

Histopathology analysis of thyroid cancer tumor size in Sulaymaniyah-Kurdistan Region-Iraq

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Abstract

Objective Thyroid cancer is not an uncommon disease and its histology is varied. The current study investigates the correlation between thyroid cancer and tumor size.

Methods Reports of 100 patients with thyroid carcinoma biopsy submitted to histopathological review from July 2018 to December 2019 in Sulaymaniyah city of Iraq were studied. Only malignant thyroid glands were included in the study. Gender, age, tumor size, multifocality, extrathyroid extension, nodal metastasis, perineural and capsular invasion were studied. The tumor size in relation to other parameters analysis were performed by using SPSS program.

Results The sample were predominantly female (83%). The tumor affects 1 lobe in 67% with 1.4 times more in right lobe than left lobe but bilaterality was 12%. Papillary thyroid carcinoma (PTC) accounts for 94%. Two-third (66%) of the glands surface was nodular. Only 10% were totally encapsulated. Multifocal tumor found in 28% of the cases. The lymphovascular invasion identified in 30%, perineural invasion 25%, lymphocytic thyroiditis in 42%. Lymph node involvement detected in 17%. Regarding the tumor size (T), 79% of the patients were T1. The tumor size had significant relation to: margin involvement, lymphovascular invasion and lymph node involvement (N1) as found more in T1 & T2.

Conclusions PTC was the commonest pathology with female predominance. Two-third affects only one lobe with more in right lobe. Smaller size tumor may have more lymph node or margin involvement. Size of the tumor was significantly related with encapsulation and lymphovascular invasion.

Keywords Thyroid, Cancer, Histology, Correlation

Introduction

The thyroid gland is an important endocrine gland. It is a butterfly-shaped and straddles the trachea in the front of the neck. Embryological development of the gland is from an evagination of the floor of the pharynx. Thyroglossal duct imprints the pathway of the thyroid from the tongue to the neck. This duct sometimes persists in the adult. Both lobes of the thyroid are connected by a bridge of tissue, the thyroid isthmus. Sometimes, a pyramidal lobe may arise from the isthmus in front of the larynx. The gland has two main functions. Releasing the thyroid hormones, is its chief function, which maintain the level of metabolism in the tissues that is supreme for cell normal function. Oxygen consumption by most of the cells in the body are stimulated by these hormones which help to regulate lipid and carbohydrate metabolism; hence has an impact on body mass and mentation. Secretion of calcitonin is the second function of the thyroid gland that regulates circulating levels of body calcium.¹

Thyroid cancer is the commonest among all endocrine malignancies. It accounts for <1% of all malignancies and is the most rapidly increasing cancer in women. Thyroid cancer is responsible for six deaths per million persons annually.² The overall annual incidence ranges from 0.5 to 10 cases/100,000 population. The great majority of the thyroid carcinoma etiology is unknown but below 5 years age thyroid irradiation is a well-known factor for developing differentiated carcinoma, especially papillary cell carcinoma in addition to that follicular carcinoma is more detected in endemic goitrous areas, possibly due to Thyroid Stimulating Hormone (TSH) stimulation. Furthermore, lymphoma sometimes develops in autoimmune thyroiditis. Papillary thyroid carcinoma (PTC) is the

commonest type of thyroid carcinoma, tumors are diagnosed in patients in the third to fifth decades of life and females are more affected.³ The major presentation of the disease is neck mass, dyspnoea or dysphagia but change in voice in advanced cases may be due to recurrent laryngeal nerve involvement. The pillar of diagnosis depends on clinical presentation, ultrasonography, fine needle aspiration biopsy and to lesser extent the other more complicated investigations. The vast majority of primary malignancies are carcinomas derived from the follicular cells. Interestingly, up to 30% of patients who die of non-thyroid disease have deposits of PTC in autopsy studies, suggesting that many patients live with this disease undetected.⁴

As patients age, tumor size and histopathological category findings of thyroid carcinoma are important for risk grouping of patients besides thyroid tumor histopathology analysis is deficient in our locality. This study tried to analyze histopathology and tumor size effect in this type of cancer.

Material and methods

This is a single-center retrospective study of pathological reports from July 2018 to December 2019. Those patients with thyroid surgery and the final diagnosis of PTC were included.

These reports from Raz, the private histopathology laboratory in center of Sulaymaniyah, were obtained from the database system. We revised demography and histopathological information with detail points related to the study.

