

Retrospective Study of a Cohort of Tunisian Patients with Thyroid Cancer

Case Study

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Abstract

Thyroid cancer is a complex disease where many factors influence its morbidity and mortality. Analyzing the clinic pathological parameters of this malignant disease in a series of thyroid cancer patients allows to evaluate their clinical behavior and outcomes.

A retrospective analysis on clinical and pathological data of 92 patients with thyroid cancer was carried. Our results indicate that the mean age of the patients was 49.3 ± 14.5 , that women accounted for 79.4% of the patients, and the mean follow-up duration was 67.4 months (range: 7–216 months). Papillary carcinoma was the most common histological type, with 84 cases (91.3%). Low pathological tumor-node-metastasis stage was observed in 39.4% of the patients. Ten year survival was 21.3%. Older patients were associated with advanced stage (stage III and IV) and with high recurrence rate. Understanding better how certain clinic pathologic variables influence disease progression in specific population groups has the potential to allow clinicians to tailor diagnostic and therapeutic options.

Keywords: Thyroid Cancer; Clinic Pathological Parameters; TNM Staging; Histology.

Introduction

Thyroid cancer is the most common endocrine cancer and its incidence is increasing strikingly in many countries [1-3]. Thyroid malignancies are classified into four main histology groups and differentiated carcinoma (DTC) (papillary carcinoma and follicular carcinoma) is the more prevalent. Thyroid cancer is more frequent in female than in male (sex ratio ≈ 3) [4] and it occurs at any age although it is common after 30 years and significantly more aggressive in older subjects [5]. Recently, many studies have shown that there is considerable variability on presentation and outcomes of thyroid cancer across ethnic/racial groups and suggested that factors beyond socioeconomics may contribute to such differences [6, 7]. In fact, diet, lifestyle, environmental exposure, and comorbid conditions are known to initiate epigenetic changes and factors that cause such epigenetic changes are known to disproportionately affect various racial and ethnic populations.

In this study, we performed a retrospective analysis of a series of 92 patients with thyroid cancer monitored in the nuclear medicine department of Sfax, aiming to evaluate their clinical behavior and outcomes and to seek if there is a difference with respect to what has been found in other ethnic groups.

Materials and Methods

A retrospective study was carried on using clinical records of 92 thyroid cancer patients consulting at Habib Bourguiba University Hospital during the period between 1997 and 2008. Clinical data were extracted from the medical record, including details on diagnosis, stage, age, tumor factors (size and histology), Tg level, treatment details, response to treatment and disease status. Follow-up program was based on periodical clinical controls and a series of investigations, including serial assessment of Tg and anti-Tg antibody, imaging (Magnetic resonance imaging, cervical echography, scanner) and ¹³¹I diagnostic whole-body scan. Patients

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with persistent or recurrent disease after radioiodine therapy were submitted to additional cancer treatment as appropriate.

All the patients included in the analysis had total thyroidectomy and were alive at the moment of the study. The primary tumor was histologically classified according to the World Health Organization criteria [8] and staged according to the tumor–node–metastasis (TNM) classification of the UICC/AJCC (Union for International Cancer Control/American Joint Committee on Cancer) [9].

Statistical analysis was performed using SPSS 21.0 software. Association between categorical variables was evaluated using a Chi-square test or Fisher's exact test. A $p \leq 0.05$ was considered significant. Data on survival for the patients were tabulated by Kaplan-Meier product-limit estimates of survival. A log-rank test was used for comparison of survival curves. A $p \leq 0.05$ was

considered significant.

Results

Clinical and pathological features of the analyzed cohort are illustrated in Table 1. Seventy three of the patients were female and female/male ratio was 2.8: 1. The mean age of the cohort at diagnosis was 49.3 ± 14.5 years ranging from 20 to 79 years and the median age was 49.5 years. In women, the mean age was 49.6 ± 15.1 years, while in men it was 48.7 ± 13 years. The patients were followed-up for a mean duration of 67.4 months (range: 7–216 months). For 84 patients (91.3%), the histology of primitive tumor was a papillary carcinoma. Follicular carcinoma was found in 6 cases (6.5%). An evidence of recurrence or metastases was observed in 34 patients (37%). Metastases' prevalence was 41.2% for node metastases, 32.3% for pulmonary metastases and 17.6%

Table 1. Clinical and pathological features of thyroid cancer patients.

