ORIGINAL ARTICLE

Prognostic factors pertaining to disease-free status in differentiated thyroid carcinoma patients

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ABSTRACT

Background: Radioiodine resistance in differentiated thyroid cancer (DTC) and unsuccessful ablation may adversely affect the prognosis of patients with DTC; therefore, identifying the factors that affect the success of ablation is very important in the management of patients with DTC. Our goal was to assess the factors associated with DTC after thyroidectomy and radioactive iodine ablation for achievement of disease-free status.

Methods: This was a retrospective study in which 277 patients were included. Age, gender, extent of thyroid surgery, tumor size, nodal metastases, distant metastases, and pre-ablation thyroglobulin (Tg) were analyzed initially in univariate analysis and then with significant variables by multivariate analysis.

Results: On univariate analysis, variables such as pre-ablated stimulated Tg level ≤ 20 ng/ml, absence of locoregional and distant metastases, tumor ≤ 4 cm, total thyroidectomy, and low and intermediate risk groups appeared to be significant. On multivariate analysis, stimulated Tg level ≤ 20 ng/ml, absence of locoregional metastases, and total thyroidectomy were associated with disease-free status.

Conclusion: The most important predictors for succeeding a disease-free status were low pre-ablation Tg level, i.e., 20 ng/ml, appropriate total thyroidectomy, and absence of lymph node metastasis.

Keywords: Differentiated thyroid carcinoma, good prognosis, radioiodine therapy, disease-free status, thyroglobulin (Tg).

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Introduction

Thyroid cancer is one of the commonest endocrine malignancies. About 90% of thyroid cancers are differentiated (papillary or follicular) thyroid cancers. differentiated thyroid cancer (DTC) makes up for 98% of the thyroid cancer with neoplasms arising from the follicular cells (papillary, follicular, and Hurthle cell thyroid cancer) and parafollicular cells (medullary thyroid cancer). Overall, the prognosis in patients with DTC is good [1].

In recent decades, the incidence of thyroid cancer in several affluent countries has markedly increased, although mortality from thyroid cancer has remained relatively low and stable or has steadily declined in these and other countries. This increase in incidence has predominantly been a reflection of the growing scrutiny of the thyroid gland with ultrasonography and other diagnostic techniques [2]. It has an overall excellent prognosis and a low mortality rate with long-term disease-free survival rates approaching 90% over 20 years. This likely results from a combination of the indolent biological behavior of most cases of DTC. Predictors are used to support medical decisions regarding the initial treatment and the clinical follow-up for papillary thyroid cancer (PTC). In the past, the analyses were fundamentally focused on predictors for mortality; however, the staging systems have improved for estimating PTC persistence and recurrence, which are two major concerns regarding treatment. Usually, the outcome predictors for PTC do not estimate persistence and recurrence independently. However, predicting each outcome individually would provide additional information to facilitate tailored treatment. Age, gender, size of the tumor, stage of disease, distant metastasis, and completeness of resection are elements that influence the prognosis significantly [3]. Surgical resection is the mainstay of treatment for DTC. Radioactive iodine (RAI) is used as adjuvant therapy in

many patients [4]. Previously, total thyroidectomy with RAI was the standard treatment in most cases to reduce the risk of tumor recurrence and to facilitate future cancer surveillance [5]. Hypothetically, 131I therapy is thought to reduce the rate of relapse and mortality in DTC patients by destroying microscopic residual tumor foci, which also promotes early detection of recurrence by improving the sensitivity and reliability of serum thyroglobulin (Tg) and RAI whole-body scan (WBS) [6].

Objectives

The purpose of this retrospective study was to evaluate the prognostic factors that influence the achievement of disease-free state in well-DTC patients who were treated with thyroidectomy and radioiodine at a single institute using the criteria of the revised American Thyroid Association (ATA) management guidelines for patients with thyroid nodules and DTC [4].

