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Differentiated Thyroid Cancer Recurrence and Mortality Prognostic Factors: A Retrospective Cohort Study on 350 Adult Patients

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Abstract

Introduction:

Differentiated thyroid cancer (DTC) accounts for the most common types of thyroid cancer. The aim of the present study was to investigate the factors associated with recurrence and mortality after thyroidectomy in patients with diagnose of DTC in Hamadan, Iran.

Materials and Methods:

In this retrospective cohort study, 350 patients over 18 years old who underwent total thyroidectomy and ablation with radioactive iodine (RAI) and had DTC based on pathology and followed up for ten years were studied. The univariate and multivariate logistic regression was used for determining the risk factors of recurrence and mortality of DTC at a significance level of 0.05. SPSS software (Version 26) was applied to analyze the data.

Results:

In the present study, 16.6% of the participants were male and 83.4% were female with a mean age of 40.7 ±14.7 years. Recurrence and mortality rates were obtained to be 26.9% and 4.9 %, respectively. Overall, the risk of recurrence and death was significantly higher in older age, men, smokers, tumors larger than 4 cm and regional lymph node ($p<0.05$). For each additional year of life, the risk of recurrence and death increased by 4% and 9%, respectively ($P =0.001$ and $p<0.001$). Recurrence in men were 5.111 times more likely than women ($p<0.001$). A 6.002-fold increase in the risk of death was associated with smoking ($P=0.008$).

Conclusion:

Due to the high prevalence of DTC and on the other hand the good prognosis of this type of cancer, timely diagnosis and identification of risk factors of recurrence and death are very important.

Keywords: Differentiated thyroid cancer; Recurrence; Prognose

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Introduction

Cancers are one of the major public health and economic problems in the 21st century. They are responsible for 16.8% of global deaths . Differentiated thyroid cancer (DTC) accounts for the most common types of thyroid cancer (1). According to 2022 Globocan estimates, thyroid cancer ranked 7th worldwide in incidence, with a rate of 4.1%, and was responsible for 0.5% of all cancer deaths that year (2).

papillary thyroid carcinomas (PTC), follicular thyroid carcinoma (FTC) and Oncocytic thyroid carcinoma (OTC) are the most common types of thyroid cancers and together account for more than 90% of all thyroid cancers (3). The incidence and prevalence rates of DTC are rising worldwide, though the mortality rate remains low (4-6). The primary treatment in patients with DTC is surgery eventually followed by radioactive iodine ablation and these patients have excellent prognosis with high survival level (7). Recurrence is an important outcome to evaluate treatment of DTC. Though the DTC have a good prognosis, patients should be followed up regularly after treatment due to the possibility of recurrence (8). The recurrence rate of DTC is reported vary widely in scientific reports duo to different definitions of recurrence, different inclusion criteria and different duration of follow up (8-13). In one study, during 35 years' follow up after treatment recurrence rate was up to 30% (9). In other cohort studies recurrence rate reported between 4 to 42% of patients (10-13). So, the fear of recurrence and additional treatment can significantly decrease the patients' quality of life and increase the burden for the health care system (14-15).

Previous studies have identified several risk factors for recurrence and mortality in DTC patients. Several factors, including age, gender, a family history of thyroid cancer (in a first-degree relative), tumor size, and tumor multifocality have been reported to affect recurrence and mortality in the DTC patients (16). Furthermore, recent data highlight significant racial disparities exist in thyroid cancer outcomes (17-19). Ethnic groups in the Asian population are not homogenous and risk factors for DTC recurrence and death have not been adequately studied for all Asian racial. Hence, the present study aimed to evaluate the incidence of DTC recurrence and factors associated with recurrence after thyroidectomy in the patients with DTC during 10-year time in Hamadan, Iran. Moreover, the factors associated with death rate in the studied patients was investigated.

