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Defining a New Tumor Dimension in Staging of Papillary Thyroid Cancer

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ABSTRACT

Background: Papillary thyroid carcinoma [PTC] is the most common malignant thyroid tumor, making up over 85% of cases in regions with adequate iodide intake. It can manifest as a solitary nodule or as multiple non-contiguous foci within the thyroid gland.

The aim of the work: This study aims to investigate the correlation between the presence of multiple foci and cervical lymph node metastasis in PTC, taking into consideration the size of the malignant nodules discovered in the removed thyroid gland.

Patients and Methods: In this study, 60 patients diagnosed with PTC were prospectively enrolled. The diagnosis was confirmed using neck ultrasonography, fine-needle aspiration cytology [FNAC], or true-cut biopsy from thyroid nodules or suspicious lymph nodes. All patients underwent total thyroidectomy and central neck dissection. Based on the pathological evaluation after surgery, the patients were divided into two groups: Group I included those with a single thyroid nodule, while Group II comprised patients with multiple thyroid nodules.

Results: The size of the largest thyroid foci in the study ranged from 0.5 to 8 cm, with an average size of 2.8 ± 1.69 cm. For patients with multiple thyroid foci, the sum of their sizes ranged from 0.7 to 10 cm, with an average size of 3.8 ± 2.2 cm. The radiological size of the largest thyroid foci ranged from 1 to 5.2 cm, with an average size of 2.58 ± 1.17 cm. The results demonstrated a significant correlation between the incidence of malignancy recurrence and the presence of multiple foci. Additionally, there was a statistically significant relationship between the involvement of lymph nodes with malignancy and the presence of multiple nodules, with a p-value of less than 0.05.

Conclusion: Multifocal PTC is more aggressive than unifocal PTC so it needs aggressive treatment and restrictive follow up

Keywords: Papillary Thyroid Carcinoma; Cervical Lymph Nodes, Thyroid Foci.

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INTRODUCTION

Thyroid cancer accounts for 2.3 % of all malignancies in Egypt [1]. 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 [noncontiguous] 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 [2].

Systematic sectioning and examination of the thyroid gland reveals a notable increase in the number of neoplastic nodules [3]. Multifocality can be linked to either large, easily noticeable nodules or multiple microcarcinomas [PTC nodules <10 mm]. Multifocal papillary thyroid carcinoma [MPTC] can be present in either a single lobe of the thyroid [unilateral disease] or both lobes [bilateral disease] [4].

The discovery of multifocal papillary thyroid carcinoma [MPTC] in a single lobe of the thyroid does not necessarily imply that both lobes will be affected, as bilateral involvement can occur in 13-71% of cases. However, the incidence of bilateral involvement is significantly higher when the entire gland is systematically examined compared to cases where only representative sampling is performed [60% vs. 37%] [5].

Patients who have large, aggressive, or metastatic papillary thyroid cancer [PTC] necessitate a total thyroidectomy, which may include the removal of adjacent structures if necessary, as well as appropriate nodal surgery [6]. Following the surgery, radioiodine ablation with long-term TSH suppression is required. Total thyroidectomy allows for the use of radioiodine for postoperative scanning, which is useful in detecting and subsequently eradicating metastases [7].

The American Joint Committee on Cancer [AJCC] employs the TNM classification system to stage thyroid cancer, dividing it into four stages. T1 lesions are further classified into T1a [tumors ≤ 1 cm] and T1b [tumors > 1 to 2 cm] that are confined to the thyroid. Furthermore, the T category descriptors distinguish between solitary tumors [s] and multifocal tumors [m]. N1 nodal disease is also subdivided based on the involved lymph node location. N1a denotes nodal metastases to level VI lymph nodes [pretracheal, paratracheal, and prelaryngeal], while N1b denotes nodal metastases to lymph nodes in levels I to V or level VII. This distinction in lymph node status is significant in staging, as it differentiates stage III patients from stage IV patients with papillary thyroid cancer based on tumor size [8].

The purpose of this study is to assess how the presence of multiple foci in PTC and the size of malignant nodules detected in the excised thyroid gland are related to cervical lymph node metastasis.