Methods

A total of 277 patients with DTC who had undergone total or near total thyroidectomy, followed by radioiodine therapy and subsequent follow-up at Atomic Energy Medical Center, Jinnah Postgraduate Medical Center (JPMC) from January 2007 to December 2018, were included in the study. Hospital records of the patients were reviewed for the treatment outcomes and the following predictive variables, i.e., gender, age at surgery, histopathological variant, extent of thyroid surgery, size of tumor, presence of regional or distant metastases, risk group of recurrence, unifocal/multifocal tumor involvement, stimulated serum Tg at first RAI therapy were evaluated. Age was further categorized as ≤45 years and >45 years and ≤55 years and >55 years. Staging was carried out according to the updated American Joint Committee on Cancer (AJCC)/ Tumor, Nodes, Metastasis (TNM) staging system and patients were risk stratified according to the ATA guidelines [4].

Patients with Hurthle cell carcinoma were merged with follicular carcinoma, while patients with medullary thyroid cancer were excluded. Neck node dissection was performed in 111 patients.

RAI therapy and post-ablative WBS

RAI was given in fixed doses in the range of 30-100 mCi, 6-8 weeks after the surgery to the patients without any evidence of metastases. For lymph node (LN) and lung metastases, 150 mCi RAI was given. The activity was higher for bone metastases, i.e., 200 mCi. Blood was tested for stimulated serum Tg, anti-Tg antibody (TgAb), and thyroid-stimulating hormone (TSH) with ultrasound of neck before RAI therapy to find evidence of local and distant metastasis.

A post-ablative WBS was performed 5-14 days after RAI therapy. Whole-body planar scintigraphy was acquired using a dual-head gamma camera (GE Xeleris). We classified the findings into negative WBS, locoregional disease (uptake at thyroid bed and/or cervical LN), and distant metastasis (abnormal uptake at other sites with or without uptake at thyroid bed and/ or cervical LN).

All patients received thyroxin suppression according to the ATA guidelines [4].

Follow-up

The mean period of follow-up was 4.6 ± 2.78 years. Patients were investigated for disease status 6-12 months after RAI therapy. Patients were physically examined and ultrasound neck was performed. Serum TSH, Tg, and TgAb were carried out after 3 weeks of thyroid hormone withdrawal and diagnostic WBS was carried out subsequently.

Whenever Tg concentration was elevated or clinical symptoms (bone pains, any cervical swelling, dyspnea, etc.) were presented with negative diagnostic WBS, other imaging modalities [X-ray, computed tomography (CT), magnetic resonance imaging, bone scintigraphy, and positron emission CT] were used for detection of metastases. Surgical resection for LN metastasis, external beam radiotherapy, and bisphosphonates for bony metastasis were also carried out.

Criteria

Disease-free status was declared when on follow-up patients' stimulated Tg levels were of <1 ng/ml without interfering anti-Tg antibodies, and there was no imaging evidence of tumor on diagnostic whole-body RAI scans or on ultrasonography, according to the ATA guidelines [4].

Statistical analyses

Continuous variables like age, tumor size, and follow-up duration were presented as mean ± SD. Survival analysis was carried out with SPSS 20. Time to disease-free status was estimated with the Kaplan-Meier method. Potential prognostic factors were evaluated in univariate analysis (log-rank test). Significant variables in univariate analysis were further evaluated in multivariate Cox regression analysis. Significance was defined as p-value < 0.05.

Results

Table 1 shows the characteristics of 277 DTC patients: 76.5% of the patients were female and 23.5% were male, with a female to male ratio of 3.26:1. The mean age of the patients was 35.94 ± 12.98 years (range = 12-74 years). Follicular carcinoma was found in 58 (20.9%) patients and papillary carcinoma in 219 (79.1%) patients. 169 (61%) were rated as low-risk. The majority of patients were in stage I, i.e., around 216 (80%). All patients received RAI therapy after total or near total or after completion of thyroidectomy and followed up for at least 1 year. Median time in achieving disease-free status was 6 ± 0.38 years, including patients who received multiple doses.

Table 1. Characteristics of patients.

