

The Predictors of Multicentricity in Well-Differentiated Thyroid Cancer

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Abstract: *Introduction:* The detection of the multicentricity of thyroid cancer is essential to provide the appropriate surgical decision for the patients aiming to decrease the rate of redo surgery and recurrence

Methods: A cohort study was conducted at the surgical unit of the oncology center, Mansoura university on fifty patients with well-differentiated thyroid cancer, all of them underwent total thyroidectomy then entire gland dissection technique for histopathological examination.

Results: Preoperative radiology revealed unicentric suspicious nodules in 40 cases (80%) and no suspicious nodules in 10 cases (20%). Among the ten patients those showed no suspicious nodules radiologically, multicentricity was confirmed in 5 patients (50%) pathologically, and unicentric tumors was seen in 5 patients (50%). FNAC was done in the 40 mentioned cases and was diagnostic for them as papillary thyroid carcinoma. Among many variants of prediction during searching for the true incidence of multicentricity, only isthmic invasion and, the extra thyroid extension were the significant variants.

Conclusion: Among many variants of prediction during searching for the true incidence of multicentricity, only isthmic invasion and, the extra thyroid extension were the significant variants.

Keywords: Multifocality, papillary, thyroid nodule, hemithyroidectomy, total thyroidectomy.

INTRODUCTION

Thyroid carcinoma is considered one of the most popular solid malignancies among the humans with increasing rate [1]. The most increased rate occurred in patients with early (T1) papillary cancers [2]. Papillary thyroid microcarcinoma (PTMC) with nodule size ≤ 1 cm is considered the most prevalent type of papillary thyroid carcinoma (PTC) [3]. Furthermore, the incidence of (PTMC) has currently been raised. The explanation of this increase is due to the wide availability of detection modalities and awareness with screening programs. Patients with older age affected draining lymph nodes, tumor extension outside the gland, and multiple foci of tumor or both lobe affection have a higher risk than other patients with cancer thyroid [4].

According to the American Thyroid Association (ATA) guidelines, the patients with overt PTC with high-risk factors are advised to be treated with total thyroidectomy plus nodal dissection [5]. Either hemithyroidectomy or subtotal thyroidectomy can be accepted as an adequate treatment for unifocal cases with (uPTMC), although surgical extension for the multifocal cases still in controversies [6]. The detection



Figure 1: Left lobe nodule of the one case of papillary cancer thyroid.

of the multifocality of thyroid cancer is essential to provide the appropriate surgical decision for the patients aiming to decrease the rate of redo surgery and recurrence and that is the target of this work.

PATIENTS AND METHODS

A cohort study was conducted at the surgical unit of the oncology center, Mansoura university, during the period between September 2015 and November 2016 on one group formed of fifty patients with well-differentiated thyroid cancer, all of them underwent total thyroidectomy with or without neck dissection then

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entire gland dissection technique for histopathological examination.



Figure 2: Right lobe nodule of the same case.



Figure 3: Another view of the left lobe revealing infiltration with the tumour.

Inclusion Criteria

We included patients with pathologically verified well-differentiated thyroid carcinoma affecting one lobe of the gland in this study.

Ethics Statement

The Institutional Review Board of the faculty of medicine, Mansoura University approved this study. Informed written consent was taken.



Figure 4: Another view of the right lobe during completing dissection.



Figure 5: Dissection of the isthmus revealing infiltration by the same tumour.

Treatment Planning

- Total thyroidectomy was done for all cases plus ipsilateral central node dissection as a routine. Lateral neck dissection according to the clinical

and radiological assessment of node status was considered. The final pathological examination of the whole gland with entire gland dissection technique was done to determine the true rate of multicentricity.

- Entire gland dissection technique was done through dissection of the whole glandular tissue including the normal tissue as well as that shows abnormality.
- Analysis of multiple variants was done to determine the true incidence of multicentricity with age, sex, size of the tumor, typing, grading, central and lateral node status.