PATIENTS AND METHODS

The present prospective study was carried out on sixty patients who had PTC scanning from November 2018 to November 2021 at the Department of General Surgery, Faculty of Medicine, Al-Azhar University Hospitals and Tanta Cancer Center. We followed the Helsinki declaration principals. The study has been approved by the ethical committee at Faculty of Medicine [Al-Azhar University]. Patients were included in the study according to the following criteria:

Inclusion criteria: 1] Patients manifesting pathological evidence of PTC. 2] Patients with cervical lymph nodes metastasis.

Exclusion criteria: 1] Patients diagnosed with other types of cancer thyroid. 2] Patients with distant metastatic thyroid cancer.

Data collection: All patients were submitted for the following preoperatively: 1] History taking, general examination, and local examination of the thyroid gland and cervical lymph nodes. 2] Laboratory investigations including CBC, Free T_3, Free T_4, TSH, Liver function tests, and renal function tests. 3] Radiological investigations including; thyroid and neck ultrasound examination to determine the size and laterality of thyroid nodule and to evaluate the lymph node metastases, chest X ray, and CT neck. 4] Indirect laryngoscope for assessment of vocal cords mobility. 5] FNAC or true cut biopsy from thyroid nodules or suspicious LN. 6] Excisional LN biopsy.

Surgical procedure

All patients underwent total thyroidectomy and central neck dissection, regardless of whether they require bilateral or unilateral modified neck dissection.

A collar incision two fingers breadth above the sternal notch was done followed by elevation of the flap in sub-platysma plane to the superior border of the thyroid cartilage's level, superficial to the anterior jugular veins, then, to retract the strap muscles, dissection in the midline was done. The middle thyroid vein is ligated first, after which we proceed with the dissection of the superior pole. We then mobilize the inferior pole to locate the recurrent laryngeal nerve, using the inferior thyroid artery as a reference point. Finally, we ligate the inferior thyroid artery medially to safeguard the blood supply to the parathyroid gland.

We enlarged the collar incision in an upward and lateral direction along the posterior edge of the sternocleidomastoid muscle. We dissected the area between the sternocleidomastoid and strap muscles. By retracting the sternocleido-mastoid muscle laterally, we were able to easily reach the paraglandular, paratracheal, internal jugular, scalene, and posterior triangle nodes. We were able to locate and safeguard the spinal accessory nerve and submandibular salivary gland. The internal jugular nodes were dissected from the vein and removed, along with the surrounding fat. The node-bearing tissue from the posterior triangle was removed along with the jugular nodal specimen. The cervical fat pad, which contains lymphatics and nodes, was detached from below the clavicle and lifted upward. The thoracic duct, phrenic nerve, and brachial plexus were protected during the procedure.

We passed the specimen under the omohyoid muscle and pulled it upwards to mobilize it. The specimen was successfully removed, and both the sternocleidomastoid and omohyoid muscles remained intact. We were able to preserve the common carotid artery, internal jugular vein, vagus nerve, phrenic nerve, spinal accessory nerve, greater auricular nerve, and hypoglossal nerve. A drain was inserted after ensure hemostasis. Strap muscles were closed over the trachea [to prevent trachea tethering to skin] then the wound was closed.

Postoperative assessment

Patients were assessed to exclude the recurrent laryngeal and superior laryngeal nerves injuries, Hypocalcemia, and the development of seroma or wound infection. Following the surgery, a pathological evaluation was conducted, which involved determining the location of the thyroid nodule and the dissected lymph nodes. In the case of multifocal nodules, the size was determined by adding the largest dimensions. The malignant nodule was staged based on its pathological size [T stage] [Figure 1], and the presence of metastatic lymph nodes and the number of positive lymph nodes were assessed. The evaluation also included examining for lymphovascular embolization, capsular invasion, and evidence of Hashimoto thyroiditis.

After the pathological assessment, the patients were separated into two groups: Group One, consisting of patients having a single thyroid nodule, and Group Two, which included patients having multiple thyroid nodules. All patients received a radioactive iodine scan and were treated with radioactive iodine. Follow-up involved monitoring TSH and thyroglobulin levels, as well as conducting neck ultrasounds to detect any signs of recurrence.

