Whitney test
TgPA [ng/mL] Median (Q_1–Q_3)	0.0 (0.0–20.5)	6.73 (0–105)	**0.0001** for Mann-Whitney test
Papillary	500 (92.9%)	31(79.4%)	**0.0071**
Oxyphil	5 (0.9%)	1 (2.6%)	0.8450
Follicular	30 (5.6%)	3 (7.7%)	0.8509
Insular	3 (0.6%)	4 (10.3%)	**< 0.0001** for chi-square test

[1]p value corresponds to all Ts and to all Ns

TgPO and normal neck ultrasound). Patients who had pT2-4/Nx stage were assigned for high 131-I activity.

Table I presents in detail the distribution of patients by pTNM classification according to IUCC/AJCC TNM staging system 2010.

Patients are under continuous observation with periodic clinical assessments. Median (Q_1–Q_3) for the follow-up period is 5 (2.0–9.0) years. At the moment of analysis, 538 patients (93.2%) are in remission, and 39 patients (6.8%) were diagnosed with persistent disease.

Remission was determined on the basis of normal results of ultrasound neck examination, absence of radiotracer uptake foci in whole body scintigraphy, undetectable Tg concentration during the treatment with suppressive dose of l-thyroxine, and TgPA concentration < 1 ng/mL on recombinant human thyroid-stimulating hormone (rh TSH) stimulation, or TgPA concentration < 2 ng/mL on endogenous thyroid-stimulating hormone (TSH) stimulation.

Diagnostic imaging

Ultrasound examination of the neck was performed with the use of devices with colour Doppler function: Siemens Versa pro and Hitachi EUB-6500, EUB-5500, with a linear transducer 7.5 MHz. Neck and whole body scintigraphy was performed with the use of a Symbia T2 gamma camera by Siemens, following administration of ^{131}I diagnostic capsule of 80 MBq activity under endogenous TSH stimulation, and 200 MBq with rh TSH stimulation.

Thyroglobulin

TgPO was assessed 3–6 weeks after the thyroidectomy, at qualification for the adjuvant ^{131}I treatment, prior to implementation of substitute treatment with l-thyroxine. TgPA was assessed 6–9 months after the ^{131}I treatment, under endogenous TSH stimulation or rh TSH stimulation (Thyrogen, Genzyme Corp., amp. 0.9 mg). One ampoule of Thyrogen i.m. was administered on two consecutive days, TgPA was measured on day 5 after the administration of the first dose. TgPO and TgPA were assessed with TSH ≥ 30 IU/mL (range from ≥ 30 to > 100 IU/mL). During the l-thyroxine treatment, Tg was assessed every six months. Thyroglobulin was determined with the use of chemiluminescence — until 2007 on an Immulite 1 analyser by DPC, and since 2007 on an Immulite 2000 xpi Immunoassay System analyser by Siemens. The method's analytical sensitivity was < 0.2 ng/mL.

Statistical analysis

For the measurable parameters tested the basic statistics were determined (mean, standard deviation, median, quartiles: first and third). For the qualitative characteristics, frequencies were determined. The Mann-Whitney test, Kruskal-Wallis test, and chi-square test were also used. Correlation analysis was used for pairs of measurable characteristics. ROC (Receiver Operating Characteristic) curve analysis was performed for TgPO and TgPA concentrations. Calculating the area under the curves (AUCs) allowed for comparison of the data. P-values were presented for the tests used. The value of $p < 0.05$ was adapted as denoting statistically significant relationship, difference, or correlation. The statistical analyses were performed with the use of MedCalc Statistical Software version 13.0.

The study was approved by the Local Bioethical Committee.

Results

Remission

Among 577 study patients, in 538 (93.2%) disease remission was observed, and in the remaining 39 patients (6.8%) at the moment of analysis persistent disease was found.

Characteristics of patients with remission and with persistent disease are presented in Table I.

Patients with persistent disease or disease recurrence were older, more frequently they were males originally with a higher stage of clinical advancement T3–T4, and with lymph nodes metastases. The insular carcinoma type was associated with a higher risk of absence of remission. TgPO and TgPA concentrations were significantly higher in the patients without remission.

