

Does a negative thyroglobulin level exclude recurrence in patients treated for differentiated thyroid neoplasm?

Original
Article

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ABSTRACT

Introduction: Differentiated thyroid carcinomas (DTC) are the most common endocrine malignancy. Despite the good survival rate of these cancers, recurrence is still seen in practice. The recurrence is sometimes occult, and the use of tumor markers like serum thyroglobulin level (Tg) could be helpful to predict any recurrent or persistent disease.

Objectives: We aim to investigate the role of serum Tg as a single tumor marker to assess for any recurrent or residual disease in patients who were treated for DTC.

Patients and Methods: We performed a retrospective review for all patients who had DTC in our department over 7 years. We compared the levels of serum Tg with the recurrence rate. Our cut-off value for Tg was 0.1 µg/l.

Results: One hundred two patients (67 females and 35 males) with DTC were included in our study. The average age was 45.9±16 years of age. We reported a sensitivity rate of 100%, specificity was 97.9%, positive predictive value was 80%, negative predictive value was 100%, and diagnostic accuracy was 98%.

Conclusion: With our cut-off value of 0.1 µg/l, serum Tg is an excellent negative predictor of the disease recurrence or persistence; however, with low levels (<0.5 µg/l), further investigations are required to exclude a small tumor focus.

Key Words: Diagnostic accuracy, differentiated thyroid carcinoma, recurrence, sensitivity, specificity, thyroglobulin.

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INTRODUCTION

Thyroid malignancy is the most common endocrine malignancy in humans^[1]. Papillary and follicular thyroid cancers, which are also known as well-differentiated thyroid cancers (DTC), form about 90% of thyroid malignancy. These cancers have a better prognosis compared with the rest of thyroid neoplasm^[2]. Papillary thyroid carcinoma tends to occur in young adults with early central lymph node involvement and then spread to the lateral cervical compartments^[3]. The usual treatment for DTC is total thyroidectomy plus or minus central lymph node dissection based on the tumor size or the presence of metastatic nodes on preoperative imaging^[4]. Lateral cervical lymph node dissection is performed in the case of pathologically confirmed involved nodes^[4]. Postoperative radioactive iodine (I-131) ablation therapy is indicated in high-risk patients, while in moderate and low-risk patients, treatment with radioactive iodine is still controversial^[5,6]. Most of these patients will need TSH suppression using levothyroxine^[7].

Serum thyroglobulin (Tg) is the most sensitive and recommended biomarker for assessing any residual or recurrent disease because the only source of Tg is the

thyroid tissues, which may be normal or neoplastic^[8,9]. Studies suggested that the serum Tg level should reach its lowest level within 3-4 weeks after thyroid gland surgery. Thus, from that point, it could be used to assess for any residual or recurrent disease^[10]. Although some studies suggested that the measurement of the serum Tg level is a reliable negative predictor of persistent and recurrent DTC^[11], other studies failed to prove that^[12].

In the current study, we tried to assess if Tg level could be used as a single test to exclude persistent or recurrent disease in patients treated for well-DTCs. This could help predict early recurrence and reduce morbidity and mortality in these cases.

PATIENTS AND METHODS:

In the current study, we retrospectively reviewed all patients who had thyroid surgery for well-DTC (papillary and follicular) in our General Surgery Department over 7 years. Inclusion criteria were patients who had well-DTC (follicular or papillary), patients who had thyroid surgery plus or minus lymph node dissection, had Tg level regularly check postoperatively, and had followed of a minimum of three years. Exclusion criteria included patients who

had other subtypes of thyroid malignancy (medullary carcinoma, undifferentiated carcinoma, metastatic carcinoma, and lymphoma), patients who did not have any surgical intervention, and patients with incomplete or missed data. All patients' data were collected from the hospital recording system. Informed consent was obtained from every patient before any surgical intervention. All cases were discussed in our endocrine multidisciplinary team and managed according to the guidelines from the British Association of Endocrine and Thyroid Surgeons (BAETS).

During the period from 2013 to 2019, more than 600 patients had thyroid surgery in our department. Of them, about 120 patients had thyroid carcinomas. DTC was found in 102 of their patients. Eighty-two patients had thyroid surgery for diagnostic or therapeutic surgery for thyroid cancer, and 20 patients had an incidental finding of microcarcinoma after surgery planned for treating a benign thyroid condition. Patients with tumor more than 4 cm, aggressive histology, multifocal disease, extrathyroidal extension, incomplete resection, multiple pathologically positive lymph nodes with at least one node equal to more than 3 cm in the largest dimension, distant metastasis, all had radioactive iodine ablation after surgery.