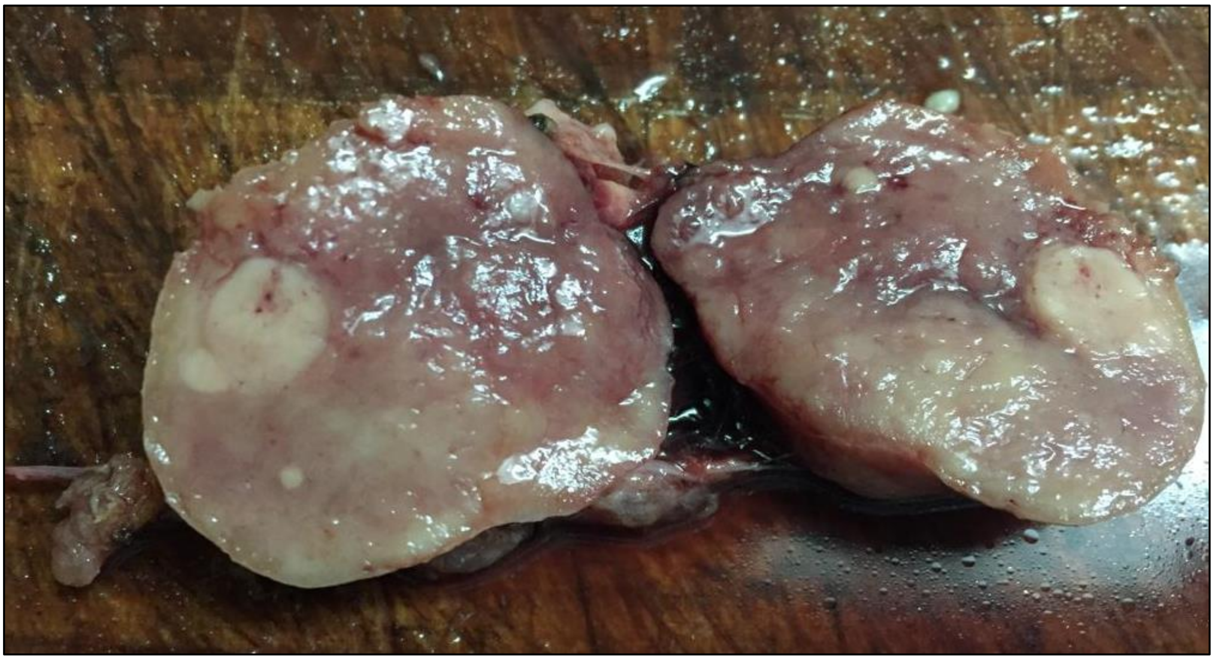

Figure [1]: Cut section of PTC showed multiple nodules variable in size firm in consistency grayish white in color

Statistical analysis: Data were gathered, organized, and analyzed through the Statistical Package for the Social Sciences [SPSS] version 17.0 on an IBM compatible computer [SPSS Inc., Chicago, IL, USA]. Quantitative data were reported as mean ± SD, and a comparison between the two groups was performed using an independent t-test. Qualitative data were presented as numbers and percentages, and a comparison between the two groups was performed using the Chi-square test or the Fisher exact test. Pearson correlation was used to determine the relationship between the different study variables. P value less than 0.05 was considered significant.

RESULTS

Our research involved 60 patients, consisting of 39 females and 21 males, who had been diagnosed with papillary thyroid carcinoma with cervical lymph node metastasis. Thirty of the cases had a single thyroid nodule, while the remaining thirty had multiple thyroid nodules.

The patients' ages ranged from 16 to 89 years, with a mean age of 46.75 ± 17.21 years. The size of the largest thyroid foci in the patients ranged from 0.5 to 8 cm, with a mean size of 2.8 ± 1.69 cm. For patients with multiple thyroid foci, the sum of the sizes ranged from 0.7 to 10 cm, with a mean size of 3.8 ± 2.2 cm. The radiological size of the largest thyroid foci ranged from 1 to 5.2 cm, with a mean size of 2.58 ± 1.17 cm [Table 1].