Detailed data of the patients without remission are presented in Table II.

Post-operative thyroglobulin

The analysis of TgPO concentration relationships is presented in Table III.

It was demonstrated that TgPO concentration depended on the sex of patients, and it was higher in males, as well as on the histological cancer type — the highest values were obtained in insular carcinoma. However, no statistically significant relationship was found between TgPO concentration and age at the onset of the disease, clinical advancement of the cancer, and lymph nodes condition.

Considering further course of the disease, on the basis of ROC curve analysis, we established that TgPO concentration ≤ 6.99 ng/mL, with 75.7% sensitivity and specificity of 94.7% enabled us to anticipate remission of the disease ($p < 0.001$). This is shown in Figure 1.

Among 410 patients with TgPO ≤ 6.99 ng/mL, the absence of remission was observed in three patients, whereas out of 167 patients with Tg over this threshold remission was absent in 36 patients ($p < 0.0001$).

Post-ablative thyroglobulin

TgPA was assessed under endogenous thyroid-stimulating hormone (TSH) stimulation in 254 patients, and under recombinant human thyroid-stimulating hormone (rh TSH) stimulation in 323 patients.

Mean (SD) TgPA concentration under endogenous TSH stimulation was 1.98 (9.62) ng/mL. Mean (SD) TgPA concentration under rh TSH stimulation was 1.57 (8.15) ng/mL. The observed difference was statistically non-significant. Median stimulated TgPA concentrations in both groups were zero.

The analysis of TgPA concentration relationships is presented in Table IV.

It was demonstrated that stimulated TgPA concentration depended on the sex of patients and was higher in males. No statistically significant relationship was found between stimulated TgPA concentrations and age at the disease onset.

The median for papillary carcinoma, follicular carcinoma, and oxyphil carcinoma was zero, and for insular carcinoma it was 1.91 ng/mL. A statistically significant difference was observed in median TgPA concentrations (calculated in total for endogenous TSH and rh TSH stimulation) between individual histological types of carcinoma (papillary and insular carcinoma). In T1 and T3 groups a statistically significant relationship between TgPA and N1/N0 feature was observed. This was probably due to a larger number of patients in these groups compared to groups T2 and T4.

On the basis of ROC curve analysis we established that TgPA concentration ≤ 1.16 ng/mL under endogenous TSH stimulation with a sensitivity of 91.1% and specificity of 94.7% enabled us to anticipate remission of the disease. ($p < 0.001$). This is shown in Figure 2.

Among 215 patients with TgPA ≤ 1.16 ng/mL for endogenous TSH, remission did not occur in one patient, whereas out of 39 patients with TgPA > 1.16 ng/mL the absence of remission was observed in 18 patients ($p < 0.0001$). TgPA concentration ≤ 1.24 ng/mL under rh TSH stimulation with sensitivity of 95.4% and specificity of 95.0% enabled us to anticipate remission of the disease ($p < 0.001$). This is shown in Figure 3.

Among 290 patients with TgPA concentration under rh TSH stimulation ≤ 1.24 ng/mL, remission did not occur in one patient, whereas out of 33 patients with concentration > 1.24 ng/mL the absence of remission was observed in 19 patients ($p < 0.0001$).

The difference between AUCs (TgPO *vs.* TgPA) was 0.0255 ($p = 0.3133$), which means the both parameters are of the same prognostic value. However, compared to TgPO, TgPA concentration demonstrates significantly higher sensitivity: 95.4% for rh TSH stimulation and 91.1% for endogenous TSH stimulation (*vs.* 75.7% for TgPO) with at least the same specificity as TgPO in anticipating the disease remission — as shown in Table V.

Discussion

Our study involved 577 patients with DTC. Remission was observed in 93.2% of patients, and absence of remission in 6.8% of patients.

A similarly low percentage of patients with disease recurrence (9%) was reported by Toubeau et al. in a study on 212 patients, after the patients with distant metastases present at the moment of diagnosis had been excluded from the observation [17].

