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Research Article

Recurrence Risk in Thyroid Cancer Patients after Thyroidectomy

Shaza Fadel Alkilany[1], Eman Mohamed Mahfouz[1], Eman Sameh Mohamed[1], Eman Ramadan Ghazawy[1], Yasser Mohammed Abdelgwad[2], Nsreen Ragab Ali Mohamadien[3], Medhat Mounir Soliman[2] and Marwa Gamal Abdelrehim[1]

[1] Department of Public Health, Faculty of Medicine, Minia University, Minia, Egypt
[2] Department of Surgical Oncology, Minia Oncology Center, Minia, Minia, Egypt
[3] Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, Assuit, Egypt

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Abstract

Background: With rising thyroid cancer incidence in Egypt, understanding recurrence patterns and risk factors is crucial for optimizing survivorship care. This study examined disease-free survival (DFS) and prognostic factors for recurrence in Egyptian patients. **Methods:** Retrospective analysis of 99 pathologically confirmed thyroid cancer patients treated at the Minia Oncology Center between April 2022 and March 2023. DFS was estimated by Kaplan-Meier method. Multivariate Cox regression identified factors associated with recurrence. **Results:** Out of the 99 TC patients, 8 patients recurred (8.8%). Cumulative 1-, 5-, 10-year DFS was 98%, 94.6% and 83.5%. Regional metastasis at diagnosis (Hazard ratio [HR]=7.2, 95% CI 1.38-37.02, p=0.019) and diabetes (HR=26.2, 95% CI 1.03-33.6, p=0.047) were independent predictors of recurrence after adjusting for age and sex. **Conclusions:** Thyroid cancer patients treated at Minia Oncology center showed long-term DFS, with advanced stage at presentation and diabetes indicating greater recurrence risk. Understanding risk factors for recurrent disease could help personalize treatment and long-term follow-up in these patients.

Keywords: thyroid cancer, recurrence, survival, disease-free survival

Introduction

Thyroid cancer represents the most common endocrine malignancies, with rising incidence rates observed globally over recent decades [(1)].

Although most thyroid cancers have favorable prognoses with appropriate treatment, disease recurrence poses a persistent clinical challenge[(2)]. Around 5-30% of patients experience recurrent thyroid cancer depending on initial tumor characteristics and treatment modalities [(3,4)]. Recurrence rates further differ among histological subtypes. For instance, approximately 10-15%[(5)] of patients with papillary thyroid carcinoma (PTC) have recurrence compared to higher rates exceeding 30% in those with more aggressive variants like tall cell, columnar cell and diffuse sclerosing PTC [(6)].

Around 60% to 75% of recurrence instances are observed in cervical lymph nodes, with approximately 20% occurring in the thyroid bed, and the remaining 5% manifesting in the trachea and muscles [(5)].

Recurrence risk is multifactorial - encompassing not only clinicopathologic features like tumor size, lymphovascular invasion and extrathyroidal extension, but also emerging molecular markers such as BRAF V600E mutation status and microRNA expression[(7,8)]. Improving recurrence risk prediction allows clinicians to better select who should receive aggressive multifaceted treatment to minimize future relapse versus lower-intensity regimens to limit overtreatment.

A number of clinical and molecular factors have been studied for their potential to predict risk of recurrence in thyroid cancer patients. Among the most consistent clinical predictors of recurrent thyroid cancer are primary tumor size, extrathyroidal extension at initial diagnosis, and lymphovascular invasion. Multiple studies have shown tumor size over 4 cm confers higher risk of both locoregional and distant recurrence on long-term follow-up [5]. Extrathyroidal spread into surrounding soft tissues and vascular structures also remains significantly associated with thyroid cancer persistence/recurrence in multivariate adjustment models[5,9]. The presence of cervical lymph node metastases in thyroid cancer patients is associated with worse recurrence-free survival [10]. The American thyroid association (ATA) guidelines recommend total thyroidectomy plus therapeutic lymph node dissection for clinically involved cervical nodes in differentiated thyroid cancer. However, routine prophylactic node dissection remains controversial due to questionable long-term benefits versus increased risks of surgical complications like hypoparathyroidism and nerve damage [11].

This study aimed to investigate factors associated with the recurrence of thyroid cancer in patients treated at the Minia Oncology Center.

Methods:

Study Design

This is a cross-sectional design with retrospective review of clinical data from medical records of thyroid cancer patients.

