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Ocena wartości pierwszego oznaczenia tyreoglobuliny w diagnostyce przerzutów wcześnie po operacji zróżnicowanego raka tarczycy

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Streszczenie

Wstęp: Celem pracy była ocena wartości różnicowej pierwszego oznaczenia stężenia tyreoglobuliny (Tg) po tyreoidektomii (Tx), a przed ablacją kikutów tarczycy u chorych ze zróżnicowanym rakiem tarczycy (DTC, *differentiated thyroid carcinoma*) jako wskaźnika obecności przerzutów i/lub ognisk nowotworowych (M).

Materiał i metoda: Retrospektywnej analizie poddano dane 517 chorych po Tx z powodu DTC skierowanych w celu ablacji kikutów tarczycy, obserwowanych następnie dłużej niż 1,5 roku. Z analizy wykluczono pacjentów o niepewnym przebiegu choroby i z interferencją w badaniu Tg (a-TgAb[+], odzysk Tg < 80%). Ostatecznie analizowano wyniki 247 chorych z DTC (14–79 lat; 223 kobiet, 24 mężczyzn). Porównano wyniki badań TSH, wychwytu ^{131}I nad szyją (T_{up24}), objętości resztek tarczycy (V) i Tg u chorych z rozpoznanymi w chwili badania M (Grupa M1; n = 35) z tymi samymi parametrami u pacjentów bez obserwowanego powyżej 1,5 roku nawrotu choroby (Grupa M0; n = 212). Obliczono pole pod krzywą ROC stężeń Tg w badanej grupie. Wyznaczono wartość referencyjną stężenia Tg dla podejrzenia M za pomocą krzywej wydajności badania Tg.

Wyniki: Grupy M0 i M1 nie różniły się pod względem stężenia TSH (mediana 49,7 jm./l *vs.* 44,3; p = 0,16), objętości kikutów tarczycy (1,4 *vs.* 1,1 ml; p = 0,79), różnice dotyczyły natomiast T_{up24} (7,6 *vs.* 3,2%; p = 0,01) oraz Tg (4,5 *vs.* 96,7 ng/ml; p = 0,000000). Pole pod krzywą ROC dla Tg dla badanej grupy wynosiło 0,78 ± 0,05 (śr. ± s.e.m.). Wartość referencyjną Tg dla podejrzenia M wyznaczono na 38,1 ng/ml, czułość oznaczenia Tg wynosiła 0,57 (95%CI 0,39–0,74), a swoistość 0,96 (95%CI 0,92–0,98).

Wnioski: Pierwsze stężenie Tg oznaczone po Tx przybiera u chorych z przerzutami raka tarczycy wartości większe niż u chorych bez tych przerzutów, co wskazuje, iż wymieniony parametr może być stosowany jako wczesny wskaźnik obecności przerzutów raka tarczycy (również w obecności kikutów tarczycy).

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Słowa kluczowe: *rak tarczycy, tyreoglobulina, tyreoidektomia*

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An evaluation of the value of first thyroglobulin determination in the diagnostics of metastases immediately following differentiated thyroid carcinoma surgery

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Abstract

Introduction: Evaluation of the differential value of the first thyroglobulin (Tg) concentration, measured after thyroidectomy (Tx) but before thyroid remnant ablation, in patients with differentiated thyroid carcinoma (DTC) as a marker of either metastases or residual cancer (M).

Material and methods: Data from 517 patients with DTC after Tx, with follow-up > 1.5 year were analysed retrospectively. Patients in whom either the course of the disease was unclear or interference in the Tg test was possible (a-TgAb [+], Tg recovery < 80%) were excluded from the study. Finally, the data from 247 patients were evaluated (age: 14––79 years; 223 women, 24 men). The results of TSH, thyroid radioiodine uptake (T_{up24}), thyroid remnant volume (V) and Tg in patients with diagnosed M (group M1; n = 35) were compared with the same parameters in patients with remission > 1.5 year (group M0; n = 212). The area under the ROC curve was calculated. The clinical decision limit of Tg level to be suggestive of metastases was determined by means of efficiency curve.

Results: Groups M0 and M1 did not differ from each other with respect to TSH concentration (median 49.7 mIU/l *vs* 44.3; p = 0.16) or thyroid remnant volume (1.4 *vs* 1.1 ml; p = 0.79). However, they did differ with respect to T_{up24} (7.6 *vs* 3.2%; p = 0.01) and Tg (4.5 *vs* 96.7 ng/ml; p = 0.000000). Area under ROC for Tg was 0.78 ± 0.05 (mean ± ± s.e.m.). The decision limit of Tg for suspected M was determined at 38.1 ng/ml, Tg sensitivity was 0.57 (95% CI 0.39––0.74) and specificity 0.96 (95% CI 0.92–0.98).