The median follow-up period was five years, i.e. the time when the risk of thyroid cancer recurrence is highest (18), although the disease may recur at any moment in the patient's life [2, 8]. TgPO concentration is a prognostic factor which enables early anticipation of the course of the disease. The cut-off point for TgPO concentration, indicating favourable prognosis, has not been arbitrarily established. Values described in the literature range from ≤ 10 to ≤ 50 ng/mL.

Table II. *Characteristics of patients without remission*
Tabela II. *Charakterystyka pacjentów bez remisji*

No.	Sex	Age	Histopathology	Absence of remission		Diagnostic method	Time to recurrence	TgPA [ng/mL]
				Biochemical/ /persistent disease	Recurrence			
3	F	63	ins.		Cerv. lymph nodes	PET	12 months	1.91
20	F	69	pap.	(+)				8.67
23	F	43	pap.	(+)				4.67
29	F	49	pap.		Cerv. lymph nodes	USG	36 months	2.86
62	M	58	pap.		Cerv. lymph nodes	USG	3 months	3.93
73	F	71	oxy.	(+)				61.6
84	F	57	pap.	(+)			13 months	5.45
109	F	62	pap.	(+)			17 months	<0.2
124	F	29	pap.	(+)				38.4
125	F	79	fol.	(+)				1.29
137	F	32	pap.		Cerv. lymph nodes	PET	30 months	2.83
141	M	66	pap.	(+)				1.20
178	F	55	pap.	(+)				10.3
186	F	71	ins.		Cerv. lymph nodes Lungs	PET		64.2
195	M	44	pap.	(+)				14.9
199	M	64	pap.		Cerv. lymph nodes	USG	10 months	16.3
247	M	51	ins.		Lungs	CT	12 months	78.0
294	M	61	pap.	(+)				2.97
307	F	65	pap.		Cerv. lymph nodes	PET	12 months	1.80
317	F	61	pap.	(+)				27.8
323	F	73	pap.		Cerv. lymph nodes	PET	46 months	2.06
327	F	56	pap.	(+)				25.7
334	F	62	pap.		Lungs	PET/CT	10 years	< 0.2
348	F	70	pap.		Cerv. lymph nodes	USG	30 months	105
410	F	50	pap.	(+)				8.68
428	F	53	pap.	(+)				18.4
435	M	75	pap.	(+)				7.71
445	F	40	fol.	(+)				1.27
461	M	29	pap.	(+)				4.32
463	M	55	pap.	(+)				1.44
467	M	34	pap.		Cerv. lymph nodes	USG	6 months	80.5
477	M	68	ins.		Lungs	CT	5 years	32.6
487	M	64	pap.	(+)				6.73
520	F	27	pap.	(+)				70.4
540	M	72	fol.	(+)				5.45
550	F	72	pap.		Cerv. lymph nodes	USG	6 months	41.5
553	M	57	pap.		Lungs	CT	36 months	36.9
558	F	53	pap.	(+)				3.00
562	F	75	pap.	(+)				1.60

pap. — papillary carcinoma; fol. — follicular carcinoma; oxy. — oxyphil carcinoma; ins. — insular carcinoma; Cerv. lymph nodes — cervical lymph nodes, PET — 18-FDG tracer

Table III. *Analysis of relationships between mean or median TgPO concentrations and sex, histological type of the cancer, and TN feature*

Tabela III. *Analiza zależności średniego stężenia oraz mediany stężenia TgPO w stosunku do płci, typu histologicznego raka i cechy TN*

