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The Association of Age and Gender with the Histopathological Features among Thyroid Cancer Patients in Erbil City, Iraq: Clinical Analysis of 153 Cases

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Abstract

Background: Thyroid cancer (TC) is an increasingly prevalent malignancy throughout the world. It has long been recognized that the incidence of TC is higher in women which increases with age. However, the association of gender disparity and age with TC aggressiveness and outcomes are still controversial. The aim of this study was focused on the association of age and gender with histopathological characteristics in TC. **Methods:** 153 patients who met the criteria, were selected. The included cases were divided into four age groups (≤24 years, 25-44 years, 45-64 years, and ≥65 years). Demographic, age and pathological parameters were compared among them. The association of gender and age with histopathological features were then evaluated. **Results:** Females were significantly more frequent in almost all age groups with the highest female frequency found the age group of 25-44 years old. Females are more susceptible for TC even when they are young. The four groups showed highly significant differences regarding extrathyroidal extension (ETE) which is more aggressive in older individuals' tumor. However, there were no significant differences regarding tumor size, multifocality, LV invasion and LN metastasis. Moreover, increasing age was significantly associated with increases risk of ETE. In addition, old patients and males were significantly more likely to have larger tumor size. Nonetheless, both gender and age non-significantly associated with multifocality and LV invasion. **Conclusion:** Our results confirmed that increasing age could really exert a negative prognostic effect, at least in terms of ETE risk and larger tumor size. In addition, TC risk in females was more frequent in all age groups and significantly more likely than men to present at younger, nonetheless, males represented larger tumor size.

Keywords: Thyroid cancer, Histopathological features, Age, Gender disparity, Tumor size, Extrathyroidal extension.

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علاقة العمر والجنس بالسمات النسيجية المرضية لدى المرضى المصابين بسرطان الغدة الدرقية في مدينة اربيل: التحليل السريري لـ ١٥٣ حالة

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الخلاصة

ازداد انتشارسرطان الغدة الدرقية في السنوات الاخيرة على مستوى العالم. من المعروف أن معدل الاصابة أعلى عند النساء ويزداد مع تقدم العمر، ومع ذلك فأن علاقة اختلاف الجنس والعمر مع عدوانية وحصيلة مرض سرطان الغدة الدرقية مايزال مثير للجدل. تهدف هذه الدراسة إلى التركيز على ارتباط العمر والجنس بالخصائص النسيجية المرضية في سرطان الغدة الدرقية. تم اختيار 153 مريضا تنطبق عليهم المعايير، فقد قسمت مجموعة المرضى الى اربع فئات عمرية (≤24و25−44 و45−64 وأكبر من 65)، وقد تم مقارنة التوزيع السكاني، العمر والمعلمة المرضية بين الفئات الاربعة، فضلا عن تحديد علاقة الجنس مع التشريح المرضي في كل مجموعة.

اظهرت النتائج تكرار نسبة الاصابة بين الاناث وخاصة في الفئة العمرية (25−44)، مما يظهر ان الاناث اكثر عرضة للمرض خاصة في سن الشباب. وبينت الدراسة ايضا ارتفاع معنوي للنمو الثانوي للورم في جميع الفئات العمرية وبالأخص في المتقدمين بالعمر وذلك بالرغم من عدم وجود فارق معنوي في تعدد المواقع وغزو الاوعية والعقد اللمفية، وايضا حجم الورم الذي قد يكون اكبر في الذكور مقارنة بالاناث خاصة مع التقدم بالعمر.

نتائجنا تؤكد بأن زيادة العمر لها تأثير سلبي، وتزيد من فرص انتشار الورم وازدياد حجمه. وأن الاناث بشكل عام اكثر استعدادا للاصابة في جميع الفئات العمرية وبالأخص في فئة الشباب مقارنةً بالذكور، بينما حجم الاورام تكون أكبر عادة عند الذكور.