The number of positive lymph nodes for metastasis in the patients ranged from no metastasis to 25 lymph nodes, with a mean number of 6.47 ± 6.19 [as shown in Table 1]. Among the patients included in the study, 18% had a history of MNG, 7% had a history of radiation exposure, and 5% had a family history of thyroid cancer. The clinical characteristics of the patients are described in Table 2. Of the patients, 73% underwent bilateral dissection, while 18% had a right-side dissection, and 8% had a left-side dissection.

According to the capsular invasion 23% had capsular invasion and 23 % had lympho-vascular embolization. In terms of recurrence, 6 cases [10%] were recurrent, one patient recurred after four months, two patients recurred after five months, while one patient recurred after six months, one patient after 12 months and one other patient after 36 months. In terms of the postoperative complications, 8% had external laryngeal nerve injury, and 3% had recurrent laryngeal nerve injury, 18 % had hypocalcemia, 7% developed seroma, and 5% developed wound infection [Table 3]. The correlation analysis indicated that there was no significant statistical relationship between sex and focality groups. Furthermore, there was no significant statistical relationship observed between the residence groups and focality groups [Table 4].

The statistical analysis revealed a significant relationship between the recurrence of malignancy and the focality groups, as the incidence of recurrence was higher in patients with multifocal nodules [$p < 0.05$]. Additionally, there was a significant statistical relationship observed between the lymph node status [i.e., invasion with malignancy] and focality [$p < 0.05$]. However, the correlation analysis showed no significant statistical relationships between the side of dissection, capsular invasion, lymphovascular embolization, and evidence of Hashimoto's thyroiditis when compared to the focality groups [Table 5].

The analysis of correlations indicated that there were no significant statistical relationships between the suspected side of lymph nodes on radiology and their confirmation compared to the groups of focus. However, there was a significant statistical relationship between the side of the thyroid nodule on radiology and the focus groups. Specifically, bilateral invasion was more common among multifocal groups and right-side invasion was more common among unifocal groups [$p < 0.05$]. Similarly, there was a significant statistical relationship between the side of the thyroid nodules on pathology and the focus groups. Again, bilateral invasion was more common among multifocal groups and right-side invasion was more common among unifocal groups [with a p-value < 0.05], as shown in [Table 6].

The analysis of correlations revealed that there were no significant statistical relationships between a history of malignancy, a history of radiation, or a family history of thyroid cancer when compared to the groups of focus.

The correlation analysis indicated no significant statistical relationship between nerve injury, hypocalcemia, seroma, and wound infection when compared to focality groups. The Mann-

Whitney U test was used to compare the old and new size calculations of the lesions in the study. The comparison showed a statistically significant difference between the old and new calculations, as the size of the lesions was larger in the new group [P-value > 0.05] as shown in [Table 7].

The correlation analysis showed a statistically significant relation between the old and new staging of the lesion as the number of high staging levels was higher in new than old staging [P-value> 0.05].

In the multifocal PTC group, using the Total Tumor Dimension [TTD] to assess tumor size resulted in a significant increase in tumor size and upstaging of T stage. According to the AJCC criteria, 7 patients in the multifocal PTC group were classified as T1a stage, and 3 patients were classified as T3 stage. However, when using the aggregate size, 6 out of the 7 patients previously classified as T1a stage were upgraded to a higher T stage, and a total of 10 patients were identified as T3 stage.