Conclusions: First thyroglobulin concentration, determined after thyroidectomy but before other treatment, is higher in patients with metastatic DTC than in patients without such metastases. This indicates that Tg level may be used as an early marker of either residual or metastatic DTC (even if thyroid remnants are present).

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Key words: *thyroid cancer, thyroglobulin, thyroidectomy*

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Introduction

Measurement of serum thyroglobulin (Tg) concentration is now a standard follow-up procedure in patients with differentiated thyroid carcinoma (DTC) after total thyroid ablation [1, 2]. Its diagnostic value in patients in whom thyroid remnants are still present is less well established and few studies have been devoted to the value of first serum Tg concentration measurement as an early indicator of incomplete cancer dissection or metastases in patients who have undergone only thyroidectomy before radioiodine treatment [3–9]. Obviously, an early indicator of the possible presence of carcinoma would be a useful tool in selecting a more or less aggressive diagnostic and therapeutic approach as early as the first weeks or months after diagnosis.

The aim of this study was to assess the diagnostic value of the first Tg level measurement, performed after thyroidectomy but before other treatment, in patients with DTC, Tg level to be regarded as an early marker of either metastases or residual cancer.

Materials and methods

TSH, Tg, anti-Tg antibodies and exogenous Tg recovery (all: DYNOtest®, BRAHMS, Berlin, Germany) were determined in 517 patients with DTC submitted for

radioiodine therapy after thyroidectomy and before other treatment. Patients were excluded from analysis in whom presence of the disease could not be clearly confirmed or excluded at that time and during a follow-up period of at least 18 months, with anti-Tg antibodies > 60 U/ml or with recovery of exogenous Tg of less than 80%. Finally, 247 patients (223 women, 24 men, age: 14––79 years) were evaluated, including 177 patients with papillary carcinoma, 49 with follicular carcinoma and 21 patients with an oxyphilic variant of follicular carcinoma, at all stages according to the TNM classification. In all patients who were off L-T_4 therapy iodine uptake in the thyroid bed (T_{up24}) was measured 24 hours after oral administration of 4 MBq of ^{131}I. The total volume (V) of thyroid remnants, well delineated by ultrasound in 197 patients (AU3 Partner, EsaoteBiomedica, Italy/ /USA, 7.5 MHz probe), was calculated by means of the following formula: $\Sigma\, 0{,}5 \times (a_n \times b_n \times c_n)$, where a, b, c are the maximal dimensions of remnant n in the frontal, transverse and sagittal planes. When indicated, radioiodine therapy was administered and a whole body scan (WBS) was obtained. All patients were treated and followed up according to generally accepted recommendations. At least 6 and then 18 months after initial evaluation patients were subjected to control examinations under TSH stimulation. Whole body scanning and neck ultrasound were carried out and TSH, Tg and Tg recovery determined. When indicated, other studies were performed (chest X-ray, CT, ^{99m}Tc-MIBI scintigraphy and WBS after a large dose of ^{131}I). All patients were also examined on an ambulatory basis every 6 months.

All data obtained between first thyroid carcinoma diagnosis and the last available control examination were evaluated. The results were regarded as abnormal (i.e. indicating either metastases or residual cancer — group M1) when changes were found, subsequently diagnosed unequivocally as DTC metastases or as cancer residues. When no foci of abnormal radioisotope uptake were found, no metastases were detected by other imaging methods (US, X-ray, CT) or when lesions were found without cytological/histological confirmation of thyroid carcinoma during follow-up of at least 18 months, the patient was classified as free from metastases — group M0.

Thyrotropine concentrations, volumes of thyroid remnants (V), neck radioiodine uptake (T_{up24}) and Tg concentrations were compared between groups M0 and M1 (the Mann-Whitney U test). In all cases, $p = 0.5$ was regarded as the border of statistical significance. Receiver operating characteristic curve (ROC) analysis was performed to better define the diagnostic value of Tg concentration. The diagnostic efficiency curve of Tg determination was plotted and the cut-off was set for maximum efficiency, as described by Kairisto and Pola [10]. The calculations were performed by the Statistica 5.1 software package (StatSoft, Inc.) and GraphROC for Windows (Turku, Finland).