Materials and Methods

The protocol of this study was approved by the Ethics Committee of Hamadan University of Medical Sciences. In this retrospective cohort study, we reviewed the medical records of patients with DTC who underwent total thyroidectomy, central & lateral neck dissection and RAI administration to destroy remnant thyroid tissue and were followed up over a ten-year period in the specialized endocrine clinic in Hamadan, Iran. The inclusion criteria were histopathologically confirmed DTC and they had complete medical records.

The variables extracted from each included patients record were included age, sex (male, female), smoking, history of thyroid cancer in the first degree relative, co-existing thyroid disorder (euthyroidism, hypothyroidism and hyperthyroidism), background thyroid tissue (normal, solitary or Multinodular goiter), existence regional lymph node in the central and lateral neck compartments (Which was identified through clinical examination or ultrasound of the neck) , histological type of cancer (Papillary, Follicular, Oncocytic carcinoma), tumour focality (Unifocal, Multifocal), TNM category (primary tumor, regional lymph node and distant Metastases), Stage (I to IV), recurrence, sites of recurrence (local, distant, both local and distant), and death. TNM category was recorded based on the eighth edition of TNM AJCC/UICC scoring system (20). Staging is defined based on TMN category and age of individuals under 55 years and older or equal to 55 years. T refers to the primary tumor, which is divided from T1 to T4 based on tumor size, location and spread to adjacent areas. N means metastasis to the lymph nodes in the neck, which includes N1a and N1b. N1a means unilateral or bilateral involvement of zone VI or VII, and N1b includes unilateral or bilateral involvement of zone I, II, III, IV or V lymph nodes. M also means distant metastasis. Disease recurrence was defined as Imaging findings and thyroglobulin level.

The obtained data were analyzed using IBM SPSS software (version 26). Continuous data were expressed as mean ± standard deviation,

and categorical data were expressed as frequencies (%). Comparisons were performed using the independent sample t-test for continuous, and chi-square or Fisher's exact test for categorical variables. The primary endpoint of this study was the recurrence rate of DTC. Univariate logistic regression analysis was conducted to investigate the variables affecting DTC recurrence.

A multivariable logistic regression model with stepwise backward selection was used to identify independent risk factors for recurrence. In addition, univariate and multivariate logistic regression analysis was performed to evaluate the risk factors of death as a secondary endpoint of this study.

For univariate and multivariate analyses, the Odds Ratio (OR) and 95% CI were calculated. Two-tailed p-values of < 0.05 were considered statistically significant.

Results

The present study examined 350 patients over 18 years old diagnosed with differentiated thyroid cancer over a ten-year follow-up period. Recurrence of DTC was found in 94 (26.9%) cases and during the studied period, 17 deaths (4.9 %) occurred in the studied patients. Table 1 shows the demographic and clinical characteristics of the studied patients. 58 (16.6 %) were men and 292 (83.4 %) were women, and their mean age was 40.7±4.7. 10.6% were smoker and 5.1% reported a family history of thyroid cancer in first degree. 89.7% of patients were Euthyroid. Age, sex, smoking and the existence regional lymph node were significantly different between patients with recurrence and those without recurrence of DTC. Also, death was significantly more frequent among older patients, male, smoker and patients with regional lymph node.

Table 1: Demographic and clinical characteristics of 350 studied patients with Differentiated Thyroid cancer