In the grading and staging analysis, we have used The American Joint Committee on Cancer (AJCC 8 edition),⁵ the T describes the size of the tumor, N describes spread of cancer to nearby lymph nodes and M describes spread of cancer to

other parts of the body in TNM Classification of Malignant Tumors were applied. Using for tumor size classification (T1: the tumor is ≤ 2 cm, T2: the tumor is larger than 2 cm across but < 4 cm, T3: ≥ 4 cm) and lymph node involvement.

Procedure of histopathology was revised reports of the routine hematoxylin and eosin stained slides in formalin fixed specimens with paraffin embedded tissue.

Non-malignant pathology, recurrent thyroid cancer, and secondary thyroid tumors were excluded. Because distant metastasis full information was unavailable and the M staging is not included in this study.

Gender, age, tumor size, perineural invasion, capsular invasion, extra-thyroidal extension (ETE), lymph node metastasis, tumor localization, tumor focality, and the presence of other thyroid pathology like lymphocytic thyroiditis were evaluated.

Data entry and analysis

Data have been admitted to excel sheet and then transferred to Statistical Package of Social Science (SPSS) program version 22 for analysis. Frequencies of parameters were determined and relation of tumor size to other parameters was also

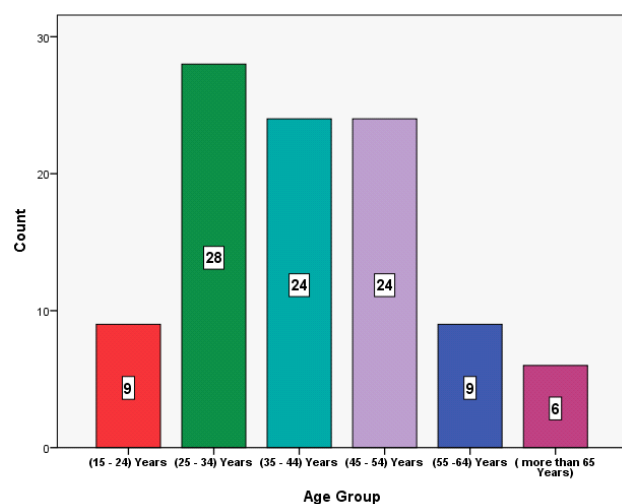


Fig. 1 Thyroid carcinoma age distribution.

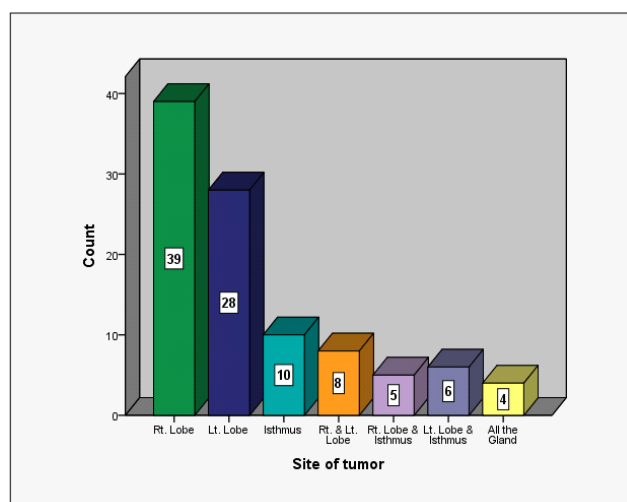


Fig. 2 The tumor presentation on different parts of thyroid gland.

discovered by using Chi-square. *P*-value equal or less than 0.05 were regarded statistically significant.

Results

We reviewed medical reports for 100 patients diagnosed with thyroid carcinoma from June 2018 to December 2019. The sample included 83 female and 17 male patients, and the female/male ratio was 4.9:1.

The mean age of our patients at presentation \pm Std. Deviation (years) was 40.7 ± 13.11 . The minimum age was 18 and maximum was 84 years

Median size (cm^3) of right lobe was 18, left lobe was 15 and isthmus was 2.5.

Looking at Fig 2, it showed that 39% of the tumors are in right lobe compared to 28% in left lobe and least in all parts of the gland 4%.

So, the tumor is 1.4 times more affected in the right lobe than left lobe alone.

Tumor in isthmus alone is found in 10% of patients but isthmus with either lobe alone collectively is 11%. Single lobe alone is affected in 67% of the patients.

Both lobes in 8%, and total gland in 4% are affected (collectively bilaterality of lobes are 12%).

