Predictors of success of the ablative/therapeutic radioiodine (^{131}I) in differentiated thyroid cancer

Original Article

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ABSTRACT

Introduction: Differentiated thyroid carcinoma (DTC) constitute approximately 90% of all thyroid tumors with an overall excellent prognosis. However, there is a small group of patients with a more aggressive form of disease, usually associated with certain poor prognostic factors. Using our large database of patients with DTC, the current study aims at identifying some of these factors.

Methods: This retrospective study was based on the registry of patients with non-medullary thyroid carcinoma. Data were collected on the clinical, laboratory, and outcome characteristics of 501 patients followed at our department.

Results: On multivariate analysis, the following variables were predictive of persistent disease: less than total thyroidectomy, residual disease on the post treatment whole body radioiodine scan (WBIS), higher received radioiodine activities, and higher levels of baseline stimulated thyroglobulin (Tg) and thyroid stimulating hormone (TSH). The greatest predictive value for the persistent/recurrent disease was attributed to the presence of residual disease on the post-treatment WBIS (odds ratio (OR): 33.72, 95% confidence interval (95% CI): 18.17-62.57), followed by type of surgical procedure (OR: 8.92, 95% CI: 2.90-27.39), radioiodine ablation dose (OR: 4.03, 95% CI: 1.56-10.39), stimulated baseline Tg level (OR: 2.79, 95% CI: 1.53-5.08) and finally, the stimulated baseline TSH level (OR: 2.21, 95% CI: 1.08-4.519).

Conclusion: In patients with DTCs, surgical procedures other than total thyroidectomy, presence of residual disease on the post-treatment WBIS, higher received radioiodine activities, higher baseline stimulated Tg and TSH levels are associated with a higher probability of having persistent disease and can be used in conjunction with other disease characteristics to reach proper decisions with regard to treatment and follow-up.

Key words: Differentiated thyroid cancer; Prognostic markers; Stratification; Thyroglobulin

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INTRODUCTION

Thyroid cancer is a rare neoplasm accounting for 1-2% of all malignancies, but representing the most common endocrine malignancy with a rapid increase in incidence over the past decades, regardless of patients' ethnicities or genders [1]. Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are responsible for 80-85% and 10-15% of a collective term determining the spectrum of follicular-epithelial cell derived tumors, namely, differentiated thyroid cancer (DTC). Anaplastic and poorly differentiated thyroid carcinomas are known for their overwhelming poor outcomes; in contrary, DTCs are generally found to have an excellent prognosis, although a significant risk of recurrence, sometimes reaching as high as 10-30%, cannot be overlooked [2]. Notwithstanding the fact that nearly 80% of patients with DTC show proper response to minimal surgical procedures and 5% mortality regardless of the type of surgery and other treatments offered, there will remain a group consisting of 15% of DTC patients in whom a more aggressive form of disease is expressed, often associated with poor prognostic factors. The latter are those who may benefit from a more aggressive oncological resection, adjuvant radioiodine treatment and sometimes external-beam radiation therapy [2], and this, explains the importance of the accurate identification of prognostic factors so as to facilitate individual patient risk group stratification and to prevent subjecting patients without recurrent disease to overtreatment [3].

With the intent to provide patients at higher risk with more aggressive treatment options while avoiding unnecessary treatments in those in lower risk disease category, a number of investigations have been carried out indicating some clinicopathologic predictors and prognostic markers helping to create specific risk stratification systems [4]. Some factors, including age, tumor size, grade, presence of local invasion, and regional or distant metastases, make up the cornerstone of the aforementioned stratification systems.

Herein, we report the results of a retrospective study on 501 patients with DTC, aiming to assess some of these core parameters as well as other upcoming markers, in order to fill this gap using our large database of patients with DTC.

MTHODS

The study was based on the retrospective registry of patients with non-medullary thyroid carcinoma of our nuclear medicine department, from 2007 till 2012. The sample for the present study comprised 501 registered patients fulfilling the inclusion criteria, including the availability of pathologic findings of well-differentiated tumor, values of stimulated Tg, anti-Tg antibody and TSH levels just before ^{131}I ablation, following total, near total, or subtotal thyroidectomy (baseline Tg), and 2 months after the ^{131}I treatment, and the results of diagnostic whole body radioiodine scan (WBIS), performed 6 months after the ^{131}I treatment. Serum Tg and anti-Tg antibody levels were determined by radioimmunoassay, using commercial kits (Dynotest Tg-plus and Dynotest anti-Tgn; Brahms Diagnostica, Berlin, Germany, respectively). Additionally, serum TSH was measured with a third-generation double antibody assay. Patients with histologic findings other than well-differentiated carcinoma or less than a year follow-up were excluded. The following clinical parameters were recorded: patients' age and sex, type of surgery, histopathology findings, primary therapy, tumor-node-metastasis (TNM) staging, risk stratification according to American Thyroid Association (ATA) guideline [5], diagnostic procedures, type of treatment, dosage of administered radioiodine, findings associated with persistent or recurrent disease, evidence of metastatic disease, evidence of metastatic nodal involvement, baseline stimulated Tg, TSH and anti-Tg antibody levels after thyroid hormone withdrawal or rhTSH stimulation measured post-operatively, just before ablation as well as suppressed Tg level, during thyroid hormone replacement therapy, 2 months after ^{131}I treatment.