	Patients number	Frequency (%)
Gender		
Male	19	20.6
Female	73	79.4
Age (years)		
< 45	39	42.4
≥ 45	53	57.6
Histology		
Papillary	84	91.3
Follicular	6	6.5
Other	2	1.2
Lymph node		
Positive	43	18.9
Negative	40	81.1
Extrathyroidal extension		
Positive	23	25
Negative	69	75
Distant metastasis		
Positive	20	23.2
Negative	66	76.8
Tumor stage		
Stage I	34	39.5
Stage II	18	20.9
Stage III	21	24.4
Stage IV	13	15.1
Patient status		
Complete response ^a	51	55.4
Evolution with therapeutic response ^b	31	33.7
No therapeutic response ^c	10	10.9

^a The scan shows no iodine capture; TG is undetectable and morphological examinations were normal.

^b The iodine capture is decreasing and the thyroglobulin level is declining.

^c Permanent iodine capture with stable or increasing thyroglobulin level or the presence of metastases.

for bone metastases, respectively. Extrathyroidal extension was found in 23 patients (25%). Regarding the tumor-node-metastasis (TNM) staging system, only the data of 86 patients were available. Thirty four patients (39.5%) had stage I tumors, 18 (20.9%) had stage II tumors, 21 (24.4%) had stage III tumors and 13 (15.1%) had a stage IV tumors.

Clinic pathological parameters and patients' gender

No significant correlation was found between the gender and the clinic pathological parameters. However, at 10% significance level, females are more likely to have papillary cancer than males (95.5% versus 82.6%, $p=0.065$). Also, stage 3 or greater disease at the time of diagnostic tends to be more frequent in males compared to females (36.9% versus 47.6 %, $p=0.09$).

Clinic pathological parameters and patients' age

Analysis of the clinic pathologic characteristics (Table 2) showed

a statistically significant difference between patients' age and disease staging ($p<10^{-3}$). Stage I was more prevalent in younger patients (<45 years, 73.6%) while the stage III and IV were more frequent in older patients (≥ 45 years). Also, a significant correlation was shown between age and patients status ($p=0.03$). A high patient recurrence rates, reaching 45.2%, was observed in older patients. Patients' remission was observed in 59% of younger patients. On the other hand, a positive correlation was found between Tg level and patients' age. The highest Tg levels were observed in elderly ($p=0.05$). These associations were also found in multivariate analysis.

Clinic pathological parameters and survival

Mean time of follow-up was 67.4 months (range: 7–216 months) from the diagnosis. Survival by Kaplan-Meier curves was 42.7% and 21.3% at 5 and 10 years, respectively (Figure 1). A better likelihood of survival over time without being significant was observed in female, papillary tumors, patients without extra

Table 2. Correlation results between clinic pathological parameters and age of patients.

	< 45 years n (%)	≥ 45 years n (%)	<i>p</i> - value
Gender			
Male	29 (31.5)	10 (10.7)	1 ^a
Female	39 (42.4)	14 (15.2)	
Histology			
Papillary	39 (42.4)	45 (48.9)	0.027 ^a
Follicular	0 (0)	6 (6.5)	
Other	0 (0)	2 (2.2)	
Tg level (ng/ml)			
mean \pm SE	11.24 \pm 6	236.9 \pm 111.63	0.05 ^b
Lymph node			
Negative	14 (16.9)	23 (27.7)	
Positive	26 (31.3)	20 (24.1)	
Extrathyroidal extension			
Positive	28 (31.5)	10 (11.2)	0.807 ^a
Negative	39 (43.8)	12 (13.4)	
Distant metastasis			
Positive	6 (6.5)	14 (15.2)	0.306 ^a
Negative	33 (35.9)	39 (42.4)	
Stage			
Stage 1	28 (32.5)	6 (7)	$<10^{-5a}$
Stage 2	6 (7)	12 (13.9)	
Stage 3	4 (4.6)	17 (19.8)	
Stage 4	0 (0)	13 (15.1)	
Patient status			
Complete response	23 (25.2)	28 (30.8)	0.0071 ^a
Evolution with response	16 (17.6)	14 (15.4)	
No therapeutic response	0 (0)	10 (11)	

^a *p*-value of fisher exact test; ^b *p*-value of student test.

thyroidal extension and patients who have responded to treatment. Also, no significant differences were observed according to age, TNM stages, metastasis status and lymph node metastasis.