All the patients who were included in our study had regular Tg and Tg antibodies (TgAb) checked at 3–6 months after surgery and then at least every 6–12 months based on the level. Measurement of TgAb is valuable in interpreting the serum Tg. TgAb concentrations decline with successful removal of Tg antigenic stimulus (following thyroidectomy and RRA) over a median time of 3 years. A new appearance or a rising trend in TgAb concentration is a significant risk factor for recurrent disease. Any suspicious cervical lump postoperatively was biopsied to exclude recurrence. Patients with rising Tg levels after surgery had further investigations to assess for recurrence. Our cut-off value for Tg was 0.1 µg/l. All patients with Tg levels more than 0.1 µg/l had further investigations to exclude any recurrence. Investigations used included ultrasonography, computed tomography (CT), MRI, and positron emission tomography (PET), including [F18] FDG PET-CT scan. Patients with Tg level less than 0.1 µg/l had regular clinical assessment and routine cervical ultrasound scan. To get the diagnostic accuracy of Tg, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) using 2x2 tables.

RESULTS:

One hundred two patients (67 females and 35 males) were included in our study. The average age was 45.9±16 years of age. Seventy-five patients had unifocal thyroid cancer, and 27 patients had multifocal disease. The average

tumor size was 22.3±18 mm. Sixty-seven patients were diagnosed with papillary thyroid carcinoma, 20 patients with a follicular variant of papillary thyroid carcinoma, nine patients with follicular carcinoma, and six patients had Hurthle cell carcinoma (Table 1).

The 20 patients who were diagnosed with incidental thyroid cancer had no lymph node dissection. Another 12 patients with favorable criteria had thyroid surgery with no lymph node dissection. The rest of the patients had total thyroidectomy with central neck dissection +/- lateral neck lymph node dissection depending on the preoperative findings. The pros and cons of prophylactic central neck dissection were discussed with every patient, and personalized decision-making was considered. Thirty-nine patients had lymph node metastasis diagnosed either preoperatively or on final histology. Average number of lymph node involvement was 7.4 lymph nodes.

All patients with high-risk cancer had radioactive iodine ablation, while patients with low to moderate-grade disease were discussed in our endocrine MDT meeting regarding the indications of radioactive iodine.

All our patients were followed up for a minimum of 3 years. Eight patients had recurrent disease, five of them had systemic disease, and three had local recurrence. Only one patient died of the disease progression.

Serum Tg level was checked regularly for all our patients. Patients with no regular check of their Tg level were excluded from our study. With the cut-off level of 0.1 µg/l, 10 patients had postoperative serum Tg levels above 0.1 µg/l; eight of them had true recurrent disease, and two were false positive after having further investigations. An unstimulated serum Tg less than 0.1 µg/l measured by a sensitive assay has a very high NPV in selected patients.

With regards to the eight patients who had a recurrence, all of them had total thyroidectomy, while seven of them were found to have lymph node metastasis. Six patients had papillary carcinoma, one patient had Hurthle cell carcinoma, and one patient had follicular carcinoma. Three patients had local recurrence, while five patients had lung metastasis. Most of the cases had recurrence within the first 2 years.

Based on that, sensitivity was 100%, specificity was 97.9%, PPV was 80%, NPV was 100%, and diagnostic accuracy was 98% (Table 2).

Table 1: Patients' characteristics

Variables	n (%)
Sex	
Males	35 (34)
Females	67 (66)
Age	45.9±16 years
Subtype	
Papillary	67 (66)
FVPC	20 (20)
Follicular	9 (8)
Hurthle cell carcinoma	6 (6)
Tumor size	22.3±18 mm
Focality	
Unifocal	75 (74)
Multifocal	27 (26)
Recurrence	
No recurrence	94 (92)
Recurrent/metastatic	8 (8)
Site of recurrence	
Local	3 (2.9)
Lung	5 (4.9)

Table 2: Thyroglobulin level compared with recurrence

Tg level	Disease recurrence	
	TP (8)	FP (2)
	FN (0)	TN (92)

FN, false negative cases; FP, false positive cases; Tg, thyroglobulin; TN, true negative cases (no recurrence); TP, true positive cases (recurrence).

DISCUSSION

DTCs form the majority of thyroid neoplasms with low malignant potential and excellent prognosis^[2]. The incidence of the disease over the last few decades has increased significantly^[13]. That could be attributed partly to the advances in imaging modalities, including ultrasonography and CT and the wide use of fine needle aspiration technique in the diagnosis of any suspicious thyroid nodule or cervical lymphadenopathy^[14].