Patients' characteristics	No. of patients	Successful ablation
Gender		
Male	65 (23.5%)	21 (32.3%)
Female	212 (76.5%)	106 (50%)
Histology		
Papillary	219 (79.4%)	102 (80.3%)
Follicular / Hurthle	58 (20.9%)	25 (19.7%)
Subtype of histology		
With aggressive histology	12 (4.3%)	02 (16.6%)
Without aggressive histology	265 (96%)	125 (47.1%)
Tumor stage		
T1	76 (27.4%)	37 (29.1%)
T2	100 (36.1%)	59 (46.4%)
T3	90 (32.5%)	28 (22.4%)
T4	11 (4.0%)	03 (2.3%)
Tumor involvement		
Unifocal	214 (77%)	97 (78.2%)
Multifocal	63 (22.7%)	30 (23.6%)
Stimulated Tg at first RAI dose		
≤20	125 (45.1%)	81 (64.8%)
>20	152 (54.8%)	46 (36.2%)
Status of cervical LNs		
Presence of LNs	68 (24.5%)	18 (14.1%)
Absence of LNs	209 (75.4%)	109 (86%)
Status of distant metastases		
Present	30 (10.8%)	03 (2.4%)
Absent	247 (89.1%)	124 (97.6%)
Risk of recurrence		
High	52 (18.8%)	08 (6.5%)
Intermediate	56 (20.2%)	20 (16.1%)
Low	169 (61%)	99 (77.9%)
Thyroidectomy		
Total thyroidectomy	153 (55.2%)	92 (72.4%)
Incomplete total thyroidectomy	124 (44.7%)	35 (27.6%)

Of the 277 patients, 27 were lost to follow-up. 127 patients achieved disease-free status, and the overall disease-free rates at 1, 2, and 3 years were 29.9%, 48%, and 71.6%, respectively, estimated with the Kaplan-Meier method. 37 patients (majority from the T1 and T2 groups) were disease-free after the first dose of RAI. For nearly half the cases, it took two or three ablative procedures to eradicate the residual thyroid tissue. External radiotherapy to the neck area was used in six patients due to either inoperable local disease (four patients suggested inoperable by surgeon for locally advanced disease) or because of iodine-131 negativity in the thyroid remnant (two patients). Both local LN involvement and the presence of distant metastases were more common in papillary cancer patients as compared to follicular cancer patients (86.8% *vs.* 13.2% and 55.6% *vs.* 44.4%, respectively).

Table 2 shows the univariate analysis along with the median time to disease-free status for each significant variable. When analyzing univariate analysis, the percentage of disease-free status in female patients was higher than male patients, but median time in both these groups was approximately same, i.e., 6 years, and hence statistically nonsignificant (p-value = 0.175).

About 50.8% of the patients achieved disease-free status. Out of which, 219 patients (79.4%) were those having PTC. However, statistically no substantial difference was observed when comparison was carried out between papillary and follicular cancer patients regarding successful ablation.

Size of tumor also showed great impact on prognostic significance of the disease. 58.4% of the patients were found to have ≤4 cm of tumor and they revealed statistically significant results for achievement of disease-free status.

Table 2. Univariate analysis.

	Median time to disease-free status (years)	*p*-value
Gender		
Male	6 ± 0.32	0.175
Female	6 ± 0.38	
Histology		
Papillary	6 ± 0.40	0.842
Follicular / Hurthle	6 ± 1.12	
Aggressive		
Yes	-	0.124
No	-	
Tumor stage		
T1	3 ± 0.59	0.000
T2	5 ± 0.72	
T3	10 ± 2.16	
T4	-	
Tumor involvement		
Unifocal	6 ± 1.11	0.541
Multifocal	6 ± 0.43	
Stimulated Tg at first RAI dose		
≤20	3 ± 0.63	0.000
>20	10 ± 1.51	
Cervical LNs		
Yes	10.17 ± 0.07	0.000
No	4.33 ± 0.69	
Distant metastases		
Yes	-	0.000
No	5 ± 0.35	
Risk category		
High	-	0.000
Intermediate	120 ± 3.14	
Low	36 ± 0.52	
Thyroidectomy		
Yes	4 ± 0.56	0.000
No	10 ± 2.07	

At the time of diagnosis, multiple tumor foci in one or both lobes of the thyroid were present in 23% of the study subjects. The prevalence of multifocality in the pathological types of DTC is shown in Table 1; no statistically significant association was observed (p = 0.541) regarding disease-free status and focality of tumor.