Introduction

Thyroid carcinoma (TC) is the most common type of the endocrine system malignancy. It has been reported that women have a higher risk of developing thyroid cancer than men [1, 2]. According to the World Health Organization database, 586,202 new cases of TC were reported and 43,645 ` died in 2020 [3]. The sharp increases in incidence may reflect an increase in real incidence due to factors such as radiation and obesity [4, 5] or associated with the detection of TC in preclinical stage due to the availability of sensitive diagnostic methods such as thyroid ultrasound and fine-needle aspiration (FNA) [6, 7]. The majority of significant guidelines, including those published in 2016 by the American Thyroid Association (ATA), suggested complete thyroidectomy or near-total thyroidectomy as the initial operative procedure of choice for TC, and radioiodine ablation (RAI) have been recommended for patients with distant metastases or functioning remnants in the thyroid bed [8].

According to the AJCC staging cancer manual, age is an additional factor for determining thyroid tumor stage besides TNM categories [9]. However, the connection between gender and age in relation to the manifestation of TC is not clear. It has been reported that older age

association with more aggressive thyroid pathology, including increased prevalence of follicular histology, capsular and vascular invasion [10]. Older cancer patients present a high level of comorbidity.

The cancer treatment choices during managing elderly patients that have a significant comorbidity are restricted and hospitalization and non-cancer-related death and also a higher in old patients [11]. Of note, tumor size, capsular infiltration and nodal metastasis are higher in patients aged ≤18 years [12]. Some reports suggest that TC features are more aggressive in men with TC than in women [13]. Other reports demonstrate that histopathological subgroups are the significant factor for prognosis clinically for TC [14].

Despite the significant progress that has been made worldwide by many researchers so as to define the exact molecular pathways related to the progression and development of thyroid cancer [15, 16], the impact of age and gender on clinicopathological features of thyroid cancer and prognosis is not clearly defined until now. The aim of this study was to indicate the association of age and gender with the prognosis and histopathological characteristics of thyroid cancer.

Patients and Methods

This study retrospectively reviewed the medical records and pathology reports of thyroid cancer patients who underwent thyroidectomy between 2018 and early 2022 in Erbil private and public hospitals. Since there wasn't certain data entries for thyroid cancer in Erbil city, so the data used in this study was derived from both private and public hospitals and private pathology laboratories throughout Erbil city. The demographic and clinicopathological characteristics over the 4-year period were analyzed. Clinicopathological characteristics of thyroid cancer were made at the time of diagnosis with tumor size, lymph node (LN) metastasis, evidence of extrathyroidal extension (ETE) and lymphovascular (LV) invasion based on AJCC staging cancer manual, eighth edition [17].

In all, 153 cases with TC that met the inclusion criteria were selected. Thus, only cases recruited with clinical assessment, ultrasound, and evaluated thyroid nodules cytologically by Fine Needle Aspiration (FNA) preoperatively and then confirmed by pathological examination. 52 cases were excluded due to the absence of significant information, including age, gender, and clinical pathological features (LV invasion, ETE, focality, and LN metastasis). The cases recruited were divided into four age groups (≤24 years, 25-44 years, 45-64 years and ≥65 years). Gender, age and pathological parameters were compared among them. Then, the association of gender and age with histopathological features was evaluated. The parameters and all important details about the patients and tumor characteristics were recorded into a specific database (Microsoft Excel).

Statistical Analysis

Variables considered in the analysis included age at diagnosis (years), sex, year of diagnosis, types of procedure (Total thyroidectomy and hemithyroidectomy), tumor size, which was measured in centimeters, lymphovascular invasion, ETE, LN metastasis, and tumor stage. The size of the unifocal tumor was defined and in case of multifocality, the size of the largest tumor was taken into account among all other tumors for analysis. Both age and tumor size information were expressed as median and range (25% percentile-75% percentile). Categorical variables (histopathological parameters) were expressed as relative and absolute

frequencies. Descriptive statistics were performed for qualitative variables to summarize data. Kruskal-Wallis test was used for comparing age and tumor size, followed by post hoc analysis (Dunn's). Moreover, for comparing the categorical variables, nonparametric chi-square test was selected to compare these variables. To find the odds ratio (ORs) of age and gender, binary logistic regression was used to manage the association of these variables with ETE, LN metastasis, LV invasion, and multifocality. Whereas, multiple linear regression was used to manage the association of age and gender with tumor size. A *P*-value < 0.05 was considered statistically significant. MedCalc (version 20), GraphPad Prism 9 and SPSS (version 27) were utilized for data extraction and statistical analyses.