The initial treatment for DTC is total thyroidectomy, although lobectomy only is still an option in patients with microcarcinoma with no preoperative evidence of lymph node involvement^[15,16]. Studies found that routine level VI lymphadenectomy could improve the oncological outcomes^[17]. Postoperative radioactive iodine ablation is the standard procedure in patients with DTC after total or near-total thyroidectomy; the only exception is patients with unifocal papillary

thyroid carcinoma less than or equal to 1 cm^[18]. This is followed by TSH suppression using levothyroxine. Treatment with levothyroxine in these cases was proved to improve the prognosis with a normal life expectancy^[19].

Despite the excellent survival rate for DTC, recurrent and metastatic cases are not infrequently seen. All cases of DTC will require regular follow-up after surgery. Different modalities that could be used for surveillance include ultrasonography, CT, MRI, and PET, including [F18] FDG PET/CT^[4,20]. Neck ultrasonography is a widely used, noninvasive, cost-effective technique with a lower complication rate and allows for US-guided fine needle aspiration for cytology. The sensitivity rate of US and CT for diagnosing lateral lymph node metastasis was reported as 64.0–74.3% and 68.6–78.2%, and the specificity of both techniques was 82–94.8% and 78–95%, respectively^[21,22] (Figs 1–4).

Over many years, serum Tg and anti-TgAb levels were studied as a primary biochemical tumor marker in patients with DTC to assess for any residual or recurrent diseases because the thyroid follicular cells, either normal cells or neoplastic, are the only sources of serum Tg^[4]. Thyrocytes produce the glycoprotein Tg, which is then released into the thyroid follicular lumen and has a molecular weight of roughly 660 kD^[23]. TSH, intrathyroidal iodine deficit or excess, and the presence of thyroid-stimulating immunoglobulins all work together to stimulate the production of Tg^[24]. The synthesis of the peripheral thyroid hormones triiodothyronine and thyroxine depends heavily on Tg.

Tg level could be checked by different modalities. Immunometric assay is a commonly used modality with a proposed functional sensitivity of less than or equal to 0.1 µg/ml^[10]. Anti-TgAbs are polyclonal antibodies that belong to the IgG group of antibodies with a molecular weight of 330 kD^[25]. These antibodies falsely lower the serum Tg level in immunometric assays and should be measured in conjunction with serum Tg assay by the same method to increase accuracy. TgAb usually disappears within 3 years after total thyroidectomy and radioactive iodine ablation; however, a rising level may indicate a persistent or recurrent disease^[26,27]. The half-life of serum Tg is about 1-3 days, and the majority of patients reach their postoperative therapeutic level within 3-4 weeks after surgery^[10]. In our study, all patients had their Tg level checked at least 3-6 months after surgery, followed by regular measurement every 6-12 months.

In our study, we analyzed the data of 102 patients who were diagnosed with DTC in our department. The disease was more common in females than males, with a mean age of 45.9±16 years of age; other studies

reported similar findings^[28]. Twenty patients had an incidental finding of microcarcinoma. Five of them had lobectomy; the rest had total thyroidectomy without neck dissection. Eighty-two patients had a total thyroidectomy and central neck dissection +/- lateral neck lymph node dissection. All patients with high-risk disease were referred for radioactive iodine ablation.

Previous studies reported that patients with low-risk diseases could be followed up only by neck US and serum Tg measurement^[29], while patients with intermediate and high-risk diseases may need further investigations in addition to measuring serum Tg level. The majority of recurrences of DTC occur within the first years of follow-up; nevertheless, recurrences after several years of treatment were also reported^[30].

The cutoff value for postoperative Tg level was variable between different studies. Although some studies had a cutoff value of 5 ng/ml^[31], other studies used a cut-off value as high as 30 ng/ml^[32]. In our study, we had a cut-off value of 0.1 µg/l due to the very high NPV when using this cut-off level. Patients with postoperative Tg levels of less than 0.1 µg/l were considered negative, while patients with levels more than 0.1 µg/l had a further investigation to assess for any recurrent or residual disease. Ten patients in our study had Tg level more than 0.1 µg/l; eight of them had a recurrent disease. Two patients had their Tg level higher than 0.1 µg/l (0.3 and 0.4 µg/l); however, further investigations failed to prove any residual or recurrent disease.