Table [1]: Means ± SD of patient's data [n=No. of the cases]

	No.	Mean	S.D.	Minimum	Maximum
Age	60	46.75	17.21	16	89
Size of largest foci	60	2.8	1.69	0.5	8
New size Summation	30	3.8	2.2	0.7	10
Positive LN	60	6.47	6.19	0	25
Radiological size of largest foci	60	2.58	1.17	1	5.2

Table [2]: Distribution of the clinical findings among cases [n=60]

		Distribution	%
Side of dissect	Bilateral	44	73%
	Right side	11	18%
	Ltef side	5	8%
Capsular invasion	No	46	77%
	Yes	14	23%
Lymphovascular embolization	No	46	77%
	Yes	14	23%
Recurrence	No	54	90%
	Yes	6	10%
Duration of recurrence [months]	No	54	90%
	5	2	3%
	36	1	2%
	12	1	2%
	6	1	2%
	4	1	2%
Evidence of Hashimoto's	No	55	92%
	Yes	5	8%
Side of thyroid nodule by radiology	Right lobe	27	45%
	Bilateral	18	30%
	Left lobe	15	25%
Side of suspicion LN radiological	Bilateral	36	60%
	Right	15	25%
	Left	8	13%
	No	1	2%
Confirmation	FNAC	40	67%
	LN biopsy	9	15%
	LN FNAC	5	8%
	FNAC+LN FNAC	4	7%
	True cut	2	3%
Side of thyroid nodules by pathology	Right lobe	25	42%
	Bilateral	22	37%
	Left lobe	13	22%

FNAC: Fine Needle Aspiration Cytology; LN: Lymph node.

Table [3]: Distribution of the complication after operation among cases [n=60]

		Distribution	%
Nerve injury	No	53	88%
	External laryngeal	5	8%
	Recurrent laryngeal	2	3%
Hypocalcemia	No	49	82%
	Yes	11	18%
Seroma	No	56	93%
	Yes	4	7%
Wound infection	No	57	95%
	Yes	3	5%

Table [4]: Relation between the focality groups and demographic data of the studied cases

		Focality		P-value
		Uni	Multi	
Gender	Male	12 [57.1%]	9 [42.9%]	0.417
	Female	18 [46.2%]	21 [53.8%]	
Residence	Urban	9 [50.0%]	9 [50.0%]	1.000
	Rural	21 [50.0%]	21 [50.0%]	

Table [5]: Relation between the focality groups and different groups of the current malignancy complications of the studied cases

		Focality		P-value
		Uni	Multi	
Lymph node Status	Yes	21 [42.9%]	28 [57.1%]	0.020*
	No	9 [81.8%]	2 [18.2%]	
Side of dissect	Bilateral	20 [45.5%]	24 [54.5%]	0.324
	Lt side	4 [80.0%]	1 [20.0%]	
	Rt side	6 [54.5%]	5 [45.5%]	
Capsular invasion	Yes	5 [35.7%]	9 [64.3%]	0.222
	No	25 [54.3%]	21 [45.7%]	
Lymphovascular embolization	Yes	9 [64.3%]	5 [35.7%]	0.222
	No	21 [45.7%]	25 [54.3%]	
Recurrence	Yes	0 [0.0%]	6 [100.0%]	0.010*
	No	30 [55.6%]	24 [44.4%]	
Evidence of Hashimoto's	Yes	2 [40.0%]	3 [60.0%]	0.640
	No	28 [50.9%]	27 [49.1%]	

*: Significant

Table [6]: Relation between the focality groups and different groups of the current malignancy investigations of the studied cases

		Focality		P-value
		Uni	Multi	
Side of thyroid nodule by radiology	Bilateral	0 [0.0%]	18 [10%]	0.000 *
	Left lobe	9 [60.0%]	6 [40.0%]	
	Right lobe	21 [77.8%]	6 [22.2%]	
Side of suspicion LN radiological	No	0 [0.0%]	1 [100.0%]	0.785
	Bilateral	18 50.0%]	18 [50.0%]	
	Left	4 [50.0%]	4 [50.0%]	
	Right	8 [53.3%]	7 [46.7%]	
Confirmation	True cut	1 [50.0%]	1 [50.0%]	0.192
	FNAC+LN FNAC	2 [50.0%]	2 [50.0%]	
	LN FNAC	5 [100.0%]	0 [0.0%]	
	LN biopsy	3 [33.3%]	6 [66.7%]	

	Thyroid FNAC	19 [47.5%]	21 [52.5%]	
Side of thyroid nodules by pathology	Bilateral	0 [0.0%]	22 [100.0%]	0.000 *
	Left lobe	9 [69.2%]	4 [30.8%]	
	Right lobe	21 [84.0%]	4 [16.0%]	

