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Original Research Article

Relationship between focality and cervical lymph nodes metastasis in papillary thyroid carcinoma

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ABSTRACT

Background: Papillary Thyroid Cancer (PTC) is the most common malignancy in thyroid gland and may be unifocal or multifocal. This study compares between unifocal and multifocal PTC to clarify which type has an aggressive behaviour.
Methods: This retrospective and prospective cross-sectional study was done on one hundred PTC patients who underwent papillary thyroid cancer management. The unifocal and multifocal groups each one contains 50 patients. The study was done in the period between January 2015 to January 2018. Other types of cancer thyroid and distant metastatic thyroid cancer were excluded from the study. All patients underwent follow up for one year.
Results: There are significant differences between unifocal and multifocal PTC regarding to age, the number of positive lymph nodes, history of multinodular goiter (MNG) and capsular invasion. The capsular invasion in multifocal increase the recurrence rate (P=0.03).
Conclusions: The new proposed method for PTC tumor size assessment could be a valuable in multifocal PTC patient's stratification into low risk and high-risk subgroups. Therefore, high risk multifocal PTC patients could have a poor prognosis and high rate of recurrence, for that require aggressive treatment and strict follow up.

Keywords: Cervical lymph node metastasis, Focality, Papillary thyroid carcinoma, Recurrence

INTRODUCTION

Thyroid cancer accounts only for 0.5-1.5 % of all malignancies but the incidence is increasing more rapidly than other cancers in both United States and European countries.[1] While the incidence in Egypt is 2.3% of all malignancies.[2]

Papillary thyroid carcinoma (PTC) accounts for over 85% of all malignant thyroid tumors in regions with sufficient iodide intake, it may occur as a single nodule but also as two or more anatomically separate (non-contiguous) foci within the thyroid gland. This entity is defined as multifocal papillary thyroid carcinoma (MPTC) and is usually reported in literature in 18-87 % of cases.[3] A significantly increased number of neoplastic foci are found when the thyroid gland is systematically sectioned and examined.[4] Multifocality may be associated with either large, clinically evident foci or with multiple microcarcinomas (PTC foci <10mm). MPTC may be found both in a single thyroid lobe (unilateral disease) and in both lobes (bilateral disease).[5] The finding of MPTC in a single thyroid lobe does not predict systematically a bilateral involvement that may occur in 13-71% of cases. The rate of bilateral involvement is significantly increased when the entire gland is systematically examined compared to cases undergoing only representative sampling (60 vs. 37).[4]

Patients with large, locally aggressive or metastatic PTC require total thyroidectomy with excision of adjacent involved structures if necessary and appropriate nodal surgery followed by radioiodine ablation with long-term Thyroid Stimulating Hormone (TSH) suppression. Total thyroidectomy facilitates the use of radioiodine for postoperative scanning to detect and subsequently ablate metastases.[6]

The American Joint Committee on Cancer (AJCC) staging for thyroid cancer into four stages based on the TNM classification. AJCC subdivided thyroid cancer of T1 lesions into T1a (tumors ≤1cm) and T1b (tumors >1 to 2cm) that are limited to the thyroid. In addition, T category descriptors have been added to indicate solitary tumor (s) or multifocal tumor (m). N1 nodal disease is likewise subdivided on the basis of the location of the lymph node involvement. N1a represents nodal metastases to level VI lymph nodes (pre-tracheal, paratracheal, and pre-laryngeal) while N1b represents nodal metastases to lymph nodes in levels I to V or level VII. This subdivision of lymph node status plays an important role in staging as it differentiates stage III patients from stage IV patients with papillary thyroid cancer depending on tumor size.[7] The aim of this work was to evaluate relationship between focality and cervical lymph nodes metastasis in PTC to the size of malignant nodule(s) detected in the excised thyroid gland.

METHODS

This prospective and retrospective study was done on one hundred patients with PTC who underwent management and satisfied the inclusion and exclusion criteria to be enrolled in the study during the period between January 2015 to January 2018. Informed consent was taken from all patients and after approval of the ethical committee of Faculty of Medicine, Menoufia University. Inclusion criteria were all patients with pathological evidence of PTC and cervical lymph nodes metastasis. Exclusion criteria were other types of cancer thyroid and distant metastatic thyroid cancer. For retrospective archived cases, all clinical and histopathological data were retrieved from the patient's medical records. All patients in the study were subjected preoperatively to- personal history taking such as name, age, family history, residence, radiation exposure, voice changes and other neck swelling.