Discussion

Multiple retrospective case series and registry studies have examined important prognostic factors in TC, but to our knowledge it is first study that was performed in Tunisian population group. The analysis of our TC cohort reveals interesting epidemiological and clinical points that allow us to assess the status of this malignant disease in our population and to check if there is a veritable difference in the clinical presentation of thyroid cancer across racial and ethnic groups as has been noted in some recent studies (Table 3). Our results indicate a relative distribution of papillary and follicular carcinoma which strongly unbalanced in favour of papillary forms (91.3%). This result probably reflects an increasing peak of papillary carcinoma in the last years as was registered in many different racial and ethnic groups (Table 3). Except German population group, the frequency of PTC was above 90%. The mean age of our cohort and female/male ratio were comparable with the racial groups range in the studies of Harari et al. [7] and Moo-Young et al. [6] and especially with the non-hispanic white group (49.7 and 2.79 for the mean age and female/male ratio, respectively). Stage I was the most prevalent among the patients analyzed (39.5%); but its frequency was relatively low compared to other studies where it can reach up 74% (for Hispanic) [6]. Prevalence of node metastases (18.9%) and extra thyroidal extension (25%) were in the lower range compared with previous reports (up to 45% and up to 55%, respectively) (Table 3). However, the prevalence of distant metastases was 23.2% while it doesn't exceed 10% in other studies [6, 7]. All these figures together were in favour of the finding suggesting that there is considerable variability in the clinical presentation of thyroid cancer across ethnic groups as well as socioeconomic and cultural factors [6, 7]. Racial/ethnic minorities and those in a lower socioeconomic class suffer a disproportionate morbidity and mortality [7]. Studies have attributed these healthcare inequalities to differences in access to care and/or to living in resource-poor neighborhoods. Still others suggest that providers may have inherent biases in their treatment of different races

despite equal access to care. There have also been implications of external sources affecting disease incidence and severity, including socioeconomic factors or less healthy lifestyles [6]. However, it is important to note as any other type of disease that difference in disease biology and genetic variance contribute to disparities in disease presentation and outcomes [13].

The analysis of the clinic pathologic characteristics of our cohort showed no statistically significant difference with gender. Many authors describe poorer outcomes in men with DTC than women [14-16], though others find no effect of gender on mortality [17]; thus, there is weak consensus regarding the effect of gender on outcomes of DTC.

Multiple population-based studies, have found that age was an important independent prognostic indicator for differentiated thyroid cancer [18, 19]. Also, thyroid cancer is the only malignancy with age as a prognostic indicator in the majority of staging systems [20, 21]. The current study revealed that thyroid cancer in older patients was associated with advanced stage (stage III and IV) and with high Tg level and recurrence rate. This result suggests that older patients were associated with poor prognosis. In fact, many studies focusing on age effect in patients with thyroid cancer have shown that elderly patients were present with poor prognostic factors including advanced stage, lymph node metastasis and distant metastasis, as compared with younger patients [22] and an increased mortality rate with age [23]. Alternative hypotheses for the association between advanced age and poor prognosis with thyroid cancer have been proposed including a decline in immune system with age and a general increase in mortality from all causes with age [24].

Analyzing survival, we estimated that the likelihood of a survival in patients was 21.3% at 10 years. No significant differences in the survival were observed with the clinic pathological parameters of the patients. However, a better likelihood of survival over time was observed in female, papillary tumors, patients without extra thyroidal extension and patients who have responded to treatment. In fact, it was shown in several studies that the survival rate is influenced by many parameters. A significantly reduced mortality was associated with the female gender [23]. In the study of Gilliland et al. [18], the authors showed that patients with follicular

Figure 1. Survival curve of the thyroid cancer patients.