Setting

This study was conducted at the Minia Oncology Center, Minia Governorate, Egypt. Participants consisted of thyroid cancer patients attending scheduled follow-up visits at the Nuclear Medicine outpatient clinic at the Minia Oncology Hospital during the period from April 2022 to March 2023.

Participants

A total of 99 thyroid cancer patients were recruited. To be eligible for participation in the study, individuals had to meet the following criteria: aged ≥18 years at diagnosis, histopathological confirmation of thyroid cancer, and ≥1-year post-thyroidectomy. Exclusion criteria included those with persistent metastatic disease after initial treatment.

Definition of recurrence:

In the present study, recurrence was defined as any structural evidence of disease identified one year after surgery or later during follow-up, in a patient considered disease-free after primary treatment, according to a combination of results on ultrasonography, fine-needle aspiration, and computed tomography [12]

Data Collection

After obtaining informed consent, data regarding thyroid cancer patients was primarily obtained through personal interviews conducted with each participant. These interviews were comprehensive and covered various aspects, including:

Demographic Information: This included details about the participant's age, sex, residence, marital status, income, education level, and occupation.

Medical History: Participants were questioned about their medical history, particularly any family history of thyroid cancer, any previous exposure to radioactive iodine treatment, the duration of time since their initial thyroid cancer diagnosis, and any comorbidities or other health conditions.

In addition to the information gathered during personal interviews, specific medical data related to thyroid cancer, such as surgical details, staging and recurrence information, were verified for all participants through a thorough review of their medical records at the Minia Oncology Center. Tumors were classified histologically according to the World Health Organization criteria [13]. Cancer stage was classified into localized, regional, or distant categories based on the Surveillance, Epidemiology, and End Results Program (SEER) summary stage 2000 [14].The SEER summary stage codes and their definitions are as follows:

- Code 0: In situ
- Code 1: Localized only
- Code 2: Regional by direct extension only
- Code 3: Regional lymph nodes only
- Code 4: Regional by BOTH direct extension AND lymph node involvement
- Code 7: Distant site(s)/node(s) involved
- Code 8: Benign/borderline
- Code 9: Unknown if extension or metastasis (unstaged, unknown, or unspecified)/ Death certificate only case

Statistical Analysis

Descriptive statistics are presented as mean ± standard deviation (SD) for continuous variables and percentage for categorical variables. Time to recurrence was analyzed using Kaplan-Meier curves with comparison of groups by the log-rank test. Cox proportional hazards regression analyzed factors associated with recurrence risk, adjusted for covariates. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated. Variables with a univariate p-value less than 0.1 were considered as candidates for entry into the multivariate regression models. Statistical analyses were conducting using SPSS version 27 (IBM Corp, Armonk, NY). A p-value <0.05 was considered statistically significant.

Results

In this study, 99 thyroid cancer patients were analyzed retrospectively at Minia Oncology Center, Egypt. The study included 88 females and 11 males with a mean age at diagnosis of 41.3 ± 13.9 years.

The study included 99 thyroid cancer patients, of whom 88.9% were female. Mean age at diagnosis was 41.3 ± 13.9 years. Average length of follow-up was 4.98 ± 5.28 years. Majority of patients were partnered (87.9%), resided rurally (82.8%), reported income meeting just routine expenses (51.5%), in debt (33.3%), and were unemployed (70.7%). In terms of education, 60.6% had no formal schooling while 22.2% attained secondary level or above. Family history of thyroid cancer was present in 13.1%. Comorbid diabetes and hypertension were reported in 13.1% and 18.2% respectively (Table 1).

The studied patients were predominately papillary carcinoma (88.9%), with mean tumor size of 27.9 ± 23.5 mm. Majority underwent total thyroidectomy (94.9%) and were diagnosed at localized stage (66.7%). Post-operative radioactive iodine (RAI) treatment was administered to 80.8% of patients, yielding complete ablation in 37.8% (Table 2).

Table 3 provides disease-free survival (DFS) outcomes for 99 patients with thyroid cancer, 8 (8.8%) developed recurrence over a mean follow-up of 22.4 years. Cumulative DFS at 1, 5, 10 and 15 years was 98%, 94.6%, 83.5% and 67.4% respectively for the total sample.

When stratified by sex, cumulative 1, 5, and 10-year DFS rates were high for both females (97.7%, 93.9%, 79.2%) and males (100% at 1, 5 and 10 years). There was no significant difference in DFS between males and females (log-rank p=0.602).