Different studies reported different sensitivity and specificity rates regarding using Tg as a predictor for DTC recurrence. Bernier *et al.*^[33] reported a sensitivity rate of 86.3% and a specificity rate of 64.9%, PPV was 26%, and NPV was 97.1%. In 2011, Webb *et al.*^[34] reported a sensitivity of 75%, specificity of 88.6%, PPV of 84%, and NPV of 81.6%. On the other hand, Ronga *et al.*^[35] concluded a sensitivity rate of 94.9%, specificity of 54.1%, PPV of 39.1%, and NPV of 97.2. In addition, four studies evaluated the diagnostic accuracy for persistence or the composite outcome at different Tg threshold levels. These studies found that with Tg threshold of more than 1 to more than 2.5 ng/ml, sensitivity ranged from 0.90 to 1.0 (median 0.93), and specificity ranged from 0.35 to 0.58 (median 0.48), while at a Tg threshold of more than 10 ng/ml, sensitivity ranged from 0.69 to 0.77 (median 0.71), and specificity ranged from 0.66 to 0.93 (0.77)^[36-39]. In our study, with a cut-off value of 0.1 µg/l, we had a sensitivity rate of 100%, specificity was 97.9%, PPV was 80%, NPV was 100%, and overall diagnostic accuracy of 98%. All patients with Tg levels less than 0.1 µg/l were clinically and radiologically negative for recurrence.

We had some limitations in our study. First, the sample size was relatively small. Second, it was a retrospective review. Third, we did not calculate the effect of thyroxin treatment on the level of Tg. On the other hand, we tried to collect all the data properly and we excluded any patients with missing data from our study.

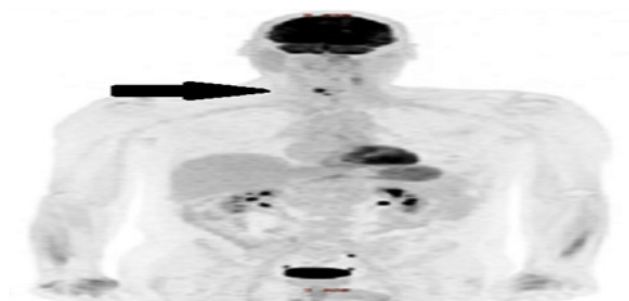


Fig. 1: PET-CT scan showing mild FDG uptake in the left neck at the site of previous neck dissection with focal FDG uptake in the lower neck at the midline, anterior to the cricoid cartilage, consistent with locally recurrent disease. PET-CT, positron emission tomography-computed tomography.

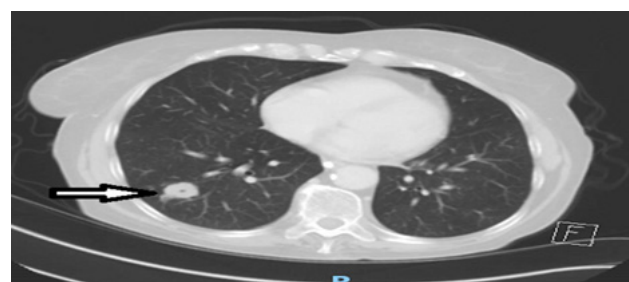


Fig. 2: CT scan showing multiple pulmonary metastases, as shown there is a right lower lobe deposit which has a small focus of central cavitation measures approximately 21x28 mm. CT, computed tomography.

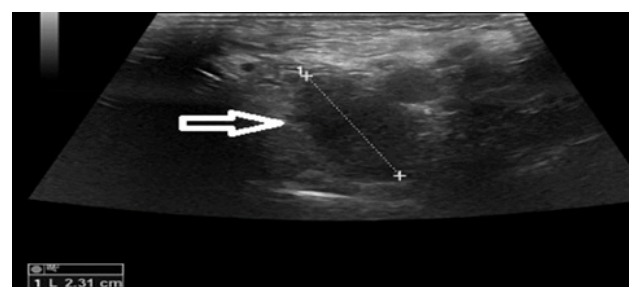


Fig. 3: Neck US scan showing a 2.4 cm suspicious irregular hypoechoic left thyroid bed nodule with minimal internal vascularity confirmed as recurrent disease on FNAC. FNAC, fine needle aspiration for cytology; US, ultrasound.



Fig. 4: Neck US scan showing a 15x11 mm hypoechoic, heterogenous, avascular irregular recurrent lesion adjacent to the bifurcation of the carotid artery. US, ultrasound.

CONCLUSION

In general, serum Tg level in patients who had total thyroidectomy +/- radioactive iodine ablation is an excellent negative predictor of the disease recurrence or persistence. With values more than 0.1 µg/l, there is a high risk of disease recurrence. However, with lower values less than 0.5 ng/l, it may be difficult to exclude a small focus of the disease that might also be not easily seen with the US and may need further investigation and regular Tg checks^[4].

CONFLICT OF INTEREST

There are no conflicts of interest.

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