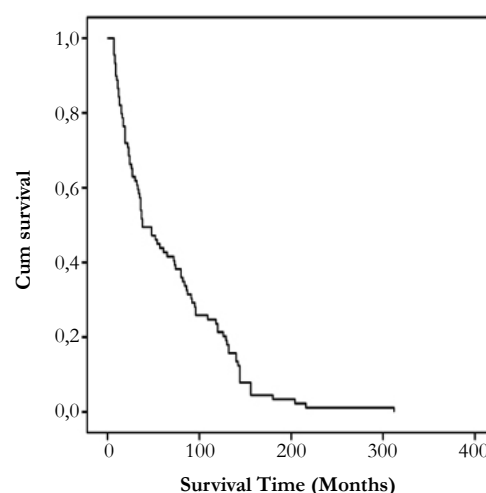


Table 3. Clinicopathological parameters variation across racial and ethnic groups.

References	Population	Age (years) (mean/median)	Gender ¹	Histology (%)	Positive lymph node metastasis (%)	Positive distant metastasis (%)	Positive Extrathyroidal extension (%)	Tumor stage (%)
Present study	Tunisian	49.3 / 49.5	2.8	PTC 91.3 FTC 6.5	18.9	23.2	25	Stage 1 39.5 Stage 4 15.1
10	Algerian	46.7 / -	0.03	PTC 62.5 FTC -	-	-	-	Stage 1 50 Stage 4 -
11	Brazilian	44.5 / -	4.5	PTC 96.6 FTC 1.3	-	-	15	Stage 1 74.6 Stage 4 -
6	African american	-/ 48	4.8	PTC 93 FTC 4	7	2	17	Stage 1 73 Stage 4 4
	Asian	-/ 47	5.2	PTC 93 FTC 4	13	3	25	Stage 1 71 Stage 4 8
	Non hispanic	-/ 49	3.1	PTC 94 FTC 3	12	1	19	Stage 1 74 Stage 4 5
	Hispanic	-/ 44	4.8	PTC 95 FTC 2	18	2	22	Stage 1 73 Stage 4 7
23	USA	44.8 / 43	3.5	PTC 88 FTC 12	28.8	1.9	-	Stage 1 76.5 Stage 4 8.13
12	Korean	48.6 / -	4.5	PTC 91.5 FTC 7.3	44.4	5.6	54.8	-
31	Italian	42.4 / 42	3.1	PTC 91 FTC 9	22.4	2	18.3	Stage 1 67.4 Stage 4 9.7
4	German	-/-	2.2	PTC 71.3	19	7	-	Stage 1 28
				FTC 21.35				Stage 4 19

¹ Female/male ratio, PTC: papillary thyroid cancer, FTC: follicular thyroid cancer.

cancer have lower survival rates than those with papillary cancer, but they noted that the prognosis is more strongly determined by tumor staging and other factors than by tumor histology. Also, patients with extra thyroidal extension were associated with more than 3-fold risk of recurrence and death [25]. Despite that patients' age was not correlated with survival rate in our cohort, many studies have shown that age played a significant role in the survival disparity [26, 27]. A shorter survival was associated with older age and as explanation to this relationship it was suggested that loss of radioiodine avidity with age likely plays a role. The incidence of radioiodine resistant disease was significantly lower in younger patients than in older patients (14.6% versus 44%, respectively), and the risk for mortality was 5.4 times higher if aged > 45 years versus < 45 years [26]. Even in the presence of distant metastases, age remains a strong prognostic indicator [27].

Much controversy exists over the clinical importance of lymph node metastases. In our study we failed to find a significant correlation between survival and patients with and without lymph node metastasis. This finding was observed in several studies [28]. However, other studies have found that the presence of lymph node metastasis leads to an increased risk of recurrence [29] and reduced survival [30, 31]. These findings were also observed in SEER (Surveillance, Epidemiology and End Results) database study [24]. The crucial factor in this study, however, was patients' age; the presence of lymph node metastases had no effect on survival in patients aged < 45 years. In patients aged > 45 years, however, there was an associated 46% increased risk of death. Failure to account for patients' age may partly explain why studies have found inconsistent patterns of clinical outcomes in the presence of lymph node metastases. For this reason, we tested the correlation between survival and lymph node metastasis but

this time taking into account the age of patients but no significant correlation was observed in the 2 age groups (p=0.09 for patients with age <45 years and p= 0.87 for patients with age ≥ 45 years).

Conclusion

This study reports a retrospective view of the thyroid cancer in Tunisian population group and to our knowledge it is first study that was performed in our population. Determining the clinic pathological variables specific to each population allows to better understanding how they influence disease progression and has the potential to allow clinicians to tailor diagnostic and therapeutic options.

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