History taking

radiation exposure and multinodular goiter. Imaging: neck ultrasound or CT. Fine needle aspiration cytology (FNAC) from thyroid nodules or suspicious LN, true cut biopsy or excisional LN biopsy. Total thyroidectomy and central neck dissection for all PTC patient with bilateral or unilateral modified neck dissection. All FNAC and surgical specimens were submitted to Pathology Department, Faculty of Medicine, Menoufia University for assessment. Histopathological assessment of received surgical specimens for tumor size that was assessed by measuring the greatest dimension of focus in unifocal while in multifocal PTC by measuring the greatest dimension of the largest focus and by summation of greatest dimensions of all foci which will be referred as total tumor diameter (TTD). Other pathological parameters were assessed which include number of positive cervical dissected lymph nodes, capsular invasion and lymphovascular embolization. Postoperative the patients were evaluated for injury of recurrent laryngeal nerve or superior laryngeal nerve, hypocalcemia, seroma and wound infections. Postoperative the patients were pathologically assessed for tumor size in unifocal nodule or summation of largest dimensions in multifocal nodules, number of positive lymph nodes, lymphovascular embolization, capsular invasion and staging the thyroid malignant nodule according to pathological size. All patients underwent radioactive iodine scan and receive radioactive iodine and followed up for one year by measuring TSH and Thyroglobulin levels with neck ultrasound to assess the recurrence. Patients were divided into two groups: group 1 (unifocal thyroid nodule) and group 2 (multifocal thyroid nodules).

RESULTS

Comparison between the studied PTC groups regarding clinicodemographic parameters

The ages of the multifocal PTC patients ranged from 16years to 68years with a median age of 40years old younger than the unifocal PTC patients that ranged from 23years to 80years with a median age of 53years old with a significant difference between the two groups (P=0.03). There was a significant association between PTC multifocality and presence of multinodular goiter (P<0.01). Whereas the incidence of multifocal PTC was higher in patients with history of multinodular goiter (26%) than unifocal PTC patients with history of multinodular goiter (8%) (Table 1).

Comparison between the studied PTC groups regarding histopathological parameters (Table 2)

Multifocal PTC patients (68%) were bilateral and (32%) were unilateral. In patients with multifocal PTC had cervical LN metastasis (90%) compared with (72%) for unifocal PTC patients with a significant difference between the two groups (P=0.02).

Regarding the number of positive LN, the multifocal PTC patients showed higher number of metastatic LN with median 10 LNs affected, while unifocal PTC patients showed lower number of metastatic LN with median 4 LNs affected (P<0.01). Regarding the capsular invasion, which showed higher occurrence in multifocal PTC than unifocal PTC with significant difference between two groups (P=0.04).

Comparison between the studied PTC groups regarding complication and recurrence

During follow up period, (24%) of multifocal PTC patients developed regional LN recurrence while in unifocal PTC patients no recurrence detected with significant statistically difference between the two group (P<0.001) (Table 3).

Comparison between the greatest dimension of largest focus and TTD in multifocal PTC groups

When using TTD in multifocal PTC group to assess the tumor size, there was a significant increase in the tumor size and upstaging of T stage. According to AJCC criteria, in the multifocal PTC group author identified 9 patients with T1a stage and 11 patients with T3 stage.

However, when using the aggregate size, 7 of 9 patients had upgraded the T stage larger than T1a and identified 20 patients with T3 stage.

In the multifocal PTC group, the size of the largest foci ranges from 0.5-6cm with a mean size 2.69±1.38cm while when author used the aggregate foci the size of aggregation ranges from 0.7-10cm with a mean size 4.09±2.28 with a significant difference between the two groups (Table 4).

Table 1: Comparison between the studied PTC groups regarding clinicodemographic parameters.

Parameters		Studied groups				U-Test	P value
		Unifocal, N=50		Multifocal, N=50			
Age/year	Mean±SD	51.48±16.13		42.92±16.91		2.19	0.03
	Median	53		40			
	Range	23-80		16-68			
		No.	%	No.	%		
Age group	<55years	26	52	33	66	2.02	0.16
	>55years	24	48	17	34		
Sex	Male	23	46	16	32	2.06	0.15
	Female	27	54	34	68		
Residence	Rural	31	62	35	70	0.71	0.40
	Urban	19	38	15	30		
History of MNG	Present	4	8	13	26	5.74	0.01*
	Absent	46	92	37	74		

U = Mann Whitney U test

Table 2: Comparison between the studied PTC groups regarding histopathological parameters.