Clinical factor	Values of clinical factors	TgPO [ng/mL]			p value[1]
		Number of patients	Mean (SD)	Median (Q_1–Q_3)	
Sex	F	491	**9.4** (24.9)	**2.00** (0–7.5)	< 0.0001
	M	86	**17.5** (47.6)	**5.21** (1.8–11.7)	
Histological type	Papillary carcinoma	531	**8.5** (20.0)	**2.2** (0.3–7.5)	0.0004[2]
	Follicular carcinoma	33	**20.1** (41.4)	**8.4** (1.8–16.2)	
	Insular carcinoma	7	**111.7** (135.3)	**29.8** (5.4–254.8)	
	Oxyphil carcinoma	6	**33.60** (66.7)	**2.0** (2–27.6)	

pTN		N0			N1			Nx			
		Number of patients	Mean (SD)	Median (Q_1–Q_3)	Number of patients	Mean (SD)	Median (Q_1–Q_3)	Number of patients	Mean (SD)	Median (Q_1–Q_3)	
	T1	68	**7.5** (15.2)	**1.4** (0.5–7.1)	23	**6.8** (7.2)	**5.6** (1.1–8.9)	192	**7.7** (17.5)	**2.22** (0–8.2)	0.3838[3]
	T2	11	**12.1** (26.1)	**2.4** (0.5–10.8)	9	**16.7** (21.3)	**7.2** (0.5–33.5)	57	**3.8** (5.6)	**1.9** (0–5.2)	0.1795[3]
	T3	45	**3.9** (6.1)	**2.1** (0.2–6.2)	34	**18.6** (52.5)	**2.3** (0.3–17.5)	83	**19.4** (48.9)	**3.1** (0.8–13.5)	0.0925[3]
	T4	5	**7.8** (13.2)	**0.4** (0.3–13.3)	6	**17.9** (27.8)	**9.1** (1–14.5)	18	**15.3** (25.2)	**0.6** (0–28.5)	0.3668[3]

[1]p value for median values for Kruskal-Wallis test; [2]p value corresponds to papillary and insular carcinoma; [3]p value corresponds to all Ns

In our study, we established, on the basis of ROC curve analysis, that TgPO concentration ≤ 6.99 ng/mL enabled us to anticipate remission of the disease with the highest sensitivity and specificity. However, TgPO determination has its limitations. First, its concentration is affected by the thyroid tissue remaining after thyroidectomy. Webb et al., on the basis of a meta-analysis of nearly 4000 DTC patients, determined that PPV for the disease recurrence with TgPO concentration > 10 ng/mL is only 47%, which they associated primarily with the thyroid tissue remaining after the surgery [19].

Moreover, low TgPO concentration does not always guarantee favourable prognosis. Usually, undetectable TgPO concentration indicates completeness of the surgical procedure. However, there are reports of patients who, despite undetectable TgPO (in the absence of Tg antibodies), developed a recurrence or persistent disease. In a study by Phan HT et al. such a course of the disease was observed in 8.5% (8/94) of patients with undetectable TgPO concentration. During a follow-up, in a few patients a detectable Tg concentration or Tg antibodies occurred. The authors explain it not only by imperfect methodology of Tg determination, but also by possible changes in the neoplasm properties. In their opinion, the frequency of the disease recurrences is the same in the group of patients with detectable and undetectable TgPO, and they emphasise the usefulness of Tg and Tg antibodies determination in the monitoring of DTC patients, despite an undetectable TgPO [20, 21].

Therefore, we decided to assess the usefulness of stimulated TgPA determination as a prognostic factor, and demonstrate its possible advantage over TgPO measurements.

It is suggested that the cut-off point for rh TSH-stimulated TgPA should be lower compared to endogenous TSH-stimulated TgPA [12], because higher sensitivity and specificity are ascribed to TgPA stimulated by endogenous TSH. It is associated with the fact that Tg concentration increases together with prolonged time of TSH stimulation, and the time is longer in the case of hypothyroidism caused by endogenous TSH than in the case of rh TSH without inducing hypothyroidism [16, 22].

In a meta-analysis comprising over 9000 patients, Eustatia-Rutten C. F et al. established the highest sensitivity and specificity of TgPA stimulated with endogenous TSH, comparable sensitivity but lower specificity of TgPA stimulated with rh TSH, and in patients who did not undergo ablation the Tg specificity was significantly lower [23].

However, we believe that the diagnostic accuracy of both measurements is comparable [24–28].