On the basis of the histopathologic findings, the imaging studies were reviewed, including radioiodine scan, neck sonogram, computed tomography (CT), positron emission tomography (PET)-CT, and magnetic resonance imaging (MRI), as well as elevated levels of suppressed (on levothyroxine) or stimulated (off levothyroxine) Tg, persistent disease was considered as active disease within a year after primary treatment, recurrent disease, as active disease after a disease-free period of 2 years, and remission as the absence of any structural disease based on imaging, cytology, absence of radioactive iodine uptake and the undetectable suppressed Tg (stimulated Tg<2 ng/ml, in the absence of anti-thyroid antibodies).

For purposes of analysis, the study population was further divided into 2 different groups according to following indices: 1) age <45 y and ≥45 y, 2) the type of surgical procedure (total thyroidectomy, and near total or subtotal thyroidectomy), 3) TNM stage (stages 1-2, and stages 3-4), 4) ATA risk stratification (low risk, intermediate and high risk), 5) the results of post-treatment WBIS performed 7 days after radioiodine ablation (negative or faint residual thyroid bed, significant residual thyroid bed or lymph node or distant metastasis), 6) the administered radioiodine activity (100 mci, ≥150 mci), 7) the baseline stimulated Tg level (<10 ng/ml, ≥10 ng/ml), 8) the baseline stimulated TSH level (<30 mIU/L, ≥30 mIU/L), and 9) the non-stimulated TSH level measured 2 months after radioiodine ablation (≤0.5

mIU/L, >0.5 mIU/L). The study was approved by the Ethical Committee of Tehran University of Medical Sciences.

Statistical analysis

The numerical data were presented as mean ± standard deviation (SD) and the categorical data as proportions. The independent t-test or the non-parametric Mann-Whitney test was used to evaluate differences between the two subgroups. In order to analyze the effect of each of the predictors on the outcome variable (the presence or absence of persistent/recurrent disease), the multivariate logistic regression model, using the stepwise regression method, was performed while controlling for possible confounding effects. The logistic regression model was used to estimate the odds ratio (OR) of each of the predictors, showing the magnitude of the effect of the predictor variable on the outcome, its p-value as well as the associated 95% confidence interval (CI). SPSS version 14.0.1 statistical software (SPSS Inc, Chicago, IL, USA) was used to perform all analyses. The P value of less than 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of patients are depicted in Table 1.

On univariate analysis, as demonstrated in Table 2, female sex, less than total thyroidectomy, higher disease stages, higher risk groups according to ATA risk stratification system, residual disease on the post-treatment WBIS, higher received radioiodine activities, higher levels of baseline stimulated Tg and TSH, higher level of anti-Tg antibody in case of stimulated serum Tg of less than 2 ng/ml, and greater amount of non-stimulated Tg levels 2 months after radioiodine treatment, significantly predicted persistent disease.

On multivariate analysis with stepwise logistic regression (Table 3), less than total thyroidectomy, residual disease on the post-treatment WBIS, higher received radioiodine activities, and higher levels of baseline stimulated Tg and TSH were the most significant independent predictors of persistent disease.

DISCUSSION

Growing trend of early detection of DTC, and higher rates of curative surgery are the phenomena witnessed in recent years. The impact of the early detection of recurrent or persistent disease on morbidity and mortality cannot be ignored. Numerous staging classifications, mostly including shared core parameters of age, tumor size, grade, presence of local invasion, and regional or distant metastases, are currently available for predicting outcomes in thyroid cancer. More frequently used staging systems exert some different features such as their difference in the predicted outcomes, as the American thyroid association ATA risk stratification predicts risk of recurrence, while the TNM staging is known to predict the risk of mortality. Keeping in mind the lack of consensus regarding the optimal approach to disease staging, evident by the development of multiple often overlapping classification systems, and the need for univariate and multivariate retrospective analysis of all potential prognostic factors, the current study has been performed so as to elucidate the significance of some of the probable indicators of disease recurrence and/or persistence.

