

Impact of Thyroglobulin on Survival and Prognosis of Differentiated Thyroid Cancer

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Abstract

Proper assessment of risk factors contributes to the principle management of differentiated thyroid carcinoma post operatively. Aim of the study: to investigate the effect of Thyroglobulin (Tg) levels on prognosis together with other risk factors for Differentiated Thyroid Cancer (DTC). Patients and methods: Medical records of all patients with DTC presented to Clinical Oncology and Nuclear Medicine Department referred from Diabetes & Endocrine unit (Internal Medicine Hospital) and Surgery Department Mansoura University from 2011-2016 were retrospectively reviewed. Patients with distant metastasis or who lost follow-up were excluded. So data of 220 patients were analyzed. Data collected included pre-surgical assessment, also surgical interference either total or near total thyroidectomy with or without lymph node neck dissection were reviewed. Different prognostic factors that affect progression free survival (PFS) include age, umorsize, ymph node status, ex, multifocality, capsular infiltration, vascular invasion and Tg level were evaluated through multivariate analysis. Results: Most of the patients included were <45 years (69.1%). Incidence of the disease was higher in female (80%) with papillary type predominance (80.9%). About 59.5% of cases presented with tumor size ≤ 2 cm and multifocality was reported in 13.6%. While 30% had lymph node metastasis, 11% had vascular invasion. Capsular infiltration was observed in 15% and most of them showed Tg level ≤ 10 ng/ml (68.2%). About 70% received ablative radioiodine. The 5-year Progression Free Survival (PFS) was 85%. On multivariate analysis of variable prognostic factors on PFS, we found that tumor size, age, lymph node status, capsular infiltration, Tg level and vascular invasion significantly affected PFS ($P = 0.01, 0.005, 0.004, 0.005, 0.02, 0.003$) respectively. While sex, pathological type and multifocality were not ($P = 0.9, 0.4, 0.6$) respectively. Conclusion: Postoperative Tg level is a statistically significant prognostic factor together with other risk factors.

Keywords

Thyroglobulin, Thyroid Cancer, Differentiated Thyroid Cancer, Risky Factors

1. Introduction

Differentiated thyroid carcinoma (DTC) includes papillary thyroid carcinoma which is the most common thyroid neoplasm (80% - 90%) followed by the follicular one (10% - 40%) [1]. DTC has a good prognosis with 10 year survival rates of 85% - 93% [2]. Thyroglobulin (Tg) is a glycoprotein produced only by follicular cells of the thyroid so used as a marker to monitor the thyroid diseases [3] [4].

Treatment of DTC is surgery and radioactive iodine; nearly 80% of patients recover after first treatment [5]. Despite most recurrences of the disease occurred within the first five years, it was observed also after 45 years [6].

Prognostic factors enable us to identify patients with high risk of disease recurrence and allow personalization of method of treatment depending on patient's risk factors [7].

After surgery, Tg levels are affected by the presence of remaining thyroid tissue. It was found that 1 g of thyroid tissue lead to increase to Tg level by approximately 1 μ /L [8]. It was reported that Tg levels could be a predictor for progressive or metastatic disease during follow-up period of patients with DTC [9] [10] [11].

This retrospective study was conducted to investigate the effect of Tg levels on prognosis together with other risk factors for DTC.

2. Patients and Methods

Medical records of all patients with DTC presented to Clinical Oncology and Nuclear Medicine department, referred from Diabetes & Endocrine unit (Internal medicine hospital) and surgery department Mansoura University from 2011-2016 were retrospectively reviewed. Patients with distant metastasis or who lost follow-up were excluded. So data of 220 patients were analyzed.

Data collected included presurgical assessment as clinical general and neck examination of the patients, radiological investigations as neck ultrasound (US), thoracic or neck computed tomography (CT), laboratory tests as T3, T4, TSH levels and histopathological type.

