

Role of postoperative serum thyroglobulin as a prognostic factor for the outcome of radioactive iodine therapy in follicular thyroid cancer

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ABSTRACT

Aim To investigate the relationship between postoperative serum thyroglobulin level and outcome of therapy with I-131 in follicular thyroid cancer.

Methods A total of 106 patients with follicular thyroid cancer who were treated and monitored at the Clinic for Nuclear Medicine at Clinical Centre of the University of Sarajevo were included in the study. The inclusion criteria were: surgery of total thyroidectomy, histopathological diagnosis of follicular thyroid cancer, and applied therapy with radioactive iodine. Exclusion criteria were patients with incomplete data, who were not treated with radioiodine treatment, or had a different histopathological diagnosis. Postoperative serum thyroglobulin levels were correlated with results of whole body scintigraphy after 12 months (first diagnostic scintigraphy), and whole body scintigraphy after 24 months (second diagnostic scintigraphy).

Results A higher frequency of recurrent disease was found in patients with elevated level of thyroglobulin compared to patients with lower postoperative thyroglobulin level. The elevated level of postoperative thyroglobulin correlated with positive scintigraphy findings, i.e., with the presence of recurrence and/or metastases in patients with follicular cancer. The cut-off level of postoperative thyroglobulin for recurrence and/or metastasis, i.e. for failure of ablative therapy with I-131, was >12.6 ng/mL.

Conclusion Our study has shown that the level of postoperative thyroglobulin is an important prognostic factor for the outcome of radiiodine therapy in follicular thyroid cancer, and should be taken into account when deciding on therapy in this type of cancer in everyday practice.

Keywords: prognosis, radioiodine, thyroid neoplasm, recurrence

INTRODUCTION

Follicular thyroid cancer accounts for about 10-15% of all cases of thyroid cancer, and is the second most prevalent type of thyroid neoplasms (1). This type of cancer usually spreads by hematogenous dissemination and is more aggressive than papillary thyroid cancer. Distant metastases are seen in about 10–15% of cases, and the most common sites of metastases are the bones and lungs (2).

The first step in the therapy of follicular thyroid cancer for all well-differentiated thyroid cancers is the operative treatment with surgical excision of the thyroid gland and lymphatic dissection of the respective cervical section (selective neck dissection) if needed (3). The main complications of the surgical

treatment include damage to the laryngeal nerve and dysphonia and hypoparathyroidism due to inadvertent damage or removal of the parathyroid glands (4). Total thyroidectomy has several advantages. First, it makes recurrence detection easier through neck ultrasounds. Second, thyroglobulin can be utilized as a marker to identify newly formed thyroid tissue or metastases, aiding in the monitoring of residual and recurrent disease. Lastly, this procedure enables the use of radioactive iodine as the primary treatment for cancer (5).

Radioiodine (I-131) is given after thyroidectomy in patients with follicular thyroid cancer to destroy the remaining normal thyroid tissue, provide adjuvant therapy for subclinical micrometastatic disease, and/or treat clinically visible residual or metastatic thyroid cancer (6). A substantial number of studies indicate lower recurrence and mortality rates in patients with differentiated thyroid cancer treated with radioactive iodine (7,8). After a total thyroidectomy, patients undergo diagnostic whole-body scintigrams using I-131 to identify any regional or distant metastatic disease (9). If any residual disease is found, radioablation will be performed. Patients are then monitored

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through regular checks of their thyroglobulin levels, neck ultrasounds, and whole-body diagnostic scintigrams, all scheduled every 12 months (10).

It is estimated that 11-39% of patients with follicular cancer will develop recurrent disease. Recurrence typically arises within the first two years following surgical treatment (11). Successful treatment with I-131 has been shown to decrease the likelihood of recurrence and enhance disease-free survival (12). However, treatment failure is not that uncommon in patients after receiving the first radioiodine treatment doses (13). A repeated therapy dose can cause inconvenience to patients, increase financial burden, and potentially raise the risk of developing a second primary malignancy (12). In this regard, individual studies have investigated different variables as predictors for successful radioiodine therapy (14,15).

Recently, significant attention has been given to postoperative thyroglobulin and its potential role as a predictor of disease progression (16-19). Most studies also investigate the role of thyroglobulin in differentiated thyroid cancer in general, but there is a very small number of studies related to follicular thyroid cancer alone (20). Similar studies have not been conducted in Bosnia and Herzegovina, although there is a large number of patients with thyroid cancer in this country (21).

The aim of this study was to investigate the relationship between the level of postoperative serum thyroglobulin and the presence of recurrence and/or metastasis of follicular thyroid cancer or the outcome of therapy for follicular thyroid cancer. Identifying postoperative thyroglobulin as a prognostic factor for patients with follicular thyroid cancer would have significant value for risk stratification as well as making decisions on the therapy of patients with follicular cancer. It would also enable better clinical monitoring of patients and a possible change in its management.

