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THYROGLOBULIN AS A TUMOR MARKER IN DIFFERENTIATED THYROID CANCER – CLINICAL CONSIDERATIONS

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SUMMARY – Initial treatment of the majority of patients with differentiated thyroid cancer (DTC) includes total thyroidectomy. Postoperative ablation therapy with radioactive iodine (I-131) is indicated in all high-risk patients, however, there is disagreement regarding its use in low- and intermediate-risk patients. Over the last few decades, thyroglobulin (Tg) has been established as the primary biochemical tumor marker for patients with DTC. Thyroglobulin can be measured during thyroid hormone therapy or after thyroid-stimulating hormone (TSH) stimulation, through thyroid hormone withdrawal or the use of human recombinant TSH. In many studies, the cut-off value for adequate Tg stimulation is a TSH value ≥30 mIU/L. However, there is an emerging body of evidence suggesting that this long-established standard should be re-evaluated, bringing this threshold into question. Recently, a risk stratification system of response to initial therapy (with four categories) has been introduced and Tg measurement is one of the main components. The relationship between the Tg/TSH ratio and the outcome of radioiodine ablation has also been studied, as well as clinical significance of serum thyroglobulin doubling-time. The postoperative serum Tg value is an important prognostic factor that is used to guide clinical management, and it is the most valuable tool in long term follow-up of patients with DTC.

Key words: *Thyroglobulin; Thyroid neoplasms; Thyroidectomy; Iodine radioisotopes; Biomarkers, tumor; Thyroid hormones; Croatia*

Introduction

Thyroid cancer is the most common type of endocrine malignancy[1]. About 90% of thyroid neoplasms are differentiated thyroid cancers (DTC) with low malignant potential and a very good prognosis[2]. Over the last few decades, the incidence of thyroid cancer has considerably increased. The age-standardized incidence rate of thyroid cancer has increased in Croatia 22.1 times in women and 5.6 times in men in the period from 1968 to 2014, with a decrease in mortality[3]. A similar trend has been observed around the world. In the United States, the yearly incidence has almost tripled from 4.9 in 1975 to 14.3 *per* 100,000 in 2009, without associated increase in mortality[4]. This perceived increased incidence of DTC is mostly caused by more intensive imaging with neck ultrasonography (US) and the aggressive use of US guided fine needle aspiration biopsy (FNA), which has led to detection of disease in early stages[5,6].

In the majority of patients with DTC, initial treatment consists of total thyroidectomy. However, lobectomy may be performed in patients with microcarci-

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noma without nodal metastases on imaging[7,8]. Postoperative ablation therapy with radioactive iodine (I-131) is indicated in all high-risk patients, however, there is disagreement regarding its indication and dosage in low- and intermediate-risk patients[9-11]. The introduction of L-levothyroxine substitution or suppression therapy is the next step in the treatment of these patients, which depends on balancing the degree of response to initial therapy and increasing the risk of adverse effects related to thyroid-stimulating hormone (TSH) suppression[12]. With this treatment approach, the majority of patients have an excellent prognosis with normal life expectancy[13]. However, in some patients, persistent disease is present after initial therapy, or disease recurrence is detected during follow-up.

Thyroglobulin (Tg) is a glycoprotein with a molecular weight of approximately 660 kDa, which is synthesized by thyrocytes and released into the lumen of thyroid follicles[14]. Production of Tg is stimulated by TSH, intrathyroidal iodine deficiency or excess[15], and the presence of thyroid-stimulating immunoglobulins. Thyroglobulin plays a crucial role in the synthesis of the peripheral thyroid hormones triiodothyronine (T3) and thyroxine (T4), containing tyrosine residues which are iodinated using tyrosine oxidase in monoiodotyrosine and diiodotyrosine forms (MIT and DIT), which then form T3 and T4. Over the last few decades, the role of Tg as the primary biochemical tumor marker in patients with DTC has been established. Serum Tg measurements, neck ultrasonography, and occasionally diagnostic I-131 whole body scintigraphy are used in the follow up of DTC patients[16-18]. Neck ultrasonography is a readily available, noninvasive, cost-effective method, which can guide diagnostic procedures with low complication rates[19]. Recently, some authors have proposed the combined use of the above mentioned modalities with computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) including [F18] FDG PET/CT when necessary[11,20,21]. Patients at low risk of disease recurrence may be followed up only by neck US and serum Tg measurement[22].