	Total (n=350)	**Recurrence**			**Death**		
		Yes(n=94)	**No(n=256)**	**P-value**	**Yes(n=17)**	**No(n=333)**	**P-value**
Age (year)	40.7±14.7	45.9±17.9	38.8±12.8	< 0.001*	64.2±13.6	39.5±13.7	< 0.001**
Sex							
Male	58 (16.6)	34 (36.2)	24 (9.4)	< 0.001	9 (52.9)	49 (14.7)	< 0.001††
Female	292 (83.4)	90 (63.8)	232 (90.6)		8 (47.1)	284 (85.3)	
Smoking	37 (10.6)	24 (25.5)	13 (5.1)	< 0.001	11 (64.7)	26 (7.8)	< 0.001††
History of thyroid cancer in first degree relative	18 (5.1)	7 (7.4)	11 (4.3)	0.275††	15 (88.2)	317 (95.2)	0.205††
Co-existing thyroid disorder							
Euthyroidism	314 (89.7)	89 (94.7)	225 (87.9)	0.124	16 (94.1)	298 (89.5)	0.855†
Hypothyroidism	21 (6.0)	4 (4.3)	17 (6.6)		1 (5.9)	20 (6.0)	
Hyperthyroidism	15 (4.3)	1 (1.1)	14 (5.5)		0	15 (4.5)	
Background thyroid tissue							
Normal	10 (2.9)	2 (2.1)	8 (3.1)	0.069	0	10 (3.0)	0.756
Solitary nodular goiter	207 (59.1)	57 (50.0)	160 (62.5)		10 (58.8)	197 (59.2)	
Multinodular goiter	133 (38.0)	45 (47.9)	88 (34.4)		7 (41.2)	126 (37.8)	
Cervical lymph node	98 (28.0)	70 (74.5)	28 (10.9)	< 0.001	10 (58.8)	88 (26.4)	0.009**
Sites of recurrence							
Regional	-	67 (71.3)	-		5 (29.4)	62 (80.5)	< 0.001†
Distant	-	8 (8.5)	-		4 (23.5)	4 (5.2)	
Both	-	19 (20.2)	-		8 (47.1)	11 (14.3)	

P-values calculated using *Independent sample t-test, **Mann-Whitney test, †Chi Square test, ††Fisher Exact test

The pathologic characteristics of the studied patients are presented in Table 2. Papillary thyroid carcinoma (89.7%) was the most frequent type of cancer in the studied patients. The tumor was unifocal in 64.0%, primary Tumor in most of the patients was T2, the cancer has involved regional lymph nodes in 103 cases (N1a, N1b, 29.4%) and the cancer has spread to another part of the body in 13 cases (M1, 3.7%). Tumor focality, TNM category were significantly different between patients with recurrence and those without recurrence of DTC. In addition, type of cancer, tumor focality, TNM category were significantly different between patients who died of DTC and patients who survived.

Table 3 represents the findings of the univariate and multivariable logistic regression analyses identifying predictors of recurrence in patients with thyroid tumors. After adjusting for other variables in the model, a 4% increase was observed in the odds of recurrence for each additional year of age (OR 1.044, 95% CI 1.018–1.071, P= 0.001), men showed 5.11-fold higher odds of recurrence compared to women (OR 5.111, 95% CI 2.093–12.482, P= < 0.001). Moreover, the odds of recurrence in patients with regional lymph node was 2.125- fold higher than others (OR 6.125, 95% CI 1.911–19.633, P= 0.002). In addition the patients with T3 and T4 category showed significantly higher odds of recurrence compared to those with the T1 and T2 category (OR 4.179, 95% CI 1.394–12.524, P= 0.011). Furthermore, patients with N1 categories had significantly higher odds of recurrence in comparison to patients with the N0 category (OR 5.626, 95% CI 1.700–18.482, P= 0.005).

The results of univariate and multivariate analyses for identifying risk factors regarding DTC death in studied patients are presented in Table 4. After adjusting for other variables in the model, a 9% increase was observed in the odds of death for each additional year of age (OR 1.096, 95% CI 1.049–1.146, P< 0.001), the patients with smoking had 6- fold higher odds of death (OR 6.002, 95% CI 1.597–22.553, P= 0.008), additionally, odd of death in the patients with M1 category was significantly higher compared to the patients with the M0 category (OR 5.357, 95% CI 1.050–27.332, P= 0.044).