PATIENTS AND METHODS

Patients and study design

This retrospective study was conducted at the Nuclear Medicine Clinic of the Clinical Centre, University of Sarajevo, between April 2021 and June 2023. The inclusion criteria were: surgery of total thyroidectomy, histopathological diagnosis of follicular thyroid cancer, applied therapy with radioactive iodine and patients who were followed for a period of 2 years searching for possible local recurrences or metastases. Exclusion criteria included patients with incomplete data, those who were not treated with radioiodine treatment, or patients with a different histopathological diagnosis.

A total of 106 patients were included in the study. Gender, age of the patient at the time of the diagnosis, type of surgery, pathohistological findings, tumour staging according to the Tumour size, Node metastases and distant Metastases (TNM) classification (22), serum thyroglobulin values before ablative therapy with I-131, findings of the initial scintigram of the whole body with I-131 (before therapy), findings of the first control scintigram of the whole body 12 months after therapy, and findings of the second control scintigram of the whole body 24 months after therapy, were all evaluated. Information was obtained from medical charts of the patients treated at the Nuclear Medicine Clinic of the Clinical Centre, University of Sarajevo. Postoperative serum thyroglobulin level was correlated with results of whole body scintigraphy after 12 months

(first diagnostic scintigraphy) and whole body scintigraphy after 24 months (second diagnostic scintigraphy).

Aa approval was obtained from the Ethical Committee of the Medical Faculty, University of Sarajevo. All patients provided a written informed consent to participate in the study.

Methods

Measurement of thyroglobulin in serum was performed using electrochemiluminescent immunoassay (23). The analytical detection limit of the test was 0.2 ng/mL, and the functional sensitivity of the test was 0.7 ng/mL (Elecsys Tg II, Cobas 6000 System, Roche Diagnostics, USA). Serum Thyroglobulin level >2 ng/mL was considered positive.

Whole-body scintigraphy was recorded on a dual-headed gamma camera (Discovery NM/CT 670, GE Healthcare Discovery, Waukesha, USA). Anterior and posterior whole body images were performed using high-energy parallel collimators (Discovery NM/CT 670, GE Healthcare Discovery, Waukesha, USA). The width of the window was 15%, the size of the matrix was 256x1024 pixels, the recording length was 200 cm, the recording speed was 8 cm/min. Targeted scintigrams were performed in regions with suspicious focal lesions. If necessary, a single photon emission computed tomography (SPECT) was performed for better definition of thyroid uptake and precise anatomical localization of possible metastases. The interpretation of the scintigram was qualitative. The possible existence, size and intensity of accumulation of radiopharmaceutical (I-131) in the thyroid bed or in other parts of the body were assessed, i.e. the existence of possible local recurrences in the thyroid bed and lymph nodes of the neck and the existence of possible distant metastases in other regions of the body. The absence of accumulation in the region of the thyroid bed and neck, as well as in other regions presented, was considered a negative finding. Increased accumulation in the thyroid bed, as well as the presence of a focus of increased accumulation outside the regions of physiological accumulation of radioiodine, was considered a positive finding.

Statistical analysis

Data were presented in the form of tables and graphs, using classic methods of descriptive statistics, depending on the nature of the data and the scale of measurement. The examination of the normality of the distribution of continuous numerical variables was performed by the inspection of histograms, quantile diagrams and formal testing using the Kolmogorov-Smirnov test. Analysis of categorical variables was performed using Pearson's χ^2 -test or Fisher's exact probability test. Analysis of normally distributed continuous ratio characteristics was performed using the Independent Sample T test for independent samples, while nonparametrically distributed numerical variables were analysed using the Mann-Whitney U test for independent samples. Spearman's rank correlation coefficient was used to examine the linear association of non-parametrically distributed ratio characteristics. Pairwise comparisons were performed using the Bonferroni correction for multiple comparisons (statistical significance was accepted at the $p < 0.0167$ level). The measures of diagnostic accuracy (validity, predictive value, likelihood ratio) were shown using the analysis of the ROC curve (Receiver Operating Characteristic), where the finding was used as the "gold standard", that is, the method based on which we know for sure whether the disease is pres-

ent or not was scintigraphy. The Youden test was used, as a calculation that determines the overall benefit of a diagnostic test, and if its value was $\leq 50\%$, it meant that the test could not be used for diagnostic purposes. Test validity is the ability of the test to distinguish between sick and healthy individuals: sensitivity (SN) is defined as the ability of the test to identify people who actually have the disease, and specificity (SP) is defined as the ability of the test to identify people who actually do not have the disease.