Analyzed by tumor stage (Fig.1), localized disease had higher DFS compared to those with metastatic tumors at diagnosis. The 1, 5, 10 and 15-year DFS was 100%, 97.3%, 90.3% and 80.3% for localized cases, versus 93.9%, 89.2%, 66.9% and 33.5% for stage IV disease (log-rank p=0.028).

Table 4 presents the results of Cox regression analysis, examining the factors associated with recurrence in thyroid cancer patients. In unadjusted Cox regression analysis, patients with advanced tumor stage at diagnosis had a 4.4 times higher risk of recurrence (95% CI 1.04-18.6, p=0.004) compared to those with localized disease. In multivariate modeling adjusted by age and sex, regional metastasis (HR 7.15, 95% CI 1.38-37.02, p=0.019) and presence of diabetes (HR 5.9, 95% CI 1.03-33.6, p=0.047) were independent predictive factors for recurrence.

Table 1: Sociodemographic and Clinical Characteristics of Thyroid Cancer Patients (n=99)

	All cases (n=99)
Sex	
Male	11 (11.1%)
Female	88 (88.9%)
Age at diagnosis (years)	41.3±13.9 (18-76.6)
Survival time (years)	4.98±5.28 (1.03-28.79)
Partnered marital status	
No partner (Single, divorced, or widowed)	12 (12.1%)
With partner	87 (87.9%)
Residence	
Urban	17 (17.2%)
Rural	82 (82.8%)
Income	
In debt	33 (33.3%)
Just meet routine expenses	51 (51.6%)
Meet routine expenses and emergencies	14 (14.1%)
Able to save money	1 (1.0%)
Education level	
Illiterate	60 (60.6%)
Primary/Prep	17 (17.2%)
Secondary or above	22 (22.2%)
Employment status	
Unemployed	70 (70.7%)
Employed	29 (29.3%)
Family history of thyroid cancer	
No	86 (86.9%)
Yes	13 (13.1%)
DM	
No	86 (86.9%)
Yes	13 (13.1%)
HTN	
No	81 (81.8%)
Yes	18 (18.2%)

Numerical data expressed as mean ± standard deviation (SD). Categorical data are presented as numbers (percentages).

Table 2: Pathological and Treatment Characteristics of Thyroid Cancer Patients (n=99)

	All cases (n=99)
Pathology	
PTC	88 (88.9%)
FTC	8 (8.1%)
MTC	2 (2.0%)
OCA	1 (1.0%)
Size (mm)[a] (n=49)	27.9±23.5 (2.0-100.0)
Surgery	
Total or near-total thyroidectomy	94 (94.9%)
Hemithyroidectomy	5 (5.1%)
Stage	
Localized	66 (66.7%)
Regional metastasis	33 (33.3%)
Radiotherapy	
No	96 (97.0%)
Yes	3 (3.0%)
RAI[b]	
No	19 (19.2%)
Yes	80 (80.8%)
Outcome of RAI (n=45)	
Failed	1 (2.2%)
Partial response	27 (60.0%)
Complete ablation	17 (37.8%)

Numerical data expressed as mean ± standard deviation (SD). Categorical data are presented as numbers (percentages).
[a] 50 missing values for this item
[b] 34 missing values for this item from who had RAI
PTC= papillary thyroid carcinoma, FTC= follicular thyroid carcinoma, OCA= Oncocytic carcinoma; PDTC: poorly differentiated thyroid carcinoma; ATC: anaplastic thyroid carcinoma; MTC: Medullary thyroid carcinoma
RAI = Radioactive Iodine

Table 3: Disease-free survival (DFS) of patients with thyroid cancer

	Total cases	Recurrence	Censored cases	Survival time in years		Cumulative 1-year survival	Cumulative 5-year survival	Cumulative 10-year survival	Cumulative 15-year survival
	No.	N (%)	N (%)	Mean±SE	95% CI	%	%	%	%
All cases	99	8 (8.8%)	91(91.9%)	22.4±2.2	(18-26.7)	98%	94.6%	83.5%	67.4%
Sex									
Females	88	7 (8%)	81 (92%)	22.5±2.4	(17.7-27.3)	97.7%	93.9%	79.2%	69.3%
Males	11	1 (9.1%)	10 (90.9%)	18.4±2.6	(13.3-23.5)	100%	100%	100%	66.7%
Log rank test = 0.272 ; p = 0.602									
Stage									
Localized	66	3 (4.5%)	63(95.5%)	24.9±2.2	(20.6-29.1)	100%	97.3%	90.3%	80.3%
Regional Metastasis	33	5 (15.2%)	28(84.8%)	10.7±0.8	(9.1-12.4)	93.9%	89.2%	66.9%	33.5%
Log rank test = 4.824 ; p = 0.028*									