Results

Summary Statistics

Totally, 153 cases with TC that met the inclusion criteria, were analyzed. Patient demographics and pathology characteristics are shown in Table 1. Out of 153 cases, 123 patients (80.392%) were female. The female to male ratio was 4.1:1. The median age of patients was 40 (31-50.5) years, ranging from 15-85 years and the median tumor size was 1.6 (0.73-2.9). Total thyroidectomy (TT) was done for 135 cases compared to hemithyroidectomy (HT) which was done for 18 patients. Multifocality was present in 40 cases, whereas LV invasion, LN metastasis and ETE were present in 11, 33, and 30 patients respectively. 88.235% of cases were in stage 1.

Table 1: Demographic and histopathological characteristics of patients

Characteristic	Frequency
Age, median (Range)	40 (31-50.5)
Gender (Female:Male)	4.1:1
Tumor size, median (Range) cm	1.8 (0.73-2.9)
Types of procedure (TT/HT)	135/18
Multifocality	40/153 (26.143 %)
Lymphovascular invasion	11/153 (7.189 %)
Lymph node metastasis	33/153 (21.568 %)
ETE	30/153 (19.607 %)
T1	98/153 (64.052)
T2	25/153 (16.339 %)
T3	28/153 (18.3 %)
T4	2/153 (1.307 %)
TNM stage	
I	135/153 (88.235 %)
II	11/153 (7.189 %)
III	6/153 (3.921 %)
IV	1/153 (0.653 %)

Abbreviations: TT: Total thyroidectomy; HT: Hemithyroidectomy; ETE: Extrathyroidal extension.
Median (25%-75% interquartile range) was used for age and tumor size.

Bivariate Analysis

The peak occurrence of TC was between 25-44 years in which the distribution of cases by age group was 7, 84, 43 and 19 among patient's ≤24, 25-44, 45-64, and ≥65 years old respectively (Table 2). We achieved the statistical significance in the comparison of genders

with *P* value of 0.0057 in which females were more frequent in all age groups and the highest female frequency was in the age group of 25-44 years old that comprised 85.71% of all cases in this age group. Females are more susceptible for TC even when they are younger (≤24 years old) as compared to males. Whereas, in age extremes (≥65 years old), there is not a significant difference in frequency of genders (Figure 1). Moreover, the four groups showed highly significant differences in ETE (*P* = 0.0008). Older individuals' tumors presented more aggressive characteristics regarding the ETE. Of the comparison tested, the four groups showed no significant differences regarding multifocality, tumor size, LV invasion and LN metastasis. Nonetheless, multifocality, LV invasion and LN metastasis were observed with higher frequency in patients aged between 25-44 years old compared to the other three groups.

Table 2: Demographic and histopathological features of TC patients according to age groups

		Age groups										P value
		≤24 yrs		**25-44 yrs**		**45-64 yrs**		**≥65 yrs**		**Total**		_
Age Median (Range)		20 (17-24)		34 (30-37)		50 (47-55)		71 (69-76)		40 (31-50.5)		_
Tumor Size Median (Range)		1.8 (0.55-3)		1.6 (0.725-3)		1.5 (0.525-2.85)		2 (0.8-6.5)		1.6 (0.73-2.9)		0.5801
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	_
Gender	Male	0	0.0	12	14.28	9	20.93	9	47.36	30	19.607	*** 0.0057
	Female	7	100	72	85.71	34	79.06	10	52.63	123	8.39	
Multifocality		2	28.57	26	30.95	7	16.27	5	26.31	40	26.143	0.362
LV Invasion		0	0.0	5	5.95	3	6.97	3	15.78	11	7.17	0.4163
LN Metastasis		3	42.85	12	14.28	12	27.9	6	31.57	33	21.56	0.0837
ETE		2	28.57	10	11.904	8	18.604	10	52.631	30	19.607	**** 0.0008