125 patients (45.1%) had ≤20 ng/ml stimulated serum Tg at the time of first RAI dose, and it appeared to be a significant prognostic factor for attaining disease-free status. Locoregional LN were seen in 24.5% and distant metastases were observed in 27 patients at the time of diagnosis and it seemed to be a bad prognostic factor to achieve disease-free status. Only 14.1% of the patients with cervical LNs and 3 patients with distant metastasis (including bone) achieved disease-free status; therefore, median time could not be obtained.

Age did not appear to influence the disease-free status of patients. When comparison was made between patients of age >55 and ≤55, statistically no difference was observed. Total thyroidectomy appeared to be a very important prognostic factor (p-value < 0.000) in achieving tumor-free status. It was noted that only 27.6% of the patients attained disease-free status due to incomplete total thyroidectomy versus 72.4% who underwent complete total thyroidectomy. The mean cumulative dose of RAI was higher in patients with incomplete thyroidectomy who achieved disease-free status (202.06 ± 21.81 mCi) than those patients who accomplished successful ablation after complete thyroidectomy (124.61 ± 12.04 mCi).

Patients categorized as low or intermediate risk displayed good prognostic score. As data demonstrate, 84.6% of the patients with high risk did not achieve disease-free

status, while 36% of the patients with low risk achieved disease-free status.

Table 3 shows multivariate analysis of significant variables. Stimulated Tg level below 20 ng/ml, measured before RAI treatment, was the most important independent risk factor in the multivariate analysis and was associated with a 1.940-fold increase in disease-free rate (p -0.002). Total thyroidectomy was another independent favorable prognostic factor associated with a 1.596-fold increase in disease-free rate (p = 0.000). Regional LNs involvement was independently related to a higher risk of failure in the achievement of disease-free survival. In contrast to the univariate analysis, tumor size and distant metastasis are not independent risk factors for achieving disease-free survival.

Discussion

DTC develops radioiodine resistance in approximately 2%-11% of the cases [7], after thyroidectomy patients are treated with RAI and monitored with WBS using RAI, serum tumor markers, Tg and TgAb, and cervical ultrasonography at intervals of 6-12 months with individualized care plans. Radioiodine resistance in DTC represents an aggressive subset of patients, and once iodine resistance develops, the disease becomes more challenging. Unsuccessful ablation may adversely affect the prognosis of patients with DTC; therefore, identifying the factors that affect the success of ablation is very important in the management of patients with DTC. The main goal of this study was to assess the significant prognostic factor that increased the disease-free rate using the criteria of the revised ATA management guideline for patients with thyroid nodules and DTC [4]. To this goal, we undertook both univariate and multivariate analyses to evaluate many prognostic factors in DTC patients.

Our study exhibited that 76% of DTCs were women, which is almost similar to the study published by Bukhari et al. [8], Khayamzadeh et al. [9], and Hassan et al. [10]. Similarly, the patient population was younger in our study, which coincides with the data of studies like Leboulleux et al. [11] and Khayamzadeh et al. [9]. The mean age of the patients was approximately 36 years at presentation, which is comparable to a study published about 10 years ago from our institute [8]. PTCs represented about 79% of the total cases.

Pre-ablation-stimulated Tg without TgAb intervention, absence of cervical LNs, and total thyroidectomy were the most powerful predictive factors for a successful RAI ablative outcome. Larger tumor size and distant metastasis were linked to higher therapeutic failure risk.

Tg is a well-established marker of DTC, and may be used to detect persistence or recurrence of the disease. Many studies have proved that pre-ablation-stimulated Tg is a good predictor of successful ablation in DTC patients [12]. However, Tg's cut-off values for positive prediction of ablation or recurrence were very different among the studies. Lim et al. [13] determined that a Tg value >5 ng/ml was the most powerful predictor for ablation failure. González et al. [14] conducted a study on 133 patients with DTC and reported that pre-ablation Tg of <8.55 ng/ml could predict disease remission in 18-24 months after 131I therapy, with 88% sensitivity, 72% specificity, 47% Positive predictive Value (PPV), and 95% Negative predictive value (NPV).