Table 2: Pathologic characteristics of 350 studied patients with Differentiated Thyroid cancer

	Total (n=350)	Recurrence			Death		
		Yes(n=94)	No(n=256)	P-value	Yes(n=17)	No(n=333)	P-value
Histological type of cancer							
Papillary	314 (89.7)	84 (89.4)	230 (89.8)	0.343	12 (70.6)	302 (90.7)	0.032†
Follicular	22 (6.3)	8 (8.5)	14 (5.5)		4 (23.5)	18 (5.4)	
Oncocytic thyroid carcinoma	14 (4.0)	2 (2.1)	12 (4.7)		1 (5.9)	13 (3.9)	
Tumor focality							
Unifocal	224 (64.0)	34 (36.2)	190 (74.2)	< 0.001	5 (29.4)	219 (65.8)	0.004
Multifocal	126 (36.0)	60 (63.8)	66 (25.8)		12 (70.6)	114 (34.2)	
T category (pT)							
T1 (T1a,T1b)	87 (24.9)	6 (6.4)	81 (31.6)	< 0.001	1 (5.9)	86 (25.8)	< 0.001†
T2	140 (40.0)	20 (21.3)	120 (46.9)		2 (11.8)	138 (41.4)	
T3 (T3a,T3b)	103 (29.4)	49 (52.1)	54 (21.1)		5 (29.4)	98 (29.4)	
T4 (T4a,T4b)	20 (5.7)	19 (20.2)	1 (0.4)		9 (52.9)	11 (3.3)	
N category (pN)							
N0	247 (70.6)	23 (24.5)	224 (87.5)	< 0.001	6 (35.3)	241 (72.4)	0.001*
N1 (N1a,N1b)	103 (29.4)	71 (75.5)	32 (12.5)		11 (64.7)	92 (27.6)	
M category							
M0	337 (96.3)	81 (86.2)	256 (100.0)	< 0.001	11 (64.7)	326 (97.9)	< 0.001**
M1	13 (3.7)	13 (13.8)	0		6 (35.3)	7 (2.1)	
Stage							
Stage I	339 (96.9)	83 (88.3)	256 (100)	< 0.001**	11 (64.7)	328 (98.5)	< 0.001**
Stage ≥ II	11 (3.1)	11 (11.7)	0		6 (35.3)	5 (1.5)	

P-values calculated using *Chi Square test, **Fisher Exact test, †Exact test

Table 3. The logistic regression model to identify risk factors for disease recurrence in 350 patients with Differentiated Thyroid cancer

	univariate analysis			multivariate analysis backward model		
	Odds Ratio	**95% CI**	**P-value**	**Odds Ratio**	**95% CI**	**P-value**
Age (year)	1.032	1.016–1.049	< 0.001	1.044	1.018-1.071	0.001
Sex (ref, Female)						
Male	5.478	3.022-9.928	< 0.001	5.111	2.093-12.482	< 0.001
Smoking	6.409	3.103-13.238	< 0.001			
History of thyroid cancer in first degree relative	1.792	0.673-4.769	0.243			
Background thyroid tissue (ref, Solitary nodular)						
Multinodular goiter	1.753	1.085-2.833	0.022			
Cervical lymph node	23.750	12.938-43.598	< 0.001	6.125	1.911-19.633	0.002
Histological type of cancer (ref, Papillary)						
Follicular	1.585	0.634-3.863	0.332	3.322	0.968-11.395	0.056
Oncocytic thyroid carcinoma	0.456	0.100-2.082	0.311	0221	0.034-1.441	0.115
Tumor focality (ref, unifocal)						
Multifocal	5.080	3.065-8.421	< 0.001			
Tumor size (ref, ≤ 2 cm)						
> 2 – 4 cm	2.250	0.866-5.846	0.096	0.996	0.321-3.091	0.994
> 4 cm	16.691	6.771-41.144	< 0.001	4.179	1.394-12.524	0.011
N category (ref, N0)						
N1	21.609	11.876-39.318	< 0.001	5.626	1.700-18.482	0.005