Abbreviations: TC: Thyroid cancer; n: Frequencies; yrs: Years; LV: Lymphovascular; LN: Lymph node; ETE: Extrathyroidal extension.
Note: Variables were expressed in absolute (N) and relative frequencies (%); Median (25%-75% interquartile range) was used for age and tumor size. Kruskal-Wallis test was used for comparing age and tumor size, followed by post hoc analysis (Dunn 's), and the nonparametric chi-square test on the comparison of categorical variables.

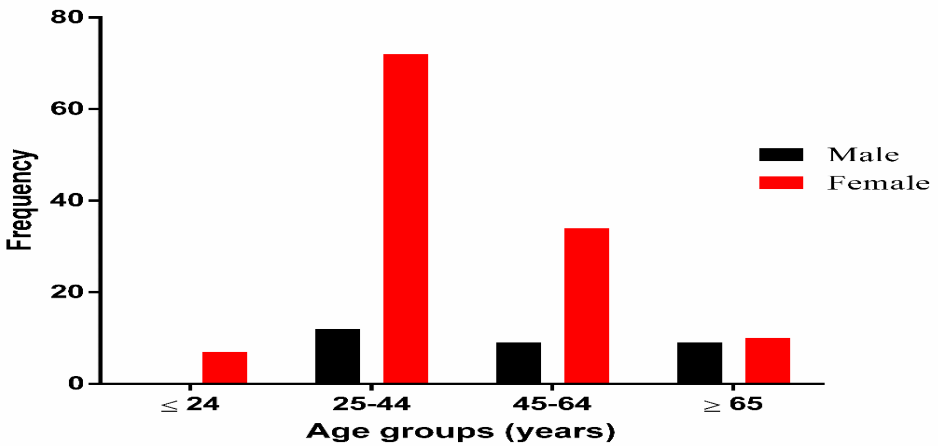

Figure 1: The frequency of males and females according to age groups (Chi-square test).

Multivariate Analysis

There was a highly significant association between age and ETE with an odds ratio of 1.04 (P = 0.004) in which the ETE increased with age (Table 3). In addition, increasing age was highly associated with increasing tumor size (P = 0.008) (Table 4). Nonetheless, there was a positive non-significant association of age with LN metastasis and LV invasion with ORs of 1.008 (P = 0.557) and 1.015 (P = 0.463) respectively, and an inverse but non-significant association with multifocality in which multifocality was higher for younger patients. Gender was significantly associated with LN metastasis and tumor size in which tumor size was larger in males compared to females with a P value of 0.002 (Table 4), while males were less likely to have LN metastasis (ORs = 0.4, P = 0.046). However, the association is non-significant, but males were less likely to have LV invasion with ORs of 0.710 and more likely to develop ETE and multifocality with odds ratio of 1.058 and 1.044, respectively (Table 3).

Table 3: Association between age and gender with ETE, LN metastasis, LV invasion, and multifocality: Binary logistic regression.

Dependent Variables	Independent Variables	B	SEM	Sig	OR
ETE	**Age**	0.039	0.014	*** 0.004	1.040
	Gender (1)	0.056	0.523	0.915	1.058
LN etastasis	**Age**	0.008	0.013	0.557	1.008
	Gender (1)	-0.916	0.458	* 0.046	0.400
LV invasion	**Age**	0.015	0.020	0.463	1.015
	Gender (1)	-0.343	0.733	0.640	0.710
Multifocality	**Age**	-0.19	0.014	0.168	0.981
	Gender (1)	0.043	0.491	0.93	1.044

The association of age and gender with one histopathological characteristic (ETE, LN metastasis, LV invasion, and multifocality) at a time. Gender (1) considered male.