Pathological Processing of the Specimen

1. We started with lobe containing the main lesion. We made serial sections in the axial plane at 3 mm intervals to identify any focal lesions, and described them. We Submitted sections in our cases (Lesion <3.0 cm: Submitted entire lesion, Lesion >3.0 cm: Submitted one section per 0.5 cm of the lesion, we made sure sampling the tumor in relation to the perithyroidal soft tissue.)
2. We repeated the dissection with the other lobe and the isthmus.
3. In addition to the sections, we documented any lesions, the entire uninvolved part from both lobes and isthmus were submitted.
4. Any perithyroidal lymph nodes, including any anterior to the isthmus ("Delphian" lymph nodes), were submitted too.

Statistical Analysis

SPSS software package (20) was used to analyze data. Multivariate logistic regression was done to detect the predictors of multicentricity. p -value < 0.05 indicated a significant difference.

RESULTS

Among the whole cohort of patients ($n=50$), 12 patients (24%) were males and 38 patients (76%) were females. Age ranged between 18 and 64 years with a mean age of 39.64 ± 11.99 . The BMI showed 22 normal patients, 26 obese patients and 2 patients with morbid obesity ranged between 22 and 41 with a mean BMI $31.33 \pm 4.4.69$. The tumor size ranged from 5 mm up to 7 cm with a mean size 2.21 ± 1.56 .

Among the 50 patients, preoperative radiology revealed 40 patients (80%) with a unicentric suspicious nodules; 22 cases with a unicentric nodule on the left side and 18 cases with a unicentric nodule on the right side. The other 10 cases showed unicentric nodules that were not radiologically suspicious, however on frozen section evaluation they were proved to be malignant.

The final pathological analysis of the 50 cases showed that all of them were a classic variant of papillary thyroid cancer. The actual mean tumor size was 2.21 ± 1.56 . FNAC was done in 40 cases and was diagnostic for them as papillary thyroid carcinoma. The FNAC in the other 10 cases that were detected by frozen section study varied between the following results: 2 cases were suspicious for malignancy, 2 cases were follicular thyroid lesions, 2 cases were atypical thyroid proliferation and 4 cases were a colloid nodular goiter.

Central lymph node dissection was done as a routine step in all cases and revealed 14 cases (28%) that had central lymph node affection, 4 cases as the only involvement and 10 cases in association with lateral lymph nodes. Extrathyroid extension was seen in 12 cases (24 %), a microscopic extension was seen in 8 cases and gross extension in the other 4 cases.

Correlation between Radiological Finding and Pathological Diagnosis Revealed the Following:

Preoperative radiology revealed unicentric suspicious nodules in 40 cases (80 %) and no suspicious nodules in 10 cases (20 %).

Among the forty patients, those showed unicentric suspicious nodules, 22 cases showed left unicentric suspicious nodule from which 11 cases were confirmed pathologically to be unicentric and 11 cases were multicentric pathologically. Right unicentric suspicious nodule was shown in 18 cases radiologically, from which 8 were confirmed pathologically as unicentric and 10 cases showed multicentricity pathologically.

Among the ten patients those showed no suspicious nodules radiologically, multicentricity was confirmed in 5 patients (50%) pathologically, and unicentric was seen in 5 patients (50%).

Preoperative radiological lymph node assessment showed 17 cases (34%) with suspicious lymph nodes from which 15 cases were confirmed pathologically with a false positive percentage of 11.8%. The

remaining 33 cases (66%) were node negative radiologically and only 4 cases from them were confirmed pathologically to have malignant lymph nodes with a false negative percentage of 12.12 %.

The Demographic Characteristics of the Patients in Unicentric and Multicentric Groups (Table 1)

Patients who showed true unicentric tumor (N=24) were 6 males (25%) and 18 females (75%) with significant female predominance. Among those patients, ten patients (41.7%) were younger than 40 years and 14 patients (58.3%) were older than 40 years.

Patients who showed true multicentric tumor (N=26) were 6 males (23.1%) and 20 females (76.9%) with significant female predominance. Among those patients, 16 patients (61.5%) were younger than 40 years and 10 patients (38.5%) were older than 40 years.