*: Significant

Table [7]: Comparison between the old and new calculation of the size of lesion [number of cases=30]

Old and new			Mean Rank	Sum of Ranks	U test	P-value
Size of lesion	Old	30	24.4	730.5	265.5	0.006*
	New	30	36.7	1099.5		

DISCUSSION

Thyroid cancer comprises only 1.5% of all cancer cases, with 52,070 new cases diagnosed in the USA [9]. Papillary thyroid carcinoma [PTC] accounts for 89.4% of all thyroid malignancies. The 5-year survival rates for PTC patients range from 98% for stage I to 90% for stage III [10]. The updated AJCC 8th edition recommends using the greatest dimension of the focus or the greatest dimension of the largest focus if there is more than one, to classify the T stage [8].

Wada *et al.* [11] conducted a study that found that skip lesions, which are characterized by involvement of lateral lymph nodes but not central lymph nodes, were infrequent, with a rate of only 9.6%. This outcome is consistent with a previous study involving microcarcinomas [equal to or smaller than 1 cm] that underwent both prophylactic and therapeutic neck dissections of the central and lateral compartments.

Qu *et al.* [12] reported that multifocality in thyroid cancer is more frequently observed in patients over 45 years old, which could be attributed to differences in how age is determined. In our study, we grouped patients based on age below and above 55, according to the AJCC 8th edition guidelines. This was informed by a recent multicenter retrospective study that revealed that by increasing the age cutoff from 45 to 55 years, 17% of the patient population was reclassified to a lower risk category [8]. Additionally, **Park *et al.*** [13] found that patients with multifocal PTC tended to be older at the time of diagnosis compared to those with unifocal PTC.

In another study, multifocal involvement in PTC tumors was present in 11.5% of patients who were 45 years old or younger, and in 14.4% of patients who were older than 45 years [P= 0.374] [14].

Kim *et al.* [15] verified that multifocal PTC is linked to characteristics associated with more aggressive tumors, including older age at diagnosis, a higher incidence of extrathyroidal invasion, metastasis to cervical lymph nodes, and an advanced disease stage at the time of initial surgery.

In contrast to our results, **Coburn and Wanebo** [16] observed that the incidence of multifocality did not increase in a linear fashion with age in the older age group [i.e. 21-50 years, 51-70 years, and >70 years], whereas capsular invasion was significantly more prevalent [38%, 49%, and 74%, respectively].

The present study showed no significant difference regarding to the gender which is supported with **Kim *et al.*** [15] study while in **Qu *et al.*** [12] study reported that affected PTC in females is double affected PTC in males. In another study, **Kiriakopoulos *et al.*** [17] revealed -multifocality was proved to have a statistically significant correlation with the male sex [p = 0.014]

Our study found that multifocality was more common in patients with a history of multinodular goiter [MNG] compared to unifocality. This is consistent with **Lin *et al.*** [18]'s study, which found that patients with MNG who developed PTC had a higher risk of developing multifocal cancers compared to patients with solitary nodular goiter who developed PTC. Additionally, **Kashif *et al.*** [19] reported that 50% of MNG cases transform into thyroid cancer, with 70% of these cases being PTC.

Our study revealed a higher occurrence of multifocal PTC in both thyroid lobes compared to involvement in only one lobe. This finding is consistent with **Qu *et al.*** [12]'s study, which found that bilateral thyroid lobe involvement [62%] is more frequent than involvement in only one lobe [38%]. However**, Wang *et al.*** [20]'s study reported the opposite, with a higher incidence of unilateral involvement than bilateral involvement.

In a meta-analysis included 15 studies involving 9,665 patients, unilateral multifocal papillary thyroid carcinoma [UMPTC] accounted for 10% to 36% of all PTC cases. The study found no significant differences in age, gender, tumor size, and extra-thyroidal extension [ETE] between UMPTC and unilateral unifocal papillary thyroid carcinoma [UUPTC] patients. However, significant differences [P < 0.05] were observed between UMPTC and UUPTC patients in terms of central lymph node metastasis [CLNM], lateral lymph node metastasis [LLNM], tumor-node-metastasis [TNM] stage I+II, TNM stage III+IV, recurrence/persistence of UMPTC group after total thyroidectomy, and overall recurrence/persistence [21].