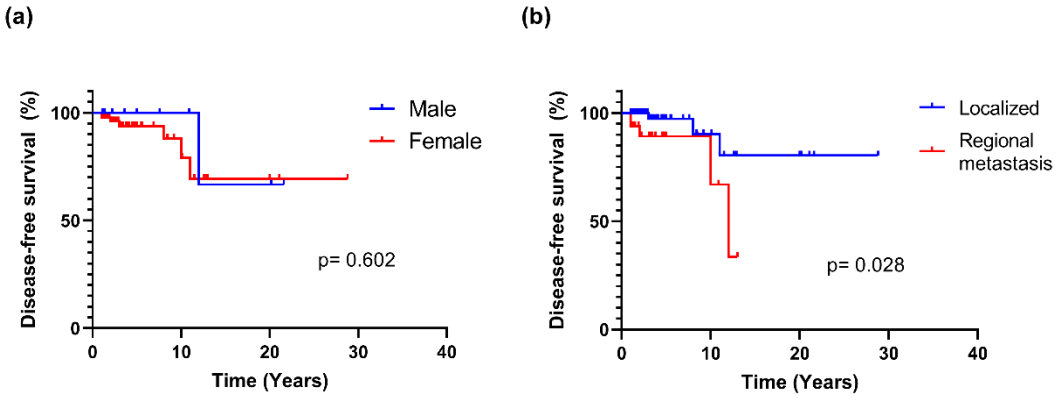

Fig.1 Kaplan-Meier curves estimating disease-free survival according to sex (**a**) and the presence of metastasis (**b**).

Table 4: Cox Regression for Factors Associated with Recurrence in Thyroid Cancer Patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Sex				
Male	1 (ref.)		1 (ref.)	
Female	1.7 (0.2-14.7)	0.607	7.25 (0.6-94.8)	0.131
Age at diagnosis (years)	1 (0.9-1.1)	0.917	1.01 (0.95-1.08)	0.785
Stage				
Localized	1 (ref.)			
Regional metastasis	4.4 (1.04-18.6)	0.004*	7.15 (1.38-37.02)	0.019*
DM	3.7 (0.9-15.9)	0.074	5.9 (1.03-33.6)	0.047*
Family history of TC	1.8 (0.4-8.9)	0.491		
Pathology				
PTC	1 (ref.)			
Others	0.04 (0-246.4)	0.467		
Size (mm)	1 (0.97-1.1)	0.511		
HTN	2.1 (0.4-10.7)	0.359		
Surgery				
Total or near-total thyroidectomy				
Hemithyroidectomy	2.3 (0.3-19)	0.452		
RAI	25.3 (0.02-322069.1)	0.503		
Radiotherapy	0.1 (0-27653.9)	0.647		

PTC= papillary thyroid cancer
RAI = Radioactive Iodine

Discussion

In this retrospective analysis of 99 thyroid cancer patients from Minia Oncology Center in Egypt, long-term disease-free survival was observed, with only 8 patients (8.8%) experiencing recurrence. Tumor stage and diabetes comorbidity were significant prognostic factors for recurrence in Cox regression modeling.

The current study observed a recurrence rate of 8.8% among individuals who underwent initial surgical intervention for thyroid carcinoma. This finding aligns with a study conducted by Amin in 2020, which reported a recurrence rate of 7.9% in differentiated thyroid cancer patients who received surgical intervention at their institution[15]. In contrast, (Lim et al. (2019) found that 37.2% of patients in their study experienced a recurrence of thyroid cancer [16]. One potential explanation for the relatively low 8.8% long-term recurrence rate observed in the current study is that the vast majority (94.9%) of patients underwent total or near-total thyroidectomy as initial treatment. More extensive primary surgical resection has been associated with reduced loco-regional relapse rates in some studies, as residual microscopic disease can be eliminated [17, 18].