In the unicentric group, normal BMI was reported in 9 patients (37.5%), 14 patients (58.3%) were obese, and only one patient (4.2%) showed morbid obesity. In the multicentric group, normal BMI was seen in 11 patients (42.3%), 14 patients (53.8%) were obese and only one patient (3.8%) with morbid obesity with a P value of 0.942.

Table 1: Demographic Data of the Patients in Unicentric and Multicentric Groups

	Post Pathology				P
	Unicentric group		Multicentric group		
	No	%	No	%	
age					
<40y	10	41.7%	16	61.5%	0.160
>40y	14	58.3%	10	38.5%	
BMI					
Normal	9	37.5%	11	42.3%	0.942
Obese	14	58.3%	14	53.8%	
Morbid obesity	1	4.2%	1	3.8%	
Sex					
Male	6	25.0%	6	23.1%	0.874
Female	18	75.0%	20	76.9%	

Table 2: The Pathological Characteristics of the Tumors in the Unicentric and the Multicentric Groups

Parameters	The unicentric group		The multicentric group		P
	No	%	No	%	
Lympho-vascular invasion	0	0.0 %	1	3.8%	0.332
Isthmic invasion	0	0.0%	12	46.2%	<0.001*
Node status					
Negative	15	62.5%	16	61.5%	0.985
Central only	2	8.3%	2	7.7%	
Lateral only	2	8.3%	3	11.5%	
Both	5	20.8%	5	19.2%	
Extrathyroid extension					
negative	21	87.5%	17	65.4%	0.007*
positive	3	12.5%	9	34.6%	

*:significance <0.05.

The Pathological Characteristics of the Tumors in Unicentric and Multicentric Groups (Table 2)

In the unicentric group, the mean tumor size was 2.38 ± 1.86 while in the multicentric group, the mean tumor size was 1.69 ± 1.25 with a P value of 0.276.

In the unicentric group 9 cases (37.5 %) showed nodal affection, 5 cases showed both central and lateral lymph node affection, 2 cases showed central lymph node affection only and 2 cases showed lateral lymph node affection only. In multicentric group 10 cases (38.46 %) showed lymph node affection, 5 cases showed central and lateral lymph node affection, 3 cases showed lateral lymph node affection only and 2 cases showed central lymph node affection only with a P value of 0.985.

In the unicentric group, no cases showed lymph-vascular invasion (0 %) while in the multicentric group 1 case (3.8 %) showed lymph vascular-invasion with a P value 0.332.

In the unicentric group, 3 cases (12.5 %) showed extrathyroid extension while in the multicentric group 9 cases showed extrathyroid extension with a nearly significant P value of 0.067.

In the unicentric group, no cases showed isthmic invasion while in the multicentric group 12 cases (46.2 %) showed isthmic invasion with a significant P value of 0.001.

In unicentric group, no patients (0 %) showed positive family history while in the multicentric group, 2 patients (7.7 %) showed positive family history.

Trying to determine the predictors of multicentricity, we had analyzed the true incidence of multicentricity with the following variants : age, sex, BMI, tumor size, family history, node affection, lymph-vascular invasion, extrathyroid extension and isthmic invasion.

Age was classified into 2 groups, less than 40 years and more than 40 years and did not show a significant difference in the true incidence of multicentricity with a P value of 0.16.

Neither sex, BMI nor family history showed a significant difference in the true incidence of multicentricity. Although tumor size was bigger in the unicentric group (2.38) than the multicentric group (1.69), it did not show a significant difference in the true incidence of multicentricity with a P value of 0.276.

Lympho-vascular invasion was seen in only one case in the multicentric group with no significant difference in the true incidence of multicentricity with a P value of 0.332. Nodal affection showed no significant difference in the true incidence of multicentricity with a P value of 0.985. Presence of malignant nodules in the isthmus showed a highly significant difference in the true incidence of multicentricity with a P value less than 0.001. Extrathyroid extension showed to be significant as well in the true incidence of multicentricity with a P value of 0.007.