Table 3. Multivariate analysis.

	p-value	HR (95%CI)
Tumor stage		
T1	0.125	0.823 (0.64-1.05)
T2		
T3		
T4		
Stimulated Tg at first RAI dose		
<20	0.002	1.931 (1.27-2.93)
>20		
Locoregional nodes		
No	0.009	0.491(0.29-0.84)
Yes		
Distant mets		
No	0.082	0.349 (0.11-1.14)
Yes		
Thyroidectomy		
Yes	0.026	1.593(1.056-2.41)
No		

HR: hazard ratio,

Heemstra et al. [15] indicated that the cut-off point of stimulated serum Tg level for effective RAI therapy was 27.5 ng/ml (positive predictive value = 98%). Thamnirat et al. [16] proved cut-off point of stimulated serum Tg level at first RAI therapy for good outcome was <30 ng/ml, but in our study, baseline-stimulated Tg value of ≤ 20 ng/ml was identified as the optimum cut [16].

The role of locoregional LNs in achieving disease-free status remains a contentious issue. There are many studies which claim that the initial presentation with cervical LN metastases are precursors for recurrence of disease [4], but whether they have deleterious effect in attaining disease-free status remains a critical area. There are several studies that have revealed a link in differentiated thyroid carcinomas between the presence of the cervical LN and poor prognoses. Hassan et al. [10], Mazzaferri et al. [17], Scheumann et al. [18], and Loh et al. [19] endorsed this concept in their studies, whereas Pacini et al. [20], Sanders and Cady [21], and Steinmüller et al. [22] seemed to deviate from this belief. Mercante et al. [23] and Leboulleux et al. [11] found LN metastases an independent risk factor for the persistence of disease. We also found LN involvement at the presentation as an independent risk factor in achieving disease-free status. Thamnirat et al. [16] did not find LN involvement as an independent risk factor in achieving disease-free status. However, they established the correlation in univariate analysis. Further work in this regard is needed to be carried out to see if different histopathological subvariants or genetic factors are causes of this different prognosis.

The 2006 [24] and 2009 [25] ATA guidelines have validated near total or total thyroidectomy as the primary initial surgical treatment option for nearly all DTC >1 cm. However, the 2015 guidelines recommended total thyroidectomy for tumors > 4 cm or with some other risk factors [4]. Anyhow, total thyroidectomy has its own advantages. Total thyroidectomy allows for more effective adjuvant treatment to permit early detection of recurrence of tumors. Although we had included only those patients who had undergone near total or total thyroidectomy and RAI ablation therapy, it was our observation that incomplete removal of thyroid tissue was seen in multiple cases after total thyroidectomy. Incomplete total thyroidectomy was noted as an independent factor for affecting disease-free status in this study. Those patients who had large remnants achieved successful ablation but they required a higher RAI dose as compared to those who had small or minimal remnants. Andresen et al. [26] also concluded in the research that large remnants need higher doses of RAI in comparison to smaller remnants for successful ablation. Good surgery and aggressive therapy like multiple iodine doses might have attenuated the impact of large size.

The presence of distant metastasis is always considered a bad prognostic sign for overall survival as well as disease-free survival of patients with thyroid cancer [4,23,27,28]. Durante et al. [29] reported that survival rate in patients with macronodular pulmonary metastases or multiple bony metastases decreased to 14%. Manxhuka-Kerliu et al. [30] validated the independent value of distant metastasis for disease-free survival. The study of Liu et al. [31] was also in accordance with the aforementioned studies, but they evaluated only the first ablation therapy. Thamnirat et al. [16] disclosed it as an increased risk for achieving disease-free status but they could not prove it as an independent factor as it could not be verified in multivariate analysis. In our study, we too found distant metastasis as an important risk factor as it was discovered to have a significant impact in univariate analysis but could not validate it in multivariate analysis.