In terms of complications, our study found a low rate of complications compared to **Christou and Mathonnet** [22]'s study, which reported higher rates of hypocalcemia [20-30%] and recurrent laryngeal nerve injury [5-11%].

Hauch *et al.* [23] reported that postoperative complications occurred in 16.4% of all cases, with an overall risk of complications after total thyroidectomy [TT] being 20.4%, which was significantly higher than after unilateral thyroidectomy [UT] [10.8%, p < 0.0001]. Hypocalcemia was the most common complication after both procedures, but it was significantly less prevalent after UT [7.1% vs. 16.1%, p < 0.0001]. Additionally, TT had a significantly higher risk for respiratory complications [0.84% vs. 1.34%, p < 0.001], bleeding [0.15% vs. 0.23%, p = 0.0403], hematoma [1.24% vs. 1.54%, p = 0.0027], tracheostomy [0.004% vs. 0.024%, p = 0.0493], and vocal cord paralysis [0.59% vs. 1.33%, p < 0.001] compared to UT. After controlling for confounders in a multivariate model, TT was found to be more likely to result in complications than UT [OR 2.15, 95% CI 1.99-2.33, p < 0.0001], and this remained true regardless of the surgeon's volume.

Neck dissection [ND] can significantly affect a patient's quality of life, with shoulder dysfunction being a particularly common issue. This dysfunction is characterized by symptoms such as shoulder drop, scapular flaring, pain, and weakness, and it can have a significant impact on a patient's overall health-related quality of life. Although the spinal accessory nerve [SAN] is typically preserved during ND, patients may still experience postoperative dysfunction, which is often linked to stretching of the SAN during retraction to clear the lymph nodes located behind and above the nerve [level IIb] [24].

When performing a lateral neck dissection for macroscopic DTC metastases, it is recommended to perform a selective neck dissection of levels IIa, III, IV, and Vb, rather than selectively removing only certain lymph nodes ["berry picking"]. Dissecting level I is often unnecessary, as metastatic thyroid disease to this level is uncommon and poses a risk to the marginal mandibular branch of the facial nerve, which could cause lower lip weakness. Dissection above the accessory nerve [IIb] is generally not necessary unless there are suspicious lymph nodes at level IIb or in the high jugular region [IIa], as this could minimize the post-operative morbidity associated with "shoulder syndrome". Shoulder syndrome is a condition characterized by weakness, stiffness, and chronic pain in the shoulder girdle, which can occur when the function of CN XI is impaired [25].

This study found a significant rise in the occurrence of cervical lymph node metastasis in cases with multifocality compared to those with unifocality. The multifocal group had more affected lymph nodes than the unifocal group, indicating the need for modified neck dissection in cases of multifocality. This is consistent with **Salter *et al.*** [26]'s study, which reported an 89% incidence of LN metastasis in multifocality and 55% in unifocality. Additionally, **Qu *et al.*** [27]'s study found a strong correlation between the number of foci and the number of cervical lymph node metastases.

Several recent studies have suggested that multifocal papillary thyroid carcinoma [PTC] is associated with a poorer prognosis, as it increases the risk of lymph node metastases and persistent or recurrent disease [28].

According to **Lim *et al.*** [29]'s study, the incidence of cervical lymph node metastases in patients with multifocal papillary thyroid micro-carcinoma [PTMC] was 55.6%, which is higher than the incidence of 28.6% observed in patients with unifocal disease.

The presence of multifocality was found to be significantly linked to lymph node metastasis [LNM] in cases of papillary thyroid microcarcinoma [PTMC], potentially due to the fact that most multifocal PTMCs have a tumor dimension of over 1 cm. **Zhao *et al.*** [28]'s study found that 66.7% of multifocal PTMCs had a tumor dimension of over 1 cm, and 60.4% of these cases were associated with lymph node metastasis.