Also surgical interference either total or near total thyroidectomy with or without lymph node neck dissection were reviewed. Staging was evaluated according to AJCC staging system [12].

Postoperative follow-up of the patients were carried out every six months through clinical examination, neck US, levels of T3, T4, TSH, Tg and 5 mci of ¹³¹I whole body scan (WBS) when TSH level was higher than 30 IU/ml.

If the patient was in need for ablative dose of radioactive ^{131}I , he received 50 - 150 mci according to risk stratification by the American Thyroid Association (ATA) [13] and WBS was performed 72 hours follow ^{131}I ingestion.

Different prognostic factors affect progression free survival (PFS) include age, tumorsize, lymph node status, sex, multifocality, capsular infiltration, vascular invasion and Tg level were evaluated through multivariate analysis.

PFS was calculated from date of surgery to date of disease progression.

Statistical methods: IBM SPSS was used for statistical analysis, Chi square test used as a test of significance, $P < 0.05$ considered significant. Kaplan-Meier test was used for survival function.

Ethical consideration: This study was approved by the Medical Ethics Committee and the study was carried out in accordance with the Declaration of Helsinki.

3. Results

Characteristics of 220 patients involved in this study are summarized in **Table 1**. Most of them were <45 years (69.1%). As suspected incidence of the disease was higher in female (80%); with papillary type predominance (80.9%). About 59.5% of cases presented with tumor size ≤ 2 cm and multifocality was reported in 13.6%. While 30% had lymph node metastasis, 11% had vascular invasion. Capsular infiltration was observed in 15% and most of them showed Tg level ≤ 10 ng/ml (68.2%). About 70% of patients received ablative radioactive Iodine.

5-year progression free survival (PFS) among studied cases was 85% **Figure 1**.

On multivariate analysis of variable prognostic factors affecting PFS ;we found that tumor size, age, lymph node status, capsular infiltration, Tg level and vascular invasion significantly affected PFS ($P = 0.01, 0.005, 0.004, 0.005, 0.02, 0.003$) respectively. While sex, pathological type and multifocality were not ($P = 0.9, 0.4, 0.6$) respectively (**Table 2**).

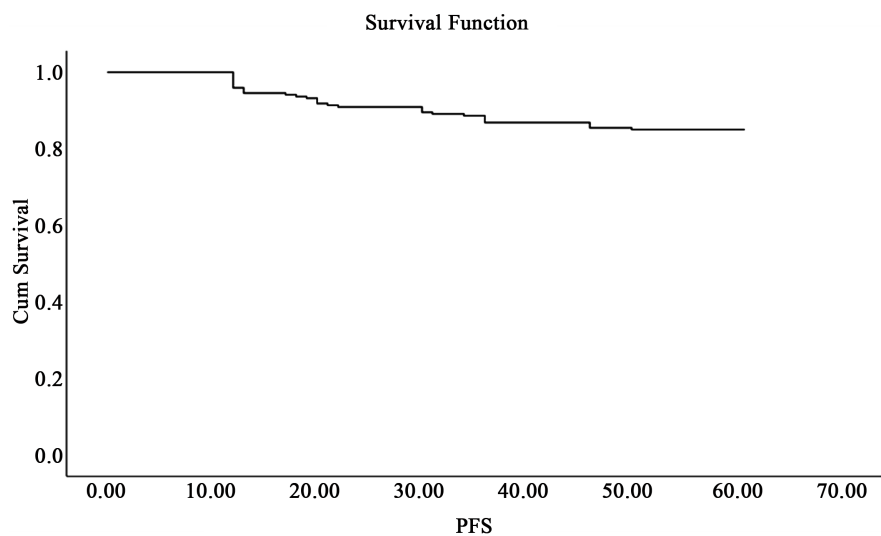


Figure 1. Progression Free Survival (PFS) of studied cases.

Table 1. Patients characteristics.