Patients with localized disease showed lower recurrence rates (4.5%) compared to those with regional metastasis (15.2%). Localized disease had 5-year survival rate of 97.3%. In contrast, regional metastasis is associated with lower 5-year survival rates (89.2%) (p= 0.028). These results align with previous research that has consistently identified an increased risk associated with advanced disease stages. The study by Amin et al. (2020) conducted a study with the objective of identifying risk factors and outcomes of recurrent well-differentiated thyroid cancer. The study included 478 patients who underwent initial surgical management of well-differentiated thyroid carcinoma between 2002 and 2017. The results indicated that

patients who experienced recurrence were more likely to have extrathyroidal extension (52.8% vs 22.2%; P < .001), nodal metastasis (88.6% vs 34.9%; P < .001), and a higher overall lymph node yield (13 vs 2 nodes; P < .001) with a greater number of positive nodes (6 vs 0 positive nodes; P < .001) at the time of initial resection compared to those who did not recur. Amin et al., (2020), identified extrathyroidal extension and the number of positive lymph nodes as independent risk factors for posttreatment recurrence [15]. Similarly, a study conducted among 43 Malaysian thyroid cancer patients who underwent total thyroidectomy with lymph node dissection revealed that individuals with more advanced stages of thyroid cancer, specifically categorized as Stage IVa, IVb, and IVc, had a higher recurrence rate. The study observed a locoregional recurrence in 46.4% of Stage IV patients [16].

The findings of this study revealed that diabetic patients had a higher risk for recurrence compared to nondiabetic patients (HR 5.9, 95% CI 1.03-33.6, p=0.019). Few studies have investigated the impact of diabetes and prediabetes on thyroid cancer aggressiveness features and recurrence risk. Prior data on whether metabolic disease promotes more advanced stage at diagnosis or higher risk tumor subtypes remains conflicting. For example, some analyses link insulin resistance to worse responses to initial therapy, 45% of patients with insulin resistance were found to have a persistent structural disease of thyroid cancer, while only 36% of patients without insulin resistance exhibited the same condition [19, 20] while others find no distinction in pathological characteristics clinical aggressiveness of thyroid cancer between diabetic and normoglycemic patients [21].

Li et al., (2020) retrospectively reviewed the records of 14,167 patients who underwent primary surgery for thyroid cancer, the findings indicated that individuals with both thyroid cancer and T2DM were more likely to experience invasive tumor characteristics, such as extrathyroidal extension and lymph node metastasis, compared to those without diabetes [20]. Furthermore, in a retrospective study analyzing 1,687 adult patients with well-differentiated thyroid cancer, the findings indicated that T2DM was linked to an advanced TNM (Tumor, Node, Metastasis) than patients without DM [22]. In contrast, a study with an 3-year follow-up did not identify any significant differences in clinicopathological characteristics between the diabetic and control groups [21].

There are several potential biological mechanisms linking diabetes and thyroid cancer risk. First, chronic insulin resistance leads to elevated circulating insulin and insulin-like growth factor 1 (IGF-1) levels, which act via cell receptors regulating proliferation and apoptosis. Second, components of metabolic syndrome influencing these pathways could further compound thyroid tumorigenesis [23].
Tumor size is among the most widely recognized clinical factors prognostic for thyroid cancer recurrence in prior literature and the risk of recurrence increased when the tumor size exceeded 10 mm. [24]. However, the current study did not find tumor size to be a significant predictor of thyroid cancer recurrence. The current study's inability to identify tumor size as a significant predictor of thyroid cancer recurrence might be attributed to the fact that size information was missing for half of the patients.

Conclusions

This analysis of 99 thyroid cancer patients in Minia, Egypt found an excellent long-term disease-free survival rate of over 90% at 10 years follow-up. Regional metastatic disease and diabetes co-morbidity emerged as principal risk factors prognostic for recurrence. Prospective, multicenter Egyptian studies are needed to confirm recurrence patterns in wider populations with standardized protocols. Integrating molecular profiling with clinico-pathologic invasiveness markers could allow for a more understanding of factors influencing the recurrence. Diabetes prevention and management programs should be evaluated as adjuvant interventions for high-risk thyroid cancer survivors in resource-limited settings.

Implications of the study

The study has several key implications. For clinical practice, it supports more personalized treatment and follow-up plans based on metastatic spread and diabetes status. It also indicates a need for diabetes screening, monitoring, education, and management as part of standard thyroid cancer survivorship care. For future research, this study serves as baseline for future research, helping to assess

developments or changes over time. The study implies a need for broader and more extensive research among diverse Egyptian populations to confirm whether the results generalize more broadly. It also supports investigating whether optimal diabetes control helps mitigate recurrence risk. On a broader scale for health policy, the findings may support the integration of comorbidity management into cancer survivorship care models.

Ethical consideration

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Approvals were obtained from the Ethics Committee of Faculty of Medicine, Minia University (Approval No. 87-2021) and the General Secretariat of Specialized Medical Centers at Minia Oncology Center ensuring compliance with ethical standards and patient privacy. Informed consent was obtained from all participants prior to participation.

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Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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