The study result showed in microscopical diagnosis that papillary carcinoma was the most common type with 94% in the presented sample followed by medullary carcinoma 5% and a single case of follicular type. Total thyroidectomy was done in most 93% of the patients, accordingly fewer cases were (7%) indicated for lobectomy.

Finding of frequencies

Two-thirds (66%) of the gland surface was nodular and majority of the tumors (96%) were white in color. Only 10% were totally encapsulated, margin involved in 6%, multifocal tumor found in 28% of the cases.

The lymphovascular invasion 30%, perineural invasion 25%, extrathyroidal extension (ETE) was presented only in 4%, lymphocytic thyroiditis in 42%, lymphnode involvement in 17% and the tumor size in nearly four-fifth (79%) of the patients were T1.

Most of the females presented with T1 (83%) also for male patients but to a lesser extent (59%). In addition, T3 is more in male (17.5%) than in female (4%) ($P < 0.035$).

The lymph node involvement is detected in 17% of the patients and highly significantly related to size of the tumor (p -value < 0.001). In those with lymph node involvement, T1 & T2 are of same extent tumor size (41.2%) but twofold more than T3 (17.6%). Involved margin found in six cases, two-third of them were in stage T1 and one-third in T3 (p -value 0.011). ETE was found in four cases but statistically not significant in relation to the size of the tumor (p -value of 0.199). The tumor size to microscopic diagnosis relation (p -value < 0.001) showed 82% of papillary carcinoma presented in stage T1, and only 3% in T3. This is in contrary to medullary carcinoma that 60% in stage T3 and 40% T1. The only follicular carcinoma is in T2.

Encapsulation relation to tumor size is significant (p -value of 0.035) as T1 include 88%, 70% & least 50% for non-capsulation, partial capsulation and encapsulation in sequences. The percentage of T3 is 5%, 6% and 10% for each of them in series.

Table 1. **Frequencies of histopathological findings of parameters.**

	Frequency	%		Frequency	%
Microscopically diagnosis			Perineural invasion		
Papillary carcinoma	94	94	Present	25	25
Medullary carcinoma	5	5	Not identified	75	75
Follicular carcinoma	1	1	Extrathyroidal extension		
Surface			Extrathyroidal extension(ETE)	4	4
Smooth	34	34	Not identified	96	96
Nodular	66	66	Additional pathology		
Color			Negative	36	36
White	96	96	Lymphocytic thyroiditis	42	42
Others	4	4	Hyperplastic nodule	15	15
Capsule			Non-specific thyroiditis	4	4
Not capsulated	59	59	Graves disease	1	1
Partially capsulated	31	31	Adenoma	1	1
Totally capsulated	10	10	Granulomatous thyroiditis	1	1
Margin			AJCC:T: Tumor size (cm)		
Involved	6	6	T1 (≤2cm)	79	79
Not involved	94	94	T2 (2.1 - 4 cm)	15	15
Tumor focality			T3 (>4 cm)	6	6
Unifocal	72	72	AJCC:N		
Multifocal	28	28	0	83	83
Lymphovascular invasion			1	17	17
Present	30	30	Procedures		
Not identified	70	70	Total thyroidectomy	93	93
			Lobectomy	7	7

Table 2. **Tumor size (T) to relation to other parameters.**

T1 (%)		T (tumor size)			Total (%)	p-value
		T2 (%)	T3 (%)			
Gender	Male	10(59%)	4(23.5%)	3(17.5%)	17(100%)	0.035
	Female	69(83%)	11(13%)	3(4%)	83(100%)	
AJCC : N	0	72(86.8%)	8(9.6%)	3(3.6%)	83(100%)	<0.001
	1	7(41.2%)	7(41.2%)	3(17.6%)	17(100%)	
Margin	Involved	4(66.6%)	0(0%)	2(33.3%)	6(100%)	0.011
	Not Involved	75(80%)	15(16%)	4(4%)	94(100%)	
Extra-thyroid extension(ETE)	Limited to Thyroid	77(80%)	14(15%)	5(5%)	96(100%)	0.199
	Extension beyond thyroid	2(50%)	1(25%)	1(25%)	4(100%)	
Microscopic diagnosis	Papillary	77(82%)	14(15%)	3(3%)	94(100%)	<0.001
	Follicular	0(0%)	1(100%)	0(0%)	1(100%)	
	Medullary	2(40%)	0(0%)	3(60%)	5(100%)	
Capsule	No Capsule	52(88%)	4(7%)	3(5%)	59(100%)	0.035
	Partial Capsule	22(70%)	7(23%)	2(6%)	31(100%)	
	Total Capsule	5(50%)	4(40%)	1(10%)	10(100%)	
Lymph-vascular invasion	Present	19(63%)	8(27%)	3(10%)	30(100%)	0.045
	Not Identified	60(86%)	7(10%)	3(4%)	70(100%)	
Total		79	15	6	100	

Lymphovascular invasion found in 30% of them with significant relation to tumor size (p -value 0.045) as T1: 24%, T2: 53.3% & T3: 50%.