To date, several factors have been suggested as prognostic markers in patients with DTC, one of which is patients' age, with the most common cut-off of 45 years, as recommended by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system [6]. Herein, we did not observe any significant association between patients' age and DTC persistence, and this could be partly explained by the increasing evidence, suggesting an elevated age limit of 55 as a cut-off [7]. Tumor size stands as a much debated prognostic factor especially within papillary thyroid cancer. However, the size of greater than 4 cm has been recommended by the current British and American thyroid association guidelines as an indicator of poor prognosis. Another area of debate is the implication of gender in prognosis, as higher incidence of thyroid cancer is detected in women but disease mortality has been speculated to be twice as high in men than women in some studies [8]. In the current study, our univariate analysis revealed female sex as a marker of disease persistence. With regard to the lymph node involvement, current consensus indicates that although lymph node metastasis could not be assumed as an independent risk factor for disease specific survival; macroscopic lymph node involvement is correlated with high local recurrence rates. Nonetheless, recurrence with microscopic nodal disease stills needs to be clarified [9, 10]. Other potential prognostic factors in the case of papillary or follicular thyroid cancer include Tg, found to be present in serum samples following thyroidectomy, in case of residual thyroid tissue either normal or tumor tissue [11], TSH, and anti-Tg antibodies, commonly used as surrogate markers for disease recurrence or persistence, while, their prognostic role has not been fully recognized, thus far. Dependence of Tg levels on circulating TSH levels, even when Tg is solely produced by the tumor tissue, and the impact of anti-Tg antibodies on the reliability of serum Tg assay and its predictive value [12].

Even though TSH-suppressive LT4 therapy has long been assumed to improve outcome in patients with DTC, there has been much debate concerning which

patients should be suppressed. Several studies revealed no clear benefit with regard to DTC-specific survival and recurrence rates in low-risk patients. Hovens *et al.* showed the median TSH levels exceeding 2 mU/l to be associated with an elevated risk of recurrence or thyroid cancer–related death [13]. Jonklaas *et al.* found TSH suppression to be beneficial in patients with stage III and stage IV disease according to the National Thyroid Cancer Cooperative Treatment Study criteria. Their results suggested modest TSH suppression to be beneficial in patients with stage II disease, while no clear benefits could be identified in stage I patients [14]. On the other hand, the study performed by Ito *et al.* found TSH suppressive LT4 therapy in a population of 79 patients with advanced papillary thyroid carcinoma to be associated with improved survival [15].

Table 1: Clinical characteristics of the study population.

Characteristics		Total (n=501)	%
Gender (Female)		379	75.6
Age (y): 42.3 ± 14.5	<45	285	56.9
	≥45	216	43.1
Familial history of DTC		12	0.20
Prior radiation to head and neck		0	0
Type of surgery	Total thyroidectomy	445	88.8
	Near total thyroidectomy	41	8.2
	Subtotal thyroidectomy	15	3
Pathology	PTC	466	93
	FTC	35	7
Cervical lymph node involvement	N0	347	69.3
	N1	154	30.7
Disease stage	1	365	72.8
	2	25	5
	3	11	2.3
	4	100	19.9
ATA risk stratification	Low	228	45.5
	Intermediate	251	50.1
	High	22	4.4
Post-treatment whole body radioiodine scan	Negative	20	4
	Faint residual thyroid bed	222	44.3
	Significant residual thyroid bed	189	37.7
	Positivity for regional lymph nodes	48	9.6
	Distant metastasis	22	4.4
Radioiodine ablation dose (mCi)	100	258	51.5
	150	222	44.3
	175	14	2.8
	200	7	1.4
Stimulated baseline Tg (ng/ml)	0-2 (Tg-antibody level <100 mIU/ml)	116	63
	0-2 (Tg-antibody level >100 mIU/ml)	68	37
	0-2 (Total)	184	36.7
	2-4.99	82	16.4
	5-9.99	67	13.4
	≥10	168	33.5
Stimulated baseline TSH (mIU/L)	<30	94	18.8
	≥30	407	81.2
Non-stimulated TSH level 2 m following radioiodine ablation (mIU/L)	≤0.5	386	77
	>0.5	115	23

Table 2: Univariate analysis for persistent/recurrent disease.