Character	N	%
Age (years)		
<45	152	69.1
≥45	68	30.9
Gender		
Male	44	20
Female	176	80
Pathology		
Papillary	178	80.9
Follicular	42	19.1
Tumor size		
≤2 cm	131	59.5
>2 cm	89	40.5
Multifocality		
Yes	30	13.6
No	190	86.4
Lymph node metastasis		
Yes	66	30
No	154	70
Capsular infiltration		
Yes	33	15
No	187	85
Vascular invasion		
Yes	24	10.9
No	196	89.1
Tg level		
≤10 ng/ml	150	68.2
>10 ng/ml	70	31.8

Table 2. Multivariate analysis of risk factors.

Character	Recurrence rate	P
Age (years)		
<45	6/152 (3.9%)	0.005
≥45	10/68 (14.7%)	
Gender		
Male	4/44 (9.1%)	0.9
Female	15/176 (8.5%)	

Continued

Pathology		
Papillary	15/178 (8.4%)	0.4
Follicular	5/42 (11.9%)	
Tumor size		
≤2 cm	5/131 (3.8%)	0.01
>2 cm	11/89 (12.3%)	
5-Multifocality		
Yes	2/30 (6.6%)	0.6
No	9/190 (4.7%)	
Lymph node metastasis		
Yes	6/66 (9.1%)	0.004
No	2/154 (1.3%)	
Capsular infiltration		
Yes	6/33 (18.1%)	0.005
No	9/187 (4.8%)	
Vascular invasion		
Yes	5/24 (20.8%)	0.003
No	10/196 (5.1%)	
Tg level		
≤10 ng/ml	8/150 (5.3%)	0.02
>10 ng/ml	7/70 (10%)	

4. Discussion

Relapse of DTC is a major clinical oncological problem either local or distant relapse in which lung, bone and brain are the most common sites [14].

In our study, we found age at diagnosis is a strong prognostic factor for recurrence which is comparable to that reported by Krajewska *et al.* [15]. This was explained by association of more aggressive behavior of tumors in old age or age-related factors as immune status and nutrition [16]. However, Ozkan *et al.* [17] did not find this relation.

Similar to our results; it was reported that female patients had better prognosis than male but the difference is insignificant [18]. We observed that papillary thyroid cancer had significantly better prognosis than follicular type, this may be attributed to different biological behavior between both types as follicular variant developed distant metastasis more than papillary one [19].

As we found in our studied cases; negative impact of thyroid capsular infiltration and vascular invasion on DFS were emphasized by some studies [20] [21] [22].

Multifocality had no impact on DFS in our series, comparable to others [6] [23], while Gulcelik *et al.* [22] reported significant impact. As reported by others

[15] [24] [25], large tumor size and presence of lymph node metastasis at presentation were related to higher risk of relapse in our study.

Ronga *et al.* [26] mentioned that postoperative Tg value can result in early detection of metastasis regardless presence of thyroid remnant.

It was demonstrated that subjects with postoperative Tg value < 10 ng/ml showed a 6% likelihood of persistent DTC while those with value > 10 ng/ml had 47% [27].

It was observed that postoperative Tg concentration was higher in male [7] this may be attributed to poorer prognosis in male.

Toubeau *et al.* [11] recommended that patients with high postoperative Tg level or lymph node metastasis should be carefully followed-up. Hall *et al.* [28] demonstrated that patients with initial high tumor stage and Tg value > 20 ng/ml measured 3 months postoperatively may have disease recurrence. Some studies reported that Tg value after surgery \geq 10 ng/ml are important marker to predict prognosis in DTC [15] [29]. Malandino *et al.* [30] recommended that Tg level may be sufficient to assess the risk-adapted treatment in DTC. In our patients level of Tg > 10 ng/ml was associated with significantly poorer PFS.

The 5-year PFS was 85% in our study comparable to that reported in other studies [7] [11].

5. Conclusion

In this retrospective study, we found that postoperative Tg level is a statistically significant prognostic factor together with other risk factors.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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