In the results obtained in our study, the stimulated TgPA concentration which best correlated with the disease remission did not depend on the type of TSH stimulation, and it was ≤ 1.24 ng/mL for rh TSH and

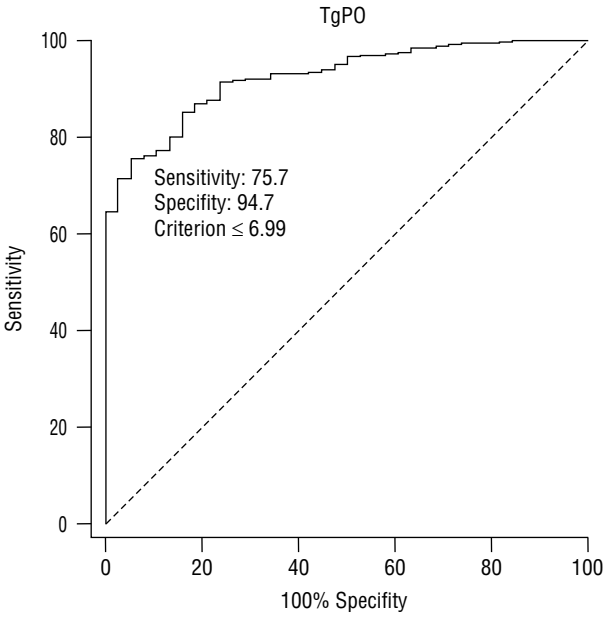

Figure 1. *ROC curve for TgPO regarding remission*

Rycina 1. *Krzywa ROC dla TgPO w odniesieniu do remisji*

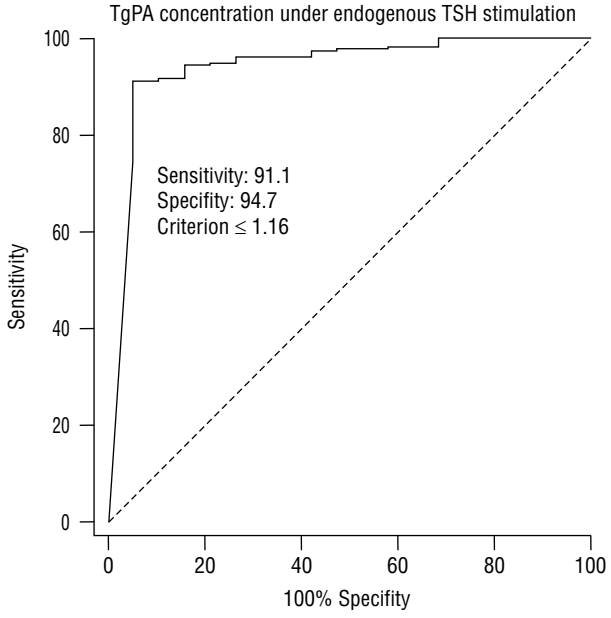

Figure 2. *ROC curve for TgPA under endogenous TSH stimulation regarding remission*

Rycina 2. *Krzywa ROC dla TgPA na stymulacji endogennym TSH w odniesieniu do remisji*

Table IV. ***Analysis of relationships between mean and median stimulated TgPA concentrations (together for endogenous TSH and rh TSH) and sex, histological type of the cancer, and TN feature***

Tabela IV. ***Analiza zależności średniego stężenia oraz mediany stężenia stymulowanej TgPA (łącznie dla endogennego TSH i rh TSH) w stosunku do płci, typu histologicznego raka, cechy TN***