Parameter		Persistent/Remission (%)	Significance
Patients, no.		222 (44.3)	
Age (y)	<45	122 (42.8)	>0.05
	≥45	100 (46.3)	
Female sex, no.		148 (39.1)	<0.0001
Type of Thyroidectomy	Total	174 (39.1)	<0.0001
	Near total/Subtotal	48 (85.7)	
Pathology	PTC	205 (44)	>0.05
	FTC	17 (48.6)	
Cervical lymph node involvement	N0	132 (38.2)	>0.05
	N1	90 (58.4)	
Disease stage	1-2	151 (38.7)	<0.0001
	3-4	71 (64)	
ATA risk stratification	Low	63 (27.6)	<0.05
	Intermediate/High	159 (58.2)	
Post-treatment whole body radioiodine scan	Negative/ Faint residual thyroid bed	19 (7.9)	<0.0001
	Significant residual thyroid bed/ LN or distant metastasis	203 (78.4)	
Radioiodine ablation dose (mCi)	100	79 (30.6)	0.004
	≥150	143 (58.8)	
Stimulated baseline Tg (ng/ml)	<10	102 (30.6)	0.001
	≥10	120 (71.4)	
Tg-antibody level (mIU/ml) in patients with stimulated baseline Tg<2	<100	24 (21.2)	0.015
	≥100	26 (39.4)	
Stimulated baseline TSH (mIU/L)	<30	58 (61.7)	0.029
	≥30	164 (40.3)	
Non-stimulated TSH level 2 m following radioiodine ablation (mIU/L)	≤0.5	160 (41.5)	0.019
	>0.5	62 (53.5)	

Table 3: Multivariate binary logistic regression analysis for persistent/recurrent disease.

Parameter	P Value	OR (95% CI)
Type of surgery (Total vs. near total & subtotal)	<0.001	8.92 (2.90-27.39)
Post-treatment WBIS (Negative & faint residual thyroid bed vs. significant residual thyroid bed, LN & distant metastasis)	<0.001	33.72 (18.17-62.57)
Radioiodine ablation dose (100 vs. ≥150) (mCi)	0.004	4.03 (1.56-10.39)
Stimulated baseline Tg (<10 vs. ≥10) (ng/ml)	0.001	2.79 (1.53-5.08)
Stimulated baseline TSH (≥30 vs. <30) (mIU/L)	0.029	2.21 (1.08-4.51)

In the present study, on multivariate regression analysis, any surgical procedure other than total thyroidectomy, residual disease on the post-treatment WBIS, higher dose of administered radioiodine, and higher levels of baseline stimulated Tg and TSH were found to be independent and significant predictors of persistent disease. However, it should be noted that the varying predictive power of such variables indicate that these cannot be accurately used alone and this signifies the importance of the development of more accurate probability prediction models, encompassing a number of independent parameters. As shown with both the univariate and multivariate analysis, the current study suggests that the Tg levels measured after thyroidectomy and before iodine treatment, serum TSH level estimated either one month after deprivation of levothyroxine therapy or following the administration of rhTSH, type of surgical procedure performed, the findings of post-treatment WBIS, together with the administered radioiodine dosage, could be related to the extent of disease demonstrating a positive predictive value for persistent disease, both when these parameters are used alone or in combination with other independent variables. On the basis of these findings, it is possible to hypothesize that patients with low baseline Tg, higher baseline stimulated TSH, negative post-treatment WBIS, lower required dosage of radioiodine therapy and those who have undergone total thyroidectomy, have a low probability to have a persistent disease during follow-up. Improvement of the predictive value of the above-mentioned parameters and stratification of patients with DTC at early time point, warrant further research to formulate a multivariate model.

Following the recent upgrade in the American Thyroid Association guideline in 2015, management of DTC has undergone considerable changes towards a risk adapted paradigm, capable of distinguishing the patients who demand a more conservative approach and who are actually in need for further therapeutic intervention, and considered as a more scientific trend than ever before. Despite identification of some common prognostic factors such as age, extra-thyroid extension, grade, size and distant metastasis in recent years, implicated in most classification systems, lack of definitive evidence of accurate prognostic information concerning the DTC patient population when determination of the most appropriate treatment regimen, continues to create confusion. Therefore, in order to offer DTC patients the best contemporary care, individualized treatment programs are required to be planned, utilizing a combined multi-disciplinary approach with consideration of the available stratification systems.

CONCLUSION

In patients with DTCs, surgical procedures other than total thyroidectomy, presence of residual disease on the post-treatment WBIS, higher received radioiodine activities, higher baseline stimulated Tg and TSH levels are associated with a higher probability of having persistent disease and can be used in conjunction with other disease characteristics to reach proper decisions with regard to treatment and follow-up.

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