Table I
Some characteristics of the groups of patients with and without metastases/residual cancer detected at the time of initial evaluation

Tabela I
Niektóre dane uzyskane w momencie początkowej oceny charakteryzujące grupy pacjentów z przerzutami/pozostałościami raka tarczycy i bez nich

	Median (range)		p
	Group M0; n = 212	Group M1; n = 35	
TSH [mIU/l]	49.7 (3.4–97.4)	44.3 (0.2–99.7)	0.16
V [ml]	1.4 (0.1–10.6)	1.1 (0.3–10.5)	0.79
T_{up24} [%]	7.6 (0.2–41.3)	3.2 (0.3–28.4)	0.01
Serum Tg [ng/ml]	4.5 (0.1–564.0)	96.7 (0.7–1210.0)	0.000000

Results

Metastases were not found in 212 patients (group M0). At the time of the initial evaluation, metastases were diagnosed in 35 patients (group M1), including 15 patients with metastases limited to the lymph nodes, 17 patients with residual cancer or distant metastases and 3 patients with both. Some characteristics of both groups are presented in Table I.

As demonstrated, statistically significant difference between groups M0 and M1 was found in the Tg concentration. This was higher among patients with diagnosed residual cancer/distant metastases than in those with metastases limited to the cervical lymph nodes (155.0 ng/ml *vs* 13.1 ng/ml, $p = 0.018$; three patients with both types of metastases were excluded from the analysis).

The areas under the ROC curves for Tg concentrations for the whole group studied, patients with lymph node metastases and residual cancer/distant metastases, were 0.78 ± 0.05 (median ± s.e.m.), 0.66 ± 0.09, and 0.83 ± 0.08, respectively. The clinical decision limit of Tg concentration for suspicion of DTC metastases/residues was identified as 38.1 ng/ml. The sensitivity of Tg at this level in the group as a whole was 0.57 (95% CI 0.39–0.74) with a specificity of 0.96 (95% CI 0.92–0.98).

Discussion

In the early phase of therapy of patients with DTC before remnant ablation by means of radioiodine, detection of metastases or local recurrence depends primarily on imaging methods: whole body scans (WBS), neck

USG, X-ray and CT. The sensitivity of WBS is, however, low in the presence of thyroid remnants and CT examinations are usually not performed without specific indications [3]. On the other hand, Tg secreted from normal thyroid cells is indistinguishable from that produced by the DTC and, as such, its serum concentration measurement has been considered inappropriate for the detection of metastases in the presence of thyroid remnants. There are, however, some reports indicating the usefulness of Tg concentration measurement in the presence of thyroid remnants [3, 6, 8, 9].

We demonstrated that in patients without DTC metastases serum Tg concentration is lower than in patients with metastatic carcinoma, especially when localised to the lungs or the bones. Similar data have been reported by others [8, 9].

The main source of error related to Tg as an early index of DTC metastases was its low serum concentration in some patients with metastatic DTC. It may be disputed whether this was caused by the insensitivity of the Tg assay used, by an underestimation of the Tg concentration as a result of the interference of anti-Tg antibodies, lack of Tg secretion by thyroid carcinoma cells or by secretion of conformationally abnormal Tg molecules not detected by the Tg assay used.

Unfortunately, there is no lower limit for anti-Tg antibodies below which no interference would be observed in Tg assays. This is certainly a limitation on the diagnostic value of Tg determination in general but no reliable method is currently known to detect and/or overcome this effect. In order to minimise the interference, we decided to include in our study only patients who fulfilled available criteria of Tg assay reliability, those, that is, with anti-Tg antibodies below the aforementioned cut-off point and with recovery of exogenous Tg of more than 80% [11, 12].

Some reduction in the sensitivity of the tests described can be also related to low tumour mass. In our group of patients small volume lymph node metastases were characterised by lower Tg levels than the generally larger distant metastases. Similar data are reported by Lima et al. [6]. Similarly, some less differentiated tumours may produce less Tg, which may result in further loss in the sensitivity of its determination [13].

In some patients without subsequently detected metastases unexpectedly high serum Tg concentrations were measured. Postsurgical trauma or coexisting thyroid inflammation could be considered as being responsible for this effect.

The analysis presented made it possible to determine the clinical decision limit for serum Tg concentration above which metastases are likely. In our opinion certain clinical decisions can justifiably be made in patients with high serum Tg concentration. A more aggressive diagnostic approach may already be considered during the first visit after the thyroidectomy, such as a greater dose of ^{131}I administered for thyroid remnant ablation (to obtain greater confidence in their early and complete destruction) and possibly an earlier follow-up visit.

Conclusions

Thyroglobulin concentration determined after thyroidectomy but before other treatment in patients with metastatic DTC is higher than in patients without such metastases. This indicates that Tg level may be applied as an early marker of either residual or metastatic DTC.

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