Clinical factor	Values of clinical factors	TgPA [ng/mL]									p value[1]
		Number of patients			Mean (SD)			Median (Q_1–Q_3)			
Sex	F	491			**1.3** (7.8)			**0** (0–0)			0.0016
	M	86			**4.1** (13.1)			**0** (0–1.7)			
Histological type	Papillary carcinoma	531			**1.3** (7.5)			**0** (0–0.2)			**0.0021**[2]
	Follicular carcinoma	33			**1.6** (4.3)			**0** (0–1.3)			
	Insular carcinoma	7			**25.3** (33.6)			**1.9** (0.2–56.3)			
	Oxyphil carcinoma	6			**10.4** (25.1)			**0** (0–0.5)			
pTN		**N0**			**N1**			**Nx**			
		Number of patients	**Mean (SD)**	**Median (Q_1–Q_3)**	**Number of patients**	**Mean (SD)**	**Median (Q_1–Q_3)**	**Number of patients**	**Mean (SD)**	**Median (Q_1–Q_3)**	
	T1	68	**0.5** (2.3)	**0** (0–0)	23	**1.9** (4.5)	**0** (0–1.0)	192	**0.6** (3.3)	**0** (0–0)	0.0448[3]
	T2	11	**0.6** (1.1)	**0** (0–0.9)	9	**20.7** (32.9)	**0.6** (0–42.1)	57	**0.5** (1.9)	**0** (0–0)	0.8505[3]
	T3	45	**0.5** (1.9)	**0** (0–0.0)	34	**3.2** (8.7)	**0** (0–1.6)	83	**4.4** (16.1)	**0** (0–1.0)	0.0439[3]
	T4	5	**0.4** (0.5)	**0** (0–0.9)	6	**0.5** (0.8)	**0** (0–1.3)	18	**1.8** (6.0)	**0** (0–0.5)	0.3274[3]

[1]p value for median values for Kruskal-Wallis test; [2]p value corresponds to papillary and insular carcinoma; [3]p value corresponds to all Ns

≤ 1.16 ng/mL for endogenous TSH. Compared to TgPO, TgPA concentration demonstrates significantly higher sensitivity: 95.4% for rh TSH stimulation and 91.1% for endogenous TSH stimulation (*vs.* 75.7% for TgPO) with at least the same specificity as TgPO in anticipating the disease remission. TgPA concentration is, therefore, as equally a significant prognostic factor as TgPO concentration [18].

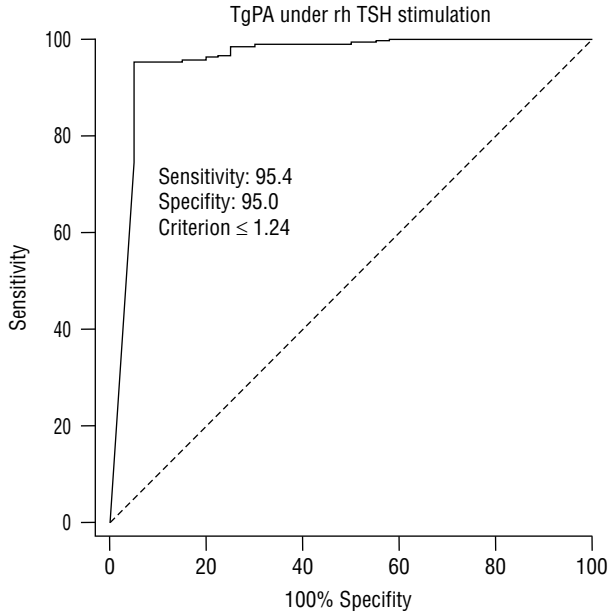

Figure 3. *ROC curve for TgPA under rh TSH stimilation regarding remission*

Rycina 3. *Krzywa ROC dla TgPA na stymulacji rh TSH w odniesieniu do remisji*

Table V. ***Comparison of sensitivity and specificity of TgPO and TgPA in predicting remission. Tg criteria for remission established on the basis of ROC curve analysis***

Tabela V. ***Porównanie czułości i swoistości TgPO i TgPA w odniesieniu do remisji. Punkt odcięcia stężenia Tg ustalony w oparciu o analizę krzywych ROC***

Tg	Sensitivity (%)	Specificity (%)	Criterion [ng/mL]
TgPO	75.7	94.7	≤ 6.99
TgPA under endogenous TSH stimulation	91.1	94.7	≤ 1.16
TgPA under rhTSH stimulation	95.4	95.0	≤ 1.24

In a study based on an analysis of 715 patients with median follow-up of 6.2 years, Brassard M. et al. arrived at a very similar cut-off point for TgPA (stimulated with endogenous or rh TSH) = 1.4 ng/mL, indicating favourable prognosis with the sensitivity of 78%, specificity of 90%, and NPV of 99% [29].