Discussion

There are various correlating factors to the prognosis of thyroid cancer, including size, age, histology, and others.

Thyroid carcinoma affects women more than men. In our study, female to male ratio (4.9:1) and this is really near to most of other studies findings. It is well known that thyroid malignancy in USA affects 2% of women and 0.5% of men (4:1).² PTC, which manifests the vast majority of the cases in the world, the female to male ratio studies are in Turkey (4.9:1),⁶ South Korea 5.5:1⁷, and Canada 5.3: 1.⁸ The estrogen hormone is mostly blamed to be a factor for this difference at reproductive period of women.

The mean age of our patients at presentation \pm Std. Deviation (years) was 40.7 \pm 13.11. The minimum age was 18 and maximum was 84 years. This finding is nearly similar to mean age at presentation is 30–40 years mentioned in textbook.²

Clearly, thyroid carcinoma is more common in young age group and early adulthood and then in decreasing frequency with advancing age. This agreed with the study obtained in Iran, the median \pm interquartile range of patients' age was 40 \pm 25 years⁹ and the cohort study in New York with median age of 48 years (range 7–91 years).¹⁰

Median size (cm³) of right lobe was 18, left lobe was 15, and isthmus was 2.5.

This study found that there is no clear difference in size of both lobes in thyroid cancer in our sample study. Normal thyroid lobe are 5 x 2.5 x 2.5 cm dimensions =31.25cm³ and the isthmus is 1.2 x 1.2 cm in dimensions.¹¹ There is no significant difference in increasing size of thyroid lobe volume between normal and malignant thyroid lobes nor right or left lobe in malignant thyroid pathology.

Single lobe alone affected in 67% of the patients. In most cases, the cancer only affects one of the thyroid glands two lobes, but it can affect both.¹²

Tumors of right lobe are 39% compared to 28% in left lobe. This reveal that the tumor 1.4 more times affect the right lobe than left lobe alone. This detection is not observed in any previous studies and its cause is not clear.

Bilaterally lobes affected are in 12% of the patients. This is same as finding of a study done in South Korea, bilaterally was 12.6%.⁷ Gaziantep University-Turkey study, recorded both thyroid lobes involvement in 32%.¹³ According to American Society of Clinical Oncology, PTC is usually found in one lobe. Only 10–20% of papillary thyroid cancer appears in both lobes.¹⁴

PTC is the predominant form of thyroid carcinoma in 94% of the cases is similar to study of New York on differentiated thyroid carcinoma patients labeled 95.8% papillary thyroid carcinoma¹⁰ and another study for 80–93%.¹⁵ The incidence of PTC is increasing rapidly across the world. This is mostly due to increased rates of imaging detecting previously occult disease.⁴

Medullary carcinoma is known to be a neuroendocrine tumor arise from C cells (parafollicular cells) of ultimobran- chial body of neural crest. This study finding is less than the study done in Tehran 7.8%⁹ but in agreement with study in

Washington by Linda et al, accounts for 4% of all thyroid cancers, and displays a variety of clinical behaviors ranging from indolent to aggressive.¹⁶

Follicular carcinoma is another category of differentiated carcinoma of thyroid gland. In a study from New York, only 2% of the patients presented with follicular type thyroid carcinoma¹⁸ and this result is near to our finding of 1% and in other study in Tehran study reaches 4.8%.⁹ In iodine insufficient dietary areas, it comprises 6–10% of thyroid carcinomas and looks to this as a risk factor.¹⁵ The overall incidence of this tumor is declining probably due to iodine supplementation and improved histologic classification.²

Total thyroidectomy were done in most (93%) of our patients. This goes with standard textbook recommendation for doing total thyroidectomy in cases >1cm.²

Two-third (66%) of the glands surface was nodular. A study with thyroid cancer showed 76.9% of the patients had multinodular goiter.⁹ Another sonographic study in Egypt showed 59% of cancer thyroid nodules were multinodular.¹⁷ Even in autopsy grossly visible in 10% of thyroid glands but microscopic nodularity is present in 40%,¹⁵ we found that surface nodularity is common in thyroid carcinoma.