Measurement of Thyroglobulin and Anti-Thyroglobulin Antibodies

Thyroglobulin has been measured by three different classes of methodology. Radioimmunoassay (RIA used since the 1970s), immunometric assay (IMA) since the 1980s, and liquid chromatography-tandem mass spectrometry (LC-MS/MS), which was developed in 2008. Immunometric assays are more sensitive than RIA and have shorter incubation time, wider working range and a stable labeled antibody reagent[23]. The proposed functional sensitivity of current assays is ≤0.1 μg/mL[24]. Serum Tg should be measured by validated immunoassays calibrated against the Certified Reference Material (CRM 457, now described as BCR 457, European Commission, Institute for Reference Material and Method). Laboratories providing Tg measurements are required to participate in certified national or international programs of quality assurance. Ideally, follow-up of DTC patients with Tg and anti-thyroglobulin antibodies (TgAb) concentrations should be performed in the same laboratory using the same assay each time[24].

Anti-thyroglobulin antibodies are 330 kd molecules which are often undetectable using older techniques. The TgAb is polyclonal, belongs to the IgG class of antibodies, not restricted to a particular subclass, although IgG2 is the predominant class in DTC[25]. Anti-thyroglobulin antibodies falsely lower serum Tg in immunometric assays and are present in approximately 25% of thyroid cancer patients and 10% of the general population[26,27]. They are the most serious problem that limits the clinical value of Tg determination. Anti-thyroglobulin antibodies should be measured in conjunction with serum Tg assay by the same method to increase accuracy. After total thyroidectomy and I-131 remnant ablation, TgAb usually disappear after 3 years in patients without persistent disease. Thyroglobulin antibody levels that decline over time are considered as a good prognostic sign, while rising levels, or a new appearance of TgAb increases the risk of persistent or recurrent disease[28-31].

Preoperative Role of Thyroglobulin

Many studies have evaluated preoperative serum Tg values as a possible predictor of malignancy in thyroid nodules. Currently, the American Thyroid Association does not recommend routine preoperative measurement of serum Tg and TgAb since there is no definite evidence that this impacts patient management or outcome. Meanwhile, the most recent EPIC study demonstrated a strong positive association be-

tween thyroid cancer risk and blood levels of Tg, but did not support the use of serum Tg level for screening and early detection of DTC[11,32].

Postoperative Measurement of Thyroglobulin

The half-life of serum Tg is 1-3 days, and the postoperative nadir is reached in almost all patients 3-4 weeks after operation[33,34]. After therapy with I-131, it takes several months for Tg to completely disappear from the circulation[35]. The measurement of Tg can be done during thyroid hormone therapy or after TSH stimulation, through thyroid hormone withdrawal or the use of human recombinant TSH (rhTSH)[36-38]. Reports have questioned the possibility of a shorter duration of thyroid hormone withdrawal prior to Tg measurement[39]. Recombinant human thyrotropin is approved in many countries for preparation of patients without distant metastases for radioiodine ablation. This exogenous method of elevating TSH levels may also be used in patients who are unable to achieve adequate TSH elevation following thyroid hormone withdrawal, or in patients with significant comorbidities[40]. The rhTSH stimulated Tg levels tend to be lower than those following thyroid hormone withdrawal[11,41].

Cut-off TSH Threshold of 30 mIU/L

In many studies, the cut-off value for adequate thyroglobulin stimulation is a TSH value ≥30 mIU/L[11,42]. This value has its diagnostic (elevation of Tg) and therapeutic (increased I-131 uptake in tumors) implications[43]. However, there is an emerging body of evidence suggesting that this long-established standard should be re-evaluated, thus bringing this threshold into question. Although the value of TSH of 30 mIU/L has been generally used in stimulation for I-131 ablation, some authors postulate different values. For example, Vrachimis *et al*. published a report on patients who received ablation with TSH <30, with the same ablation outcome[44]. On the other hand, some authors advocate the use of higher TSH values, suggesting them to be connected with better treatment outcome[45,46]. In our two previous studies, no differences were observed comparing TSH levels and the ablation outcome[47,48].