On the basis of a study involving 212 patients with median follow-up of five years, Toubeau et al. evaluated TgPA to be the most important (similarly to lymph node invasion) prognostic factor in DTC (with the value of ≤ 10 ng/mL). TgPO (≤ 30 ng/mL) was also reliable, although less significant [17].

Also Pelttari et al. in their 16-year observation of 495 low-risk patients (TNM I-II) emphasise the importance of TgPA and N1 feature as the only independent predictors of the disease recurrence [30].

A study by Molinaro et al. established that in patients with TgPA < 5.4 ng/mL, with time a spontaneous recovery occurred, despite a non-optimal response to ^{131}I ablative treatment. Simultaneously, the authors emphasised the possibly important significance of TgPA determination for prognosis [31].

Moreover, in our study we were researching the relationship between Tg concentration and the histopathological type of thyroid cancer. We observed statistically significantly higher TgPO concentrations in the follicular carcinoma than in the papillary carcinoma. Insular carcinoma was distinguished by a high TgPO concentration, as this type of cancer, despite a small number of patients [7], obtained the highest values and statistically significantly differed in that respect from papillary carcinoma. TgPA was also statistically significantly different between the papillary and insular carcinomas.

Among seven patients with insular carcinoma there were five females and two males. Remission was achieved in three female patients with pT2N0/pT2Nx advancement stage and a maximum TgPO concentration of 7.48 ng/mL, and TgPA concentrations undetectable in two cases and equal to 0.60 ng/mL in one patient. The patients who did not achieve remission included two males and two females with baseline advancement stages pT3 and pT2N1. In one case TgPO was 29 ng/mL, and in the remaining cases — 149, 290, and > 300 ng/mL (TgPA of 32.6; 1.91; 64.2; 78 ng/mL, respectively). Three patients developed metastases to the lungs, and in one patient metastases to the paratracheal lymph nodes were identified on the basis of a PET examination.

Remission did not occur in the patients who did not demonstrate sufficient response to the ^{131}I treatment, and the TgPA concentration — except for one patient (TgPA — 1.91 ng/mL) in whom it still remained significantly increased.

In our study we also assessed the relationship between TgPO or TgPA and the pTN stage. We did not observe a statistically significant difference in TgPO between the high-risk and low-risk groups, which is probably due to a large percentage of patients with the Nx feature. However, we observed higher TgPA concentrations in the patients with invaded lymph nodes in the T1 and T3 groups. The absence of a similar observation in the T2 and T4 groups is probably caused by a lower number of patients in these groups, as well as by the frequent presence of the Nx feature.

However, it appears that TgPA may be of particular prognostic importance in baseline high-risk patients (pT3-T4/N1). Sufficiently low TgPA concentration,

demonstrating good response to ^{131}I adjuvant therapy in these groups, is an indicator of improved prognosis. Prognosis becomes comparable to that assumed for the patients with lower advancement stage at the baseline (pT1-T2) [17].

On the basis of the analysis of patients with insular carcinoma, it also seems that the concentration of stimulated TgPA in DTC cases with biologically higher malignancy potential, and maintained ability to produce Tg, may be an indicator of the course of the disease.

Conclusions

No differences in clinical usefulness of the assessment of TgPO and stimulated TgPA concentrations as indicators of good prognosis were found. However, stimulated TgPA at a concentration ≤ 1.24 ng/mL enabled us to anticipate remission of the disease with significantly higher sensitivity than TgPO. No significant difference in TgPA concentrations depending on the type of stimulation (endogenous TSH and rh TSH) was observed.

It seems that stimulated TgPA may demonstrate a higher diagnostic value than TgPO in patients with more advanced stages of DTC (pT3-T4), as well as in histologically less differentiated cancers (insular carcinoma), i.e. cancers with higher malignancy potential and maintained ability to produce Tg. A sufficiently low concentration of stimulated TgPA indicates a good response to the ^{131}I ablative treatment, and a better prognosis. However, this still needs to be determined unambiguously in further investigation.

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