By review of the literature, it comes to mind that age is an important predictive factor which influences the outcome of treatment in thyroid cancer patients. Hay et al. [32] developed the distant Metastasis, patient Age, Completeness of resection, local Invasion, and tumor Size (MACIS) scoring system in 1993 for predicting survival of PTC. Davis [33] evaluated The European Organization for Research on Treatment of Cancer (EORTIC) and Age, Grade, Extent, Size (AGES) for predicting survival in follicular thyroid cancer (FTC). In 2004, D'Avanzo et al. [34] compared all scoring systems for FTC and found MACIS the most accurate among them. Age was a consistent factor for survival of patients with thyroid cancer in all of the abovementioned scoring systems. Even in TNM staging, age is considered as a vital contributing factor. Previously, in AJCC/TNM staging system, the age limit was 45 years for staging, but in the 8th edition it was changed to 55 years. Since in 8th edition it was mentioned that implementation of the 8th edition would be from 2018 and our most of patients were enrolled before 2018, we analyzed both 45 and 55 years as cut-off for age in our univariate analysis. Lei et al. [35] found that after 48 years, the likelihood of unfavorable outcome increases in thyroid cancer. From the study of Leung et al. [27], it is established that age has an independent prognostic value for both disease persistence and recurrence. Thamnirat et al. [16] showed age >45 as a prognostic factor for successful ablation but could not prove in multivariate analysis. But according to Liu et al. [31], age does not play important role in achieving the disease-free status after administration of the first ablation therapy. In our research, we also did not notice any association between age and achievement of disease-free status, similar to the results of Zubair Hussain et al. [7], another study from our country.

Gender as a prognostic variable appears to be most controversial. It is not included in scoring systems such as AGES, AMES, TNM, and MACIS. However, Cady et al. [36] considered male gender as a bad prognostic signs for survival of thyroid cancer patients. Some authors favored this concept, including Kim et al. [37]. However, the majority did not support this notion. Sarda et al. [38] retrospectively analyzed 215 DTC patients and came to a conclusion that gender did not affect the survival. Lei et

al. [35] also supported this. Gender differences in survival did not reach statistical significance in Sautter-Bihl's et al. [39] study, although it showed relatively low survival rate in males. Thamnirat et al. [16] showed no difference in achieving disease-free status. Our study and Zubair Hussain et al.'s [7] study also could not exhibit any correlation between gender and achievement of disease-free status.

The ATA guidelines show aggressive pathology as a predicting risk of disease recurrence and/or persistence [4]. We tried to evaluate the effect of aggressive histology in achievement of disease-free status but could not find any relevance, most likely due to insufficient data about subtypes of histopathology.

Hay et al. [32], Davies and Welch [1], D'Avanzo et al. [34], and Mazzaferi [3] suggested that unifocal disease has favorable outcome. Lang et al. [40] put forwarded that patients with multifocal tumor have a lower survival rate than patients with unifocal tumor (Hazard ratio = 1.79, $p = 0.048$). Thamnirat et al. [16] in their univariate analysis demonstrated that unifocal disease has better prognosis than multifocal disease in achieving disease-free status. Our study did not find any relevance between multifocality and failure rate in achieving disease-free status.

We defined risk constellations based on the ATA risk classification. We analyzed the risk groups in univariate analysis but not in multivariate analysis, as the factors from which these groups were derived were already analyzed. In univariate analysis, we identified that low and intermediate risk groups had better prognosis than high risk.

Conclusion

The study adds to the value that predictors for achieving disease-free status were low pre-ablation Tg level, i.e., 20 ng/ml, total thyroidectomy, and absence of LN metastasis. It was unlikely that patients with distant metastasis could be disease-free.

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List of Abbreviations

ATA	American Thyroid Association
CT	Computed tomography
DTC	Differentiated thyroid carcinoma
WBS	131 I whole-body scan
LN	Lymph node
PTC and FTC	Papillary and follicular cancer
RAI	Radioactive iodine
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
TSH	thyroid-stimulating hormone

Conflict of interest

The authors declare that they have no conflict of interest.

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Consent to participate

For this type of study, formal consent is not required.

Ethical approval

The study was approved by the Ethical committee of AEMC AEMC00105. dated 25/06/2018.

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