Most of papillary thyroid carcinoma are infiltrative type while some are encapsulated (10%). This is similar to others findings¹⁵ and near to the study by Pisanu et al from Italy were only 15% encapsulated.¹⁸ The encapsulated tumors have an indolent behavior and are genetically distinct from their infiltrative counterparts.²

The margin of the tumor involved in 6% of our cases and this is same as a study of longoria-Dubocq et al¹⁹ and less than two other studies (10% & 12%).^{10,8}

Our multifocality outcome is 28% and this is near to other studies often multifocal (20%).^{15,20,21} Multifocality goes with poor prognosis and lower survival rate associated with multifocal PTMC compared to that with solitary PTMC.²²

Lymphovascular invasion is an important prognostic factor in various solid tumors. Out-turn of 30% of cancers have lymphovascular invasion, our detection is more than other studies (16.1%, 13.7% & 11.6%).^{9,19,23} These different findings are subjective to pathologist variations.

A quarter of the patients have perineural invasion. This result is near to study done by Amirsina Sharifi et al of 21.9%,⁹ but less than study done by Christopher et al of 35%.²⁴ Many malignancies perineural invasion is a marker of poor outcome and is a signal of decreased survival.²⁵

ETE is presented only in 4%, while other studies show near result of 7.6%²⁶ or higher results of 13.2%²¹ and 20%.⁶

Lymphocytic thyroiditis accounts of 42%. The result is higher comparing to other studies patients with PTC had thyroiditis 24.4%,²⁷ 22.7%,²¹ and 20.6%.²⁸ We observed that autoimmune thyroiditis is twofold higher in our patients sample than other studies and the main cause of this is not clear yet.

The lymph node involvement in this study is 17%. This result is nearly similar to most of other studies.^{6,7,19} Although for papillary thyroid carcinoma, it is well known to have the lymphatic spread and cervical nodal involvement does not affect prognosis.¹⁵

The tumor sizes in nearly four-fifth (79%) of the patients were T1 and 15% T2. This result is nearly similar to other study of differentiated thyroid cancer.¹⁰

Most of the females presented with T1 (83%) also for male patients but to a lesser extent (59%). In reverse, T3 is more in

male 17.5% than in female 4%. This finding goes with a study from China that declared that mean tumor size was larger in men than in women,²⁰ but disagree with another study mentioning that there were no significant differences in primary tumor size with respect to age and gender.²⁹ This may be explained with more male negligence than female for thyroid health.

We found that the lymph node involvement may occur at any stage of the tumor size and not always has directly related to tumor size. This contradictory to findings of other studies,³⁰⁻³² Most probably because of different method of tumor size classification in different researches and some depending on either pathological or sonographic measuring of size of tumor.

Involved margin found in 6%, two-third of them were in stage T1 and one-third in T3. This result indicates that tumor size is not an important factor for margin involvement. This is opposite to finding of studies which uncovered that patients who had positive margins were more likely to have larger tumors.^{8,10}

Extension beyond thyroid (ETE) was found in four cases but statistically not significant in relation to the size of the tumor. This is discordant with other results that larger size tumor are associated with extrathyroidal extension.^{30, 33}

The capsule was found in half of T1 size. This is in parallel with another study mentioned that the presence of an intact capsule was associated with smaller tumor size.¹⁹

We established that lymphovascular invasion is less in T1 group compared to other two groups of tumor size. This is

in harmony with other previous findings that said larger size tumor are associated with vascular invasion³⁰ and the risk of lymphovascular invasion is more in larger tumor.⁶

The main limitations of the present study are the relatively small sample size, likely because of single center experience and the retrospectively collected data.

Conclusion

PTC is the commonest type with female predominance. Two-third of the tumors affects only one lobe with more in right lobe. Nodularity is common in thyroid carcinoma. Smaller size may have more lymphnode involvement and same for margin involvement. Size of the tumor significantly related with encapsulation and lymphovascular invasion but not related to extrathyroidal extension

Recommendation

We advice Fine Needle Aspiration for cases of thyroid nodules coupled with lymphocytic thyroiditis. Thus, future studies on larger sample sizes and multicenter collaboration are required.

Conflict of interest

There are no conflicts of interest.

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