RESULTS

Out of the total number of patients (N=106), most of them, i.e. 93 (87.7%), were female. More than half of the patients, 66 (62.3%), were aged ≥ 55 years. There was no statistically significant relationship between gender and age ($p=0.954$) (Table 1).

Table 1. Distribution of patients by age and gender

Variable	No (%) of patients		Total
	Age (years)		
	20-54	≥55	
Gender			
Female	35 (37.6)	58 (62.4)	93 (100.0)
Male	5 (38.5)	8 (61.5)	13 (100.0)
Total	40 (37.7)	66 (62.3)	106 (100.0)

According to the size of the tumour, 44 (40.6%) patients had a tumour size of >2 cm, but <4 cm in the largest diameter, without extra-thyroidal extension. Twenty (18.9%) patients had a tumour size <2 cm in the largest diameter confined to the thyroid gland, 17 (16.0%) had a tumour size >4 cm, one (0.9%) had extrathyroidal extension below the accompanying muscles (Table 2).

Table 2. Distribution of patients with follicular thyroid cancer according to Tumour Node Metastases (TNM) classification

TNM classification*	No (%) of patients	Cumulative frequency
pT1NxMx	20 (18.9)	18.9
pT1aNxMx	5 (4.7)	23.6
pT1bNxMx	6 (5.7)	29.2
pT2NxMx	43 (40.6)	69.8
pT2aNxMx	2 (1.9)	71.7
pT2N1bMx	1 (0.9)	72.6
pT3NxMx	17 (16.0)	88.7
pT3aNxMx	9 (8.5)	97.2
pT3N1Mx	2 (1.9)	99.1
pt4NxMx	1 (0.9)	100.0
Total	106 (100.0)	

T, the primary tumour site and size; T1, tumour ≥ 2 cm in largest diameter confined to the thyroid gland; T1a, tumour up to 1 cm in diameter limited to the thyroid gland; T1b, tumour >1 cm, but in largest diameter not greater than 2 cm confined to the thyroid gland; T2, tumour >2 cm, but <4 cm confined to the thyroid gland; T3, tumour >4 cm or tumour with minimal extrathyroidal spread; T4, tumour that extends beyond the thyroid capsule and invades surrounding structures; N, lymph node involvement; Nx, without metastases in the regional lymph nodes; N1, metastases in the regional lymph nodes of the neck; N1a, metastases in the region VI or VII; N1b, metastases in unilateral, bilateral or contralateral cervical lymph nodes, M, distant metastatic spread (22)

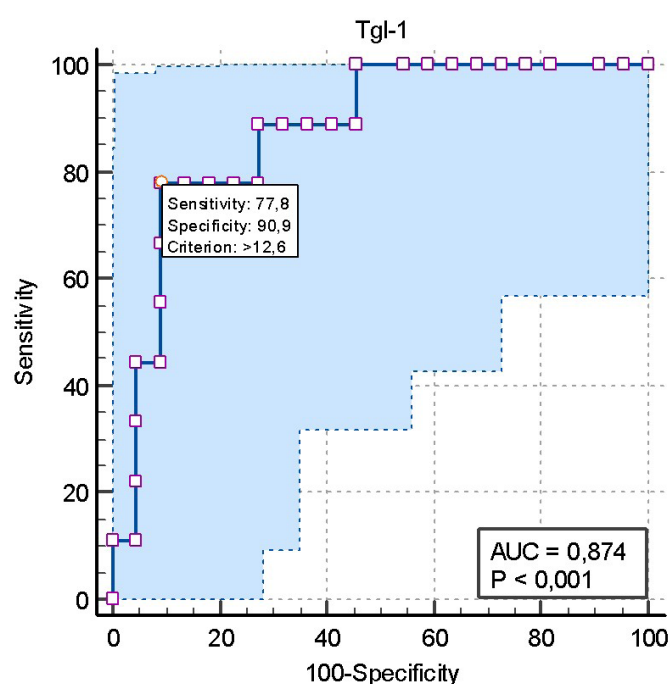


Figure 1. The ROC (Receiver Operating Characteristic) curve for serum thyroglobulin level compared to the first diagnostic scintigraphy

The elevated level of postoperative thyroglobulin in serum in the detection of recurrence and/or metastases in patients with follicular thyroid cancer confirmed by scintigraphy after 12 months showed SN=77.8% and SP=90.9% ($p<0.001$). The cut-off level was >12.6 . The SN=77.8% meant that the elevated levels of thyroglobulin were able to recognize the occurrence of recurrence/metastases after 12 months in 77.8% of cases in patients diagnosed with follicular thyroid cancer. The SP=90.9% meant that the level value of thyroglobulin <12.6 was able to recognize 90.9% of cases patients with a diagnosis of follicular thyroid cancer who really did not have relapses/metastases after 12 months. The Youden test was 68.7%, which