Thyroglobulin and Radioiodine Ablation

The postoperative serum Tg value is an important prognostic factor that can be used to guide clinical management, especially in guiding the decision-making process leading to radioiodine ablation treatment, as well as predict successful ablation of the thyroid remnant. Postoperative serum Tg values >10 ng/mL increase the probability of persistent or recurrent disease, failing I-131 ablation, presence of distant metastases, and mortality, therefore prompting additional evaluation and treatment[49-52]. It is very important to emphasize that Tg level is not the only criterion for successful ablation, and that patient risk group should also be carefully considered. In low-risk patients, suppressed or stimulated Tg <1 ng/mL confirms low recurrence risk[51,53]. In intermediate-risk patients, the same Tg values do not completely rule out the presence of small-volume I-131-avid metastatic disease. In high-risk patients, even postoperative Tg values <1 ng/mL do not rule out RAI-avid disease and therefore do not influence the decision to proceed with I-131 ablation[11].

In conclusion, there is no optimal cut-off for postoperative serum Tg values to help determine indication for I-131 ablation in the American Thyroid Association (ATA) guidelines[11]. However, some authors recommend omission of I-131 ablation in patients with low postoperative stimulated (≤1 ng/mL) and non-stimulated Tg levels (0.2-0.3 ng/mL) with negative TgAb[54-56]. A recent study by Mourão *et al*. concluded that patients with papillary thyroid carcinoma with low non-stimulated Tg levels (Tg <0.3 ng/mL) and negative nodal status in the neck following thyroidectomy did not require postoperative I-131 treatment[57]. Thyroglobulin levels are especially important in patients from low- and intermediate-risk groups, where the selection of patients for adjuvant therapy can be made based on Tg values. Additionally, some studies addressed the correlation of postoperative serum Tg values with success of remnant ablation; higher rates of ablation failure were observed with Tg values >5-6 ng/mL regardless of I-131 activity[58,59].

Thyroglobulin/Thyrotropin Ratio as a Predictive Factor for Radioiodine Ablation Outcome

In recent literature, the relationship between thyroglobulin/thyrotropin ratio and the outcome of radioiodine ablation has been extensively studied. For exam-

ple, Trevizam *et al*. bring into question the hypothesis that thyroglobulin levels and the thyroglobulin/thyrotropin ratio may accurately predict the success of radioiodine ablation therapy in patients with DTC. The Tg and Tg/TSH ratio cut-off values that predicted success of I-131 therapy were 4.41 ng/mL and 0.093, respectively. After multivariate analysis, only serum Tg emerged as an independent factor predicting ablation outcomes[60]. Further evidence for Tg/TSH as a predictive factor was confirmed in studies assessing radioiodine ablation failure and the need for re-ablation in low- and intermediate-risk groups of patients[48,61]. For example, one study evaluated 740 such patients, with the Tg/TSH ratio determined to be a more powerful prognostic factor than Tg alone, and higher Tg/TSH ratios were found to be an independent predictor of treatment failure in a multivariate logistic regression analysis. Patients with Tg/TSH >0.126 had a higher probability of radioiodine ablation failure[48].

In another study, which compared Tg and Tg/TSH ratio, also in low and intermediate groups of patients, and re-ablation outcomes, TSH significantly increased, Tg decreased, and Tg/TSH ratio decreased from 0.115±0.217 to 0.034±0.071 prior to re-ablation. A positive association was observed between treatment failure and Tg2 levels, as well as between treatment failure and Tg2/TSH2 ratio[61]. In a study by Lin *et al.*, the Tg/TSH ratio was considered as a predictive factor for treatment failure in patients with DTC[62]. Further studies are needed to evaluate the predictive and prognostic value of this easy calculable variable in patients undergoing TSH stimulation.

Value of Thyroglobulin in Dynamic Risk Stratification

The 2015 ATA guidelines have classified patients with DTC into low-, intermediate- and high-risk groups[11]. The risk of recurrence is associated with risk stratification, with the risk of recurrence in the ATA intermediate-risk group ranging from 3% to 9%, while the risk of recurrence in ATA high-risk patients ranges from 23% to 40%. However, the initially estimated recurrence risk should be continually modified during follow up, since it can change over time as a function of disease status and response to therapy[11,63]. The majority of DTC patients show elevated preoperative Tg, but the predictive role has not been clearly outlined, since immunoassays cannot differentiate between Tg secreted by normal tissue and by malignant thyroid cancer cells[64].