Parameters		Studied groups				Test	P value
		Unifocal, N=50		Multifocal, N=50			
Side of thyroid nodule	Unilateral	50	100	16	32	X2 51.52	<0.001*
	Bilateral	0	0	34	68		
Size of largest focus	Mean±SD	3.25±2.05		2.69±1.38		U 0.92	0.35
	Range	0.7-8		0.5-6			
T stages	T1a	9	18	9	18	0.7	0.99
	T1b	14	28	13	26		
	T2	16	32	17	34		
	T3	11	22	11	22		
Lymph node status	Present	36	72	45	90	5.26	0.02*
	Absent	14	28	5	10		
Number of affected LN	Median	4		10		U 4.56	<0.001*
	Range	1-11		1-25			
Side of LN dissection	Unilateral	16	32	10	20	X2 4.09	0.13
	Bilateral	34	68	40	80		
Capsular invasion	Present	7	14	16	32	X2 4.57	0.03*
	Absent	43	86	34	68		
Lymphovascular embolization	Present	8	16	14	28	X2 2.10	0.15
	Absent	42	84	36	72		
Evidence of Hashimoto	Present	2	4	6	12	FE 2.17	0.26
	Absent	48	96	44	88		

Table 3: Comparison between the studied PTC groups regarding complication and recurrence.

Operative		Studied groups				F test	P value
		Unifocal, N=50		Multifocal, N=50			
		No.	%	No.	%		
Nerve injury	External laryngeal	1	2	2	4	0.12	0.72
	Recurrent laryngeal	0	0	0	0		
	Negative	49	98	48	96		
Hypocalcemia	Positive	2	4	3	6	0.21	1.0
	Negative	48	96	47	94		
Seroma	Positive	1	2	2	4	1.38	0.44
	Negative	49	98	48	96		
Wound infection	Positive	1	2	2	4	0.21	1.0
	Negative	49	98	48	96		
Recurrence	Positive	0	0	12	24	13.63	<0.001*
	Negative	50	50	38	76		

F = Fisher's Exact test

Table 4: Comparison between the greatest dimension of largest focus and TTD in multifocal PTC groups.

Parameters		TTD		Greatest dimension in largest focus, N=50		Test	P value
		No.	%	No.	%		
T stages	T1a	2	4.0	9	18.0	X^2 Test 8.50	0.04*
	T1b	8	16.0	13	26.0		
	T2	20	40.0	17	34.0		
	T3	20	40.0	11	22.0		
Size (cm)	Mean±SD	4.09±2.28		2.69±1.38		U test 3.32	0.001*
	Range	0.7-10		0.5-6			

P value was the comparison with aggregate foci value

Table 5: Histopathological post-operative assessment in relation to recurrence.

Parameters		Recurrence				Test	P value
		Positive, N=12		Negative, N=38			
		No	%	No	%		
Side of thyroid nodule	Unilateral	2	16.7	14	36.9	X^2 Test 3.08	0.22
	Bilateral	10	83.3	24	63.2		
Size of greatest dimension largest focus	Mean±SD	3.05±1.63		2.57±1.29		U test 0.96	0.33
	Range	1.5-6		0.5-5			
TTD size	Mean±SD	4.7±2.57		3.89±2.19		U test 1.41	0.16
	Range	2.8-10		0.7-9			
T stages (before summation)	T1a	2	16.7	7	18.4	0.88	0.83
	T1b	2	16.7	11	28.9		
	T2	5	41.7	12	31.6		
	T3	3	25	8	21.1		
TTD T stage	T1a	0	0	2	5.3	3.95	0.27
	T1b	0	0	8	21.1		
	T2	6	50	14	36.8		
	T3	6	50	14	36.8		
Lymph node status	Present	12	100	33	86.8	FE test 1.75	0.32
	Absent	0	0	5	13.2		
Number of affected LN	Median	8		11		U test 1.11	0.27
	Range	2-25		1-24			
Side of LN dissection	Unilateral	2	16.7	8	21.1	X2 test 0.66	0.72
	Bilateral	10	83.3	30	78.9		
Capsular invasion	Present	8	66.7	8	21.1	FE test 8.72	0.01*
	Absent	4	33.3	30	78.9		
Lymphovascular embolization	Present	4	33.3	4	10.5	FE test 3.53	0.08
	Absent	8	66.7	34	89.5		
Evidence of Hashimoto	Present	2	16.7	4	10.5	FE test 0.33	0.62
	Absent	10	83.3	34	89.5		

Correlation between radiological size and PTC tumor size, both greatest dimension of largest focus and TTD in multifocal PTC groups (Table 6)

There was a significant positive correlation between radiological size with both pathological size and aggravated size ($p<0.05$) (Table 6).