Table 4. The logistic regression model to identify risk factors for disease-specific death in 350 patients with Differentiated Thyroid cancer

	univariate analysis			multivariate analysis backward model		
	Odds Ratio	**95% CI**	**P-value**	**Odds Ratio**	**95% CI**	**P-value**
Age (year)	1.116	1.072–1.163	< 0.001	1.096	1.049-1.146	< 0.001
Sex (ref, Female)						
Male	6.520	2.400-17.715	< 0.001			
Smoking	21.647	7.409-63.253	< 0.001	6.002	1.597-22.553	0.008
History of thyroid cancer in first degree relative	2.792642	0.556-12.553	0.222			
Background thyroid tissue (ref, Solitary nodular)						
Multinodular goiter	1.150	0.427-3.098	0.782			
Cervical lymph node	3.977	1.469-10.769	0.007			
Histological type of cancer (ref, Papillary)						
Follicular	5.593	1.639-19.085	0.006			
Oncocytic thyroid carcinoma	1.936	0.234-16.035	0.540			
Tumor focality (ref, unifocal)						
Multifocal	6.611	1.585-13.408	0.005			
Tumor size (ref, ≤ 2 cm)						
> 2 – 4 cm	1.246	0.111-13.954	0.858			
> 4 cm	11.046	1.424-85.662	0.022			
N category (ref, N0)						
N1 (N1a,N1b)	4.803	1.726-13.363	0.003	3.320	0.846-13.037	0.085
M category (ref, M0)						
M1	25.403	7.314-8.222	< 0.001	5.357	1.050-27.332	0.044

Discussion

DTC is the most prevalent cancer of thyroid DTC represents the most common cancer of the thyroid gland. PTC as the most common type of DTC is generally considered indolent, and characterized by excellent long-term survival outcomes. Its distinctive features include characteristic nuclear morphology and the potential to present as either infiltrative or encapsulated masses. FTC and OTC are the other main classifications of DTC. Overall, DTC has generally have a good prognosis with a long time survival following surgical intervention. However, the possibility of recurrence exists for some individuals after the treatment of DTC. Although DTC is curable but it's proclivity for metastasis imposes significant concerns for disease recurrence. In the present study recurrence and related factors were assessed. Our findings showed that 26.9% developed recurrence during the study period. These results are in agreement with the recurrence rates reported in some other research. In previous studies, the recurrence rate is reported very widely, between 1.4% by Pałyga et al., up to 30% in Mazzaferi et al., study (8, 22). The differences in rates reported across studies could stem from several factors, including differences in the ability to assess response to primary treatment, recurrence diagnosis, different definitions of disease recurrence, differences in the follow up period and differences in study patients' characteristics. The rate of disease recurrence in the present study was higher than the ranges reported in other studies. This discrepancy could be explained by the difference in the characteristics of the patients studied. Most recent studies examined recurrence in patients with an excellent or biochemically incomplete response to the primary treatment, while in the present study, along to these patients, also included patients who had structurally incomplete response, which is more likely to risk of recurrence. Like our study, Wang et al, in a group of children and adolescents reported rate of 28.6% recurrence at 10 years of follow up (23). In the Wang et al, study, patients with structural disease that appeared in the cervical area or progressive disease in distant metastases were documented as recurrence. In addition to all of this, these findings highlight the importance of recurrence in patients with DTC and show the essential suitable follow up after treatment to early identify patients with recurrence. This is particularly important when inadequate surveillance can lead to late identification of recurrence and delayed treatment. On the other hand, unnecessary postoperative monitoring can cause concern and negative psychological impacts and distress on the patients. So, it is need to follow the processes that purpose to identify groups of patients with similar prognosis to plan adequate surveillance and follow up to maximize the benefit for patients. Identifying factors associated with DTC recurrence is one way that can help with these processes.