All patients with high-risk according to ATA should receive I-131 treatment, as this therapy improves both disease-free and disease-specific survival. In ATA low-risk patients with tumor size ≤1 cm, there is no indication for postoperative I-131 ablation therapy. However, in low-risk group patients with other risk factors, as well as in ATA intermediate-risk patients data regarding indications for I-131 ablation are conflicting, and therefore I-131 ablation therapy is selectively utilized[11]. The response to initial therapy (with four categories of treatment response) was introduced by Tuttle *et al*. and modified in another study by Vaisman *et al.*[65,66]. Thyroglobulin measurement is one of the main factors in "response to therapy reclassification" in patients receiving radioiodine remnant ablation after total thyroidectomy[11].

Patients with suppressed Tg <0.2 ng/mL, TSH stimulated Tg <1 ng/mL, and with negative imaging studies fall into the excellent response to therapy subgroup, with a very low risk of recurrence, and almost no disease-specific mortality[65,67-69]. The "biochemical incomplete response" category includes patients with negative imaging studies, but with elevated Tg levels following treatment (suppressed Tg ≥1 ng/mL or stimulated Tg ≥10 ng/mL), or with rising TgAb values. The mortality rate in this subgroup is minimal, but a significant number of patients in this group develop structural disease recurrence[65,70].

In the group with functional or structural evidence of disease (structural incomplete response), the Tg level and the presence (or absence) of TgAb do not change the response classification of these patients. The indeterminate response group includes patients with biochemical or structural findings that cannot be classified as either benign or malignant. Patients with non-stimulated detectable levels (Tg <1 ng/mL), or stimulated Tg detectable levels (Tg <10 ng/mL) fall into this subgroup. The patients with stable or declining anti-Tg antibodies without structural or functional disease are part of this "response" group[65,70].

Thyroglobulin in Long-Term Follow-up of Patients with Differentiated Thyroid Cancer

Long-term monitoring of patients with DTC is guided by the patient's response to therapy during the

first year of follow-up. Most cases with recurrences of DTC occur during the first years of follow-up, but may occasionally also occur many years after initial treatment[71]. At each follow-up, clinicians reclassify ongoing management recommendations in accordance with the patient's current clinical status. Detection of the possible persistent or recurrent disease during the first year after thyroidectomy is obtained with neck ultrasonography and measurement of TSH, as well as serum Tg levels. Additional imaging such as MRI, CT[72], and FDG-PET-CT[73] is usually reserved for high-risk patients who typically have either biochemical or structural incomplete response to initial therapy and follow-up of intermediate-risk patients who demonstrate structural or biochemical incomplete response to treatment during the first year of follow-up. Diagnostic I-131 whole body scintigraphy has a role in the follow-up of these patients with high or intermediate risk of disease, but not in the follow-up of low-risk patients.

Serum Tg and TgAb in patients on thyroid hormone suppression are generally measured every 3 to 6 months for the first year following initial treatment. The interpretation of serum Tg depends on the type of initial therapy. For patients with total thyroidectomy and radioiodine remnant ablation, non-stimulated Tg should be <0.2 ng/mL and stimulated Tg <1 ng/mL in the absence of interfering antibodies. In patients with lobectomy, serum Tg levels are less useful because they will not reflect the presence or absence of malignant tissue, but will depend on the remaining thyroid lobe volume, current iodine status and TSH concentration. In these patients, follow-up is performed by neck ultrasonography and, when necessary, US-guided fine needle aspiration (FNA) of any suspected metastatic foci[24].

Neck US is performed at 6- to 12-month intervals depending on the patient's risk stratification. Cervical lymph nodes are the most common site of recurrence in patients with papillary carcinoma. The most sensitive technique for localization of recurrent tumor in the neck is US. Metastatic lymph nodes on US demonstrate a cystic appearance, microcalcifications, bulging shape, loss of normal hilum, and peripheral vascularization[19,74]. US-guided FNA of suspected lymph nodes with Tg measurement in aspirates (FNA-Tg) should be performed in patients with suspected nodal metastases[19]. Values under 1 ng/mL are considered normal, values of 1-10 ng/mL should be compared with the results of cytology, and values above 10 ng/mL suggest the presence of malignancy[19]. Some authors suggest comparison of FNA-Tg and serum Tg levels as worthwhile. FNA-Tg is highly reliable in the diagnosis of neck nodal metastases[75].