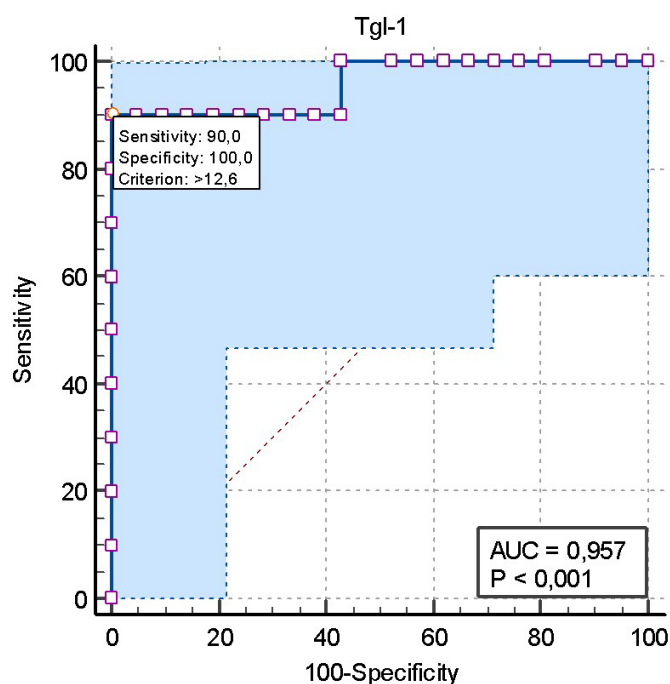


Figure 2. The ROC (Receiver Operating Characteristic) curve for serum thyroglobulin levels compared to the second diagnostic scintigraphy

is in favour of using the test for diagnostic purposes (Figure 1). The elevated level of postoperative thyroglobulin in serum in the detection of recurrence and/or metastases in patients with follicular thyroid cancer confirmed by scintigraphy after 24 months had SN=90.0% and SP=100, 0% ($p<0.001$). The cut-off level was again >12.6 . The SN=90.0%, that is, the value of thyroglobulin at the beginning (>12.6), was able to recognize the occurrence of recurrence/metastases after 24 months in 90.0% of patients diagnosed with follicular thyroid cancer. The SP=100.0%, that is, the value of thyroglobulin (<12.6) was able to recognize 100.0% of patients with a diagnosis of follicular thyroid cancer who really did not have relapses/metastases after 24 months. The Youden test was 90.0%, which is in favour of using the test for diagnostic purposes (Figure 2).

DISCUSSION

The results of our study showed a significant association of elevated postoperative serum thyroglobulin level with the outcome of therapy in patients with follicular thyroid cancer. By correlating the values of thyroglobulin with the findings of scintigraphy after 12 and 24 months, we demonstrated that elevated level of postoperative thyroglobulin (>12.6) correlated with positive findings of scintigraphy, i.e. with the occurrence of recurrence and/or metastases in patients with follicular thyroid cancer. Several studies have suggested that postoperative thyroglobulin is a significant predictive factor for the outcome of therapy with I-131 (24-26). Lower level of postoperative thyroglobulin is associated with radioiodine therapy success in patients with differentiated thyroid cancer (27,28). Our results also confirmed that the lower level of postoperative thy-

roglobulin (<12.6) correlated with the successful outcome of first radioiodine treatment. An elevated value of postoperative thyroglobulin indicates a higher risk stage of recurrence in all three risk groups, thus patients with low, intermediate and high risk (29), especially in high risk patients (30). In patients with a lower TNM (T1 and T2) (22), who belong to lower risk patients, elevated thyroglobulin values (>12.6 ng/mL) in our study correlated with the occurrence of recurrence and/or metastasis. We also proved that elevated postoperative thyroglobulin level (>12.6 ng/mL) correlates with a worse outcome of I-131 therapy in patients with a higher TNM (T3 and T4). Finally, we calculated the cut-off level of postoperative thyroglobulin for the occurrence of recurrence and/or metastases, i.e. for the failure of first radioiodine treatment, which was >12.6 ng/mL. The cut-off level in our study was slightly higher than in other studies (24,31,32), and the reason for this is most likely the fact that the initial detectable level for thyroglobulin was >2 ng/mL in our study, higher than in other studies.

In conclusion, our study showed that level of postoperative thyroglobulin was an important prognostic factor for the outcome of radioiodine therapy of follicular thyroid cancer. This is a simple and non-expensive method that should be taken into account in deciding on therapy and the management of this type of cancer in everyday practice.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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