Previously several risk factors have been identified as independent predictors of recurrence in DTC patients. Age, gender, tumor size, regional lymph nodes involvement, distant metastasis and histological type and grading are the most significant prognostic factors for recurrence (22-31). In our multivariate analysis a strong association was found between male gender, tumor size more than 4 cm (OR, 4.179) and regional lymph nodes involvement (N1 OR, 5.626) with DTC recurrence. In our study the regional lymph node increases the risk of recurrence by more than 6 times. It can be frequently associated with macroscopic lymph node metastases, more aggressive disease, multifocal tumor association, which can be effective in disease recurrence. Similar to other studies our results show that the size of the primary tumor and lymph node metastases have been recognized as statistically significant predictors of recurrence (22-28). Studies reported different tumor size as a prognostic factor for disease recurrence. One study show that tumor size > 2 cm is a significant factor for disease recurrence (26) and another concluded that tumor size > 3.5 cm is a significant factor (27). But most of the studies reported tumor size > 4 cm is a significant factor. A recent study showed that lymph nodes metastases is associated with recurrence and tumor greater than 4 cm increases the risk of recurrence by more than 8 times (24). A study by Wan et al, reported that recurrence risk rates were 3.7 and 3.6 times higher in the presence of lymph nodes and higher tumor size, respectively (25). In Pałyga et al, study (22) regional lymph node increases the risk of recurrence by more than 3.9 times and Weber et al, showed that initial

regional lymph node was significantly associated with a higher recurrence rate (28). In our study the recurrence risk was more than 5 times higher in males than females, which is consistent with previous studies that show male sex as an independent risk factor in DTC recurrence (23, 29, 30). This relationship can be explained by the following possible causes including; : thyroid cancer in men tends to present with more aggressive features, delayed diagnosis and is often diagnosed at more advanced stages of disease in men, and biological and hormonal differences between men and women. On the other hand in contrast to our study some other studies found no significant association between sex and difference DTC recurrence (22, 24, 31). The difference in findings between studies may be due to the small rate of disease recurrence in previous studies which could have led to sparse data and reduced the statistical power of the studies in finding the relationship between sex and disease recurrence. Evidence from studies over the past decades has led to the development of several prognostic staging systems based on some risk factors including tumor size and involvement lymph nodes to be able to identify patients at risk of recurrence. Most of these protocols do not consider the patient's gender in measuring the risk, which is suggested in light of the results of our study along with other studies, to consider gender of the patients as an important factor for evaluating risk of recurrence for DTC.

Mortality rate as our second objective, in the studied DTC patient was 4.9%. This is in line with several studies. In the Pałyga et al, study crude mortality rate in DTC patients was 5.6% however, 0.1% of patients died from DTC (22). In a cohort study by Jeon et al, the crude mortality rate was 3.8% and disease-specific mortality was 1.9% (32). In the present study, the crude death rate is calculated not deaths from DTC, because we assessed the patients records and the specific cause of death was not reported. The significant factors related to DTC mortality were older age, smoking, and metastases which is in line the previous findings (32-36). In general, DTC is a slow-growing cancer and its prognosis is excellent but it is important to know its related mortality risk factors. The low number of deaths in the present study could have reduced the statistical power of the study to accurately identify factors related to death, which is likely to be a problem in other studies. Therefore, cohort studies with large sample sizes need to be designed to properly elucidate factors related to death in DTC patients. It is noteworthy that in the present study the number of samples was relatively small and due to the implementation of the research in a specialized endocrine referral center. Moreover, since the present study, like many others, was conducted retrospectively, it was not possible to evaluate some related molecular and genetic markers to examine recurrence and mortality.

Conclusion

The recurrence and mortality rates were significantly higher in older age, smokers, men, the presence of regional lymph node, and high stage. Given the impact of the identified risk factors, the implementation of appropriate therapeutic interventions and regular follow-up after the initial treatment are warranted. It is suggested that a prospective multicenter study be conducted to obtain more accurate results

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Ethical Approval

This study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1402.0475).

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