Table 6: Correlation between radiological size and PTC tumor size, both greatest dimension of largest focus and TTD in multifocal PTC groups.

Parameters	Radiological size	
	r	P value
Pathological size	+0.79	<0.001*
TTD size	+0.37	<0.001*

r: sperman's correlation.

DISCUSSION

The incidence of PTC was 89.4% of all thyroid malignancies. The 5years survival of PTC patients are 98%-90% for stage I-III respectively.[8]

Updated AJCC 8th edition recommend measuring the greatest dimension of the focus or greatest dimension of the largest focus if more than one to classify T stage.[7] This study aimed to evaluate relationship between focality and cervical lymph nodes metastasis in PTC according to the size of malignant nodule(s) detected in the excised thyroid gland.

In the current study, there was a significant difference between multifocal PTC group and unifocal PTC group regarding to the age as multifocal PTC more likely to develop in younger patients while unifocal PTC more likely to develop in older patients. Qu et al, supported this study with increasing number of tumor foci in younger age persons.[10]

Multifocality was higher to occur in the patients with history of MNG than uni-focality that was significantly noted. Lin et al, study showed that patients with MNG who developed PTC had higher risk to develop multifocal cancers compared with the patients with solitary nodular goiter who developed PTC.[9]

This study shows higher incidence of multifocal PTC in both lobe 68% than in one lobe 32% this was supported by Qu et al, found that bilateral thyroid lobe involvement 62% was more common than unilateral thyroid lobe involvement 38%.[12] In this study, there was a significant increase in the incidence of cervical lymph nodes metastasis in multifocality (90%) compared with uni-focality (72%). The number of affected lymph nodes in multifocal groups was more than in unifocal group which indicate the importance of modified neck dissection in multifocality. This was supported by Salter et al, study with 89% incidence of LN metastasis in multifocality and 55% in uni-focality.[11] Qu et al, study showed strong association between number of foci and number of cervical lymph node metastasis.[12]

In the current study, there was a significant difference regarding capsular invasion which demonstrates high percentage of capsular invasion in multifocality. Liu C et al, study demonstrated that TTD more than 1cm in multifocality increases the capsular invasion incidence.[13]

In this study, when using the largest foci to assess the multifocal PTC sometimes downgrade the T staging in thyroid cancer while summation of foci leads to more advanced the T stage that was significant.

This was supported by Wang P et al, study that concluded the stage will be reduced by negligence to measure the smaller foci in multifocality and they found if the focus of the TTD was significantly larger than the largest diameter will lead to upstaging T. If the aggregate size falls within the same range as the largest size, treatment may not be altered based on multifocality alone.[14]

In present study, the incidence of recurrence was greater in the multifocal PTC group than the unifocal PTC group which demonstrates significant aggressiveness of multifocality.

In agreement with the finding, Kim HJ et al, study reported that multifocality was associated with an increased risk of recurrence and suggest that number of tumor foci was a significant predictor factor of poor clinical outcomes and recurrence.[15] In contrary with this finding Leboulleux et al, study reported that multifocality was not associated with recurrence. These discrepancies of result could be attributed to different studies designs and sample size.[16]

Capsular invasion with multifocality has higher rate of locoregional recurrence in this study which was supported by Sharifi et al, study reported that capsular invasion is a predictor of both prognosis in thyroid cancers and risk factors for central lymph node metastasis.[17] In Guo et al, study suggested that other factors, such as gender (male), tumor size, bilateral thyroid nodules, extra thyroid extension, lymph node metastasis and lymphovascular embolization were associated with locoregional recurrence.[18] Unfortunately, there was no significant difference regarding recurrence and other pathological parameters in this study. This may be due to the low number of present studies as author had 12 out of 100 patients who developed recurrence. In the current study there was positive significant correlation between radiological size and pathological size whoever with summation of multi foci there was also positive correlation between radiological size and TTD size ($p<0.01$). This was due to the high accuracy of ultrasound in the evaluation of the thyroid gland and identification of

multiple foci whatever small or large preoperatively which supported by Wang et al.[14]

CONCLUSION

Multifocal PTC patient can be subdivided in to low risk and high-risk subgroups regarding to the tumor size, cervical lymph nodes metastasis and capsular invasion. Capsular invasion is the most important predictor for recurrence. Therefore, Multifocality is more aggressive and needs aggressive treatment and strict follow up.

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