So among the variants of prediction during searching for the true incidence of multicentricity, only isthmic invasion and, extrathyroid extension were the significant variants. Further multivariate analysis showed that isthmic invasion is the most important predictor of multicentricity (Table 3).

Table 3: Multivariate Logistic Regression between Extrathyroid Extension and Isthmic Invasion

	P	OR(95% C.I.)
Extrathyroid extension		
Isthmic invasion	.014*	6.44(1.465-28.31)

OR:odd' ratio *:significance <0.05.

DISCUSSION

In this study out of the 50 patients, there was 12 males and 38 females with mean age of 39.64 ± 11.99 . Fleming *et al.* [7] reported that every three females had a thyroid malignancy are met by one male to have the disease and that most of the patients are between 30 and 50 year old and these results cope with our this study as our patients showed female predominance and were around the same age.

In our study, 26 patients out of 50 revealed multicentricity with a percentage of 52%. Pitt *et al.* [8] clarified that they found multicentricity in 29 % of their patients (n=228). De Jong, *et al.* [9] met multicentricity in 43 % of his patients (n= 100). Kim *et al.* [10] clarified multicentricity in 31 % (n= 81). Pacini *et al.* [11] reported multicentricity in 44 % (n=80).

This difference in the percentage of multicentricity may be due to the different number of patients included in these studies and the different pathological technique in evaluating the specimens (representative section study Vs entire gland dissection technique).

In the last decade, pathology guidelines for thyroid specimen examination recommended that only

representative sections of the entire gland should be examined. In our study, all specimens were examined using the entire gland dissection technique revealing 52% of multicentric cases.

Mazeh, *et al.* [5] reported that an entire gland examination offers a superior representation and better diagnosis of multicentricity than representative section study (60% vs 37 %, $P = 0.04$), so entire gland examination should be preferred.

In our patients, Age had no significant difference in the true incidence of multicentricity in both age groups <40 and >40 years old. This cope with Sevim Turanli *et al.* [12] who reported that the age of the patient has no effect on the presence of tumor in the contralateral lobe.

Among our 50 patients, FNAC was diagnostic in 40 patients with a percentage of 80 % nearly the same as SanjayLogani, *et al.* [13] who reported 45 out of 52 patients diagnosed by FNAC with 86% success rate.

In the present study, the tumor size ranged from 5 mm up to 7 cm with a mean size 2.21 ± 1.56 and showed no significant effect on the true incidence of the multicentricity coping with Sevim Turanli *et al.* [12] that reported that tumor size for the entire cohort of 97 patients showed no effect on the true incidence of multicentricity.

Analyzing nodal affection in our patients, 10 cases (38.46%) from the 26 patients that showed true multicentric tumor had lymph node involvement, but they showed no true association when statistically analyzed. On the other hand, Chow SM, *et al.* [14] demonstrated that patients with multifocal papillary thyroid cancer relatively had a high rate of lymph node involvement (26%). This difference in the results may be due to the difference in the number of cases analyzed and the different pathological technique (entire gland Vs representative section study).

Among our patients, 9 patients (34.6%) that had true multicentric tumor showed extrathyroid extension with a significant association between the extrathyroid involvement and true incidence of multicentricity coping with Pelligriti *et al.* [15] that reported higher rates of extrathyroid invasion (21%) associated with multifocal papillary thyroid cancer. In our study out of the 50 patients, 2 only had a positive family history with 0.04 % coping with Mazeh, *et al.* [5] who reported only 7 patients out of 289 with percentage 2.4%.

CONCLUSION

Multicentricity was found in 52 % of patients with well-differentiated thyroid cancer with entire gland dissection technique. FNAC was diagnostic in 80% of the patients so it can be used as a reliable method for diagnosis. Neither sonography nor intraoperative assessment can be reliable in detection of multicentricity. Tumor size has no significant value in association with multicentricity. Extrathyroid extension was found in 29 % of multicentric patients. Family history was only found in less than 1 % of multicentric patients.

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