Serum Tg may fail to identify patients with a relatively small volume of metastatic disease. These small metastases are often located in the neck region and US is the method of choice for detection of nodal disease in these patients[11]. In cases with elevated serum Tg levels and negative radioiodine scan, the explanation for such findings could be the presence of tumor deposits too small to be detected by a scintillation camera, or loss of iodine uptake through tumor de-differentiation[76]. In such patients, neck ultrasound and neck/chest CT may be performed in order to detect metastatic disease. If negative, other imaging methods should be performed. In high-risk patients and in those with serum Tg >10 ng/mL, [18F]-FGD PET/CT should also be performed[73,77].

Thyroglobulin Doubling Time

In medullary thyroid cancer, measurements of serum calcitonin and carcinoembryonic antigen (CEA) doubling-times have prognostic implications[78,79]. Miyauchi *et al.* have described the prognostic impact of serum Tg doubling time (Tg-DT) during follow up and under thyrotropin suppression. In this study, patients were divided into several groups: Tg-DT <1 year, 1-3 years, and ≥3 years. In the group with a Tg-DT of <1 year, disease-specific survival at 10 years was 50%, in the group with Tg-DT of 1-3 years it was 95%, and in other groups disease-specific survival was 100%. Thyroglobulin DT was found to be a statistically significant indicator of survival by univariate analysis. Multivariate analysis also revealed Tg-DT to be an independent predictor of distant metastases and loco-regional treatment failure[80].

Several studies addressed the issue of advanced/recurrent thyroid cancer and Tg-DT values. In a study by Rossling *et al.*, the Tg-DT and other prognostic markers in patients with recurrent/progressive DTC were evaluated in uni- and multivariate analysis. The median observed Tg-DT was 212 days. Mortality risk was two times higher in patients with Tg-DT <5 months as compared with patients with Tg-DT >14

months[81]. In a study by Giovanella *et al.*, the predictive value of Tg and Tg-DT on positive [18F]-FDG PET/CT scan in patients with biochemical recurrence of DTC was assessed. Serum Tg levels were higher in patients with positive [18F]-FDG PET/CT scan as compared to patients with negative PET/CT, and the authors concluded that the accuracy of [18F]-FDG PET/CT significantly improved with serum Tg levels >5.5 ng/mL during levothyroxine treatment, or with Tg-DT <1 year[82].

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Sažetak

TIREOGLOBULIN: TUMORSKI BILJEG DIFERENCIRANIH KARCINOMA ŠTITNJAČE – KLINIČKA RAZMATRANJA

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Početno liječenje većine bolesnika s diferenciranim karcinomom štitnjače uključuje kirurško odstranjenje štitnjače. Poslijeoperacijsko liječenje radioaktivnim jodom (I-131) indicirano je u većine visokorizičnih bolesnika, dok je primjena I-131 u bolesnika niskog i srednjeg rizika predmet rasprave. U prethodnih nekoliko desetljeća tireoglobulin (Tg) je prihvaćen kao primarni biokemijski tumorski biljeg visoke osjetljivosti i specifičnosti u bolesnika s diferenciranim karcinomom štitnjače. Mjerenje Tg može se izvoditi tijekom uzimanja hormonske terapije L-tiroksinom ili uz stimulaciju tireotropinom (TSH). Stimulacija putem TSH može se postići prekidom hormonske terapije L-tiroksinom ili uz primjenu rekombinantnog humanog TSH (rhTSH). Dugi niz godina se granična vrijednost TSH ≥30 mIU/L smatrala zadovoljavajućom za stimulaciju Tg, međutim, novije spoznaje osporavaju tu granicu i zahtijevaju nova istraživanja i preporuke. Nedavno je uvedena podjela bolesnika u 4 rizične skupine ovisno o odgovoru na liječenje jodom-131 nakon totalne tireoidekotmije, a mjerenje Tg jedna je od glavnih odrednica podjele. U posljednje vrijeme se značenje pridaje omjeru Tg-TSH u predviđanju ishoda ablacije jodom-131, kao i prognostičko značenje vremena udvostručenja Tg. Poslijeoperacijska serumska vrijednost Tg je važan prognostički čimbenik i odrednica daljnjeg liječenja, a određivanje Tg je osnovna metoda dugoročnog praćenja bolesnika s diferenciranim karcinomom štitnjače.

Ključne riječi: *Tireoglobulin; Tireoidni tumori; Tireoidektomija; Jod, radioizotopi; Tumorski biljezi, biološki; Tireoidni hormoni; Hrvatska*