Due to limitations in pathological techniques and workload, it is not possible to perform histological examinations on the entire specimen, which means that some small lesions may be overlooked. As a result, some cases of unifocal papillary thyroid microcarcinoma [PTMC] with lymph node metastasis may not actually be unifocal. If we could identify and separate these cases from true unifocal cases, there may be even more significant differences in the risk of nodal metastasis between multifocal and unifocal micro-carcinomas. In other words, the risk of lymph node metastasis in multifocal PTMCs may be even higher than what has been reported so far [28].

Moreover, studies that performed lymph node dissection on PTC patients only when there was clinical involvement found that the presence of multifocality was associated with a significantly higher incidence of local recurrence. On average, the recurrence rate increased by 2.1 to 17.9 times in the presence of multifocality [29].

On the other hand, a study conducted by **So *et al.*** [30] found that when all PTC patients, including those with multifocal tumors, underwent central neck dissection, there was no significant difference in the incidence of local recurrence between multifocal and unifocal tumors.

A different study by **Roh *et al.*** [31] found that tumor size did not independently predict lymph node metastasis in multivariate analysis. Furthermore, the same study did not find any association between tumor multifocality and lymph node metastasis.

The present study found a difference in the incidence of capsular invasion between multifocal and unifocal thyroid carcinoma, with a higher percentage of capsular invasion observed in multifocal cases. This is in line with the findings of a study by **Liu *et al.*** [32], which showed that multifocal tumors with a tumor dimension of more than 1 cm have a higher incidence of capsular invasion. **Qu *et al.*** [12] reported that multifocality is more frequent with extra thyroidal extension.

In a study by **Taskin *et al.*** [14], it was found that when both tumor size and capsule invasion were analyzed together, tumors that were between 1 and 2 cm in diameter had a significantly higher incidence of capsule invasion [57.5%] compared to other size groups.

This study found that when assessing multifocal PTC, using the largest foci alone to determine T staging sometimes resulted in a downgrading of the cancer stage, while adding up the foci led to a higher T stage that was statistically significant. This is consistent with a study by **Wang *et al.*** [20], which found that neglecting to measure smaller foci in multifocal cases could result in a reduction of the cancer stage. **Wang *et al.*** [20] also noted that if the tumor dimension of the largest focus is significantly larger than the largest diameter, the T stage may be upstaged. However, if the tumor dimension of the largest focus falls within the same range as the largest diameter, treatment may not be changed based solely on the presence of multifocality.

Our study found a higher incidence of recurrence in the multifocal PTC group compared to the unifocal PTC group, indicating that multifocality is associated with greater aggressiveness. This is consistent with the findings of a study by **Kim *et al.*** [33], which reported that multifocality is linked to a higher risk of recurrence and suggested that the number of tumor foci is a significant predictor of poor clinical outcomes and recurrence.

In a study conducted by **Ito *et al.*** [34], the risk factors for recurrence after curative surgery and radioiodine ablation therapy were evaluated by assessing the outcomes of recurrent free survival [RFS] as the primary endpoint. Previous research had demonstrated that patients aged 55 years or older, and those with a metastatic node larger than 3 cm, are more likely to experience recurrence in a previously dissected neck compartment. Additionally, primary tumor size larger than 4 cm and extrathyroidal extension were found to be predictors of recurrence in the contralateral lateral compartment.

In contrast to our findings, a study by **Leboulleux *et al.*** [35] found no association between multifocality and recurrence in PTC. These differences in results may be attributed to differences in study design. **Grigsby *et al.*** [36] also reported that bilaterality of PTC did not have any effect on recurrence or survival after treatment.

The present study found a significant positive correlation between radiological size and pathological size in PTC. However, when multiple foci were added together, there was also a positive correlation between radiological size and the total tumor dimension [TTD]. This can be attributed to the high accuracy of ultrasound in evaluating the thyroid gland and detecting multiple foci, whether they are small or large, before surgery. This is supported by **Wang *et al.*** [20]'s findings.

Lastly, we concluded that multifocal PTH is more aggressive than unifocal PTC so it needs aggressive treatment and restrictive follow up.

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