Table 4: The association of age and gender with tumor size: Multiple linear regression.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	SEM	Beta		
	(Constant)	0.707	0.412		1.716	0.089
	Age	0.025	0.009	0.238	2.719	0.008
	Gender (1)	1.106	0.352	0.275	3.144	0.002

Dependent variable: Tumor size. Gender (1): Male

Discussion

In our study, we found that thyroid cancer was more prevalent in females than males as in the case of breast cancer, and the peak occurrence of TC was between 25-44 years which is consistent with other studies [10, 18, 19]. Our study confirmed that the incidence of ETE increases with age and, hence, older patients showed larger tumor size [10, 20]. Moreover, previous studies reported the association of increasing age with advanced stage and vascular and capsular invasion [10]. Adaptive immunity is restrained in the tumor microenvironment that may lead to the development of cancer with more aggressive phenotypes, such as advanced ETE and larger tumor size [21]. It has also been confirmed that multifocality in TC is a risk factor for disease recurrence and poorer prognosis [22]. We found out that there is a reverse relationship between age and multifocality in which decreasing age was non-significantly a risk factor for multifocality. This study detected that there was no significant association between age and LN metastasis and LV invasion that contradicted the results of the other two studies, possibly due to the larger sample size they retrospectively analyzed [23, 24]. Despite non-significant association, the rate of multifocality, LV invasion and LN metastasis was higher in patients aged between 25-44 years old.

Despite the higher incidence of TC in females, the association of gender with thyroid cancer features is still controversial. The higher estrogen and thyroid-stimulating hormone (TSH) levels, especially during pregnancy or menstrual cycle, may contribute to increase the risk of females for thyroid cancer and other cancers development such as endometrial cancer [25, 26] since estrogen and TSH stimulate thyroid follicular cells to proliferate [27, 28]. However, Jonklaas, *et al.* [29] reported that both males and females represent same outcomes when getting TC at the same age [29].

In our study, gender was not a significant factor in patients that had more aggressive tumor features, except for LN metastasis and tumor size in which females were more at risk of having LN metastasis. Whereas, males were at risk to have larger tumor sizes that should be taken account as larger tumor may subsequently lead to more aggressive features. In males, the larger tumor size may be due to not taking this case seriously because of low TC frequency. However, the higher frequency of TC in females makes them seek medical care

and investigations and also striking specialists to write thyroid function tests less frequently for males, leading to later diagnosis with larger tumor sizes [30, 31].

Our research had several limitations as we only collected the pathology reports in Erbil city, thus making it small sample size that might have also affected the results. In addition, we excluded many samples because of the absence of some of the pathological characteristics. Moreover, distal metastasis for most of the patients was not identified which could be linked with age and gender. For future study, we recommend identifying the family history of thyroid cancer, distal metastasis, and whether the patients suffered from any other thyroid problems and autoimmune diseases.

Conclusion

Thyroid cancer, unlike most malignancies, is unique because the majority of staging systems identify age as a significant prognostic indication, and that the incidence of thyroid cancer is higher in women than men. In conclusion, this study found that increasing age could exert a negative prognostic role, at least in terms of risk of extrathyroidal extension and larger tumor size, in patients with TC. In addition, females were more frequent in all age groups and significantly more likely than men to present at younger. Nonetheless, males represented larger tumor size. The pathophysiological mechanisms require further studies to be clarified. At the present state of our knowledge, age and ETE are the two additional factors that could be recommended for clinical care and precisely should be identified and mentioned in both operative and pathology reports when the diagnosis of TC occurs in old patients and males as they are at risk to have larger tumor size. In addition, old patients are more predisposed to have positive ETE that should be considered as these additional factors may subsequently lead to more aggressive outcomes and features.

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Funding and Conflict of Interest:

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