Should we perform routine prophylactic central neck dissection in patients with thyroid papillary microcarcinoma?

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PURPOSE: *Cervical lymph node (LN) metastases in papillary thyroid cancer (PTC) are common in tumors especially that are larger than 1cm. Ipsilateral central neck dissection (CND) is usually preferred even in the absence of a palpable LN. This study aims to clarify the incidence and predictive factors for occult ipsilateral central LN metastasis in these patients, and the management of patients without clinical evidence of metastasis.*
METHODS: *204 PTC patients were studied. The patients were divided into two according to the tumor size of ≤5mm or larger. Patient demographics, tumor properties, LN metastasis, preoperative neck ultrasonography findings and surgical outcomes were analyzed.*
RESULTS: *There were 152 patients in study group-1 (nodule > 5 mm) and 52 patients in group-2 (nodule ≤ 5 mm). The mean tumor size was 11.9 mm. Overall, preoperative neck ultrasonography showed central neck LN in 25 (12.3%) patients, however, final pathology revealed metastatic LN at central compartment in 59 (28.9%) patients. There were 56 (27.5%) patients with metastasis in group-1 compared to 3 (1.4%) patients in group-2.*
CONCLUSIONS: *Prophylactic CND is advised in PTC for the reduction of recurrence in central compartment. According to our results, in patients with tumors smaller than 5 mm and without evidence of nodal metastasis in preoperative neck ultrasonography, we do not recommend prophylactic CND.*

KEYWORDS: Lymph node metastases, Neck dissection, Occult cancer, Papillary thyroid cancer

Introduction

The technological advances in diagnostic imaging modalities and increasing accuracy of biopsy results had led to the increase in the detection of thyroid nodules and incidence of thyroid cancer in the last decades [1]. Papillary thyroid cancer (PTC) is the most common histo-pathological subtype of the most common endocrine malignancy, the thyroid cancer [2]. It is known to be a lymphotropic cancer, thus it has increased incidence of regional lymph node metastasis up to 60% [3]. Since lymph node metastasis increases the risk of locoregional recurrence; the management of PTC without evident clinical and radiological metastatic lymph nodes in the central compartment is controversial. Although, there is consensus on performing central neck dissection (CND) on patients with metastasis in the lymph nodes; various recommendations have been suggested for the management of central compartment lymph node (CCLN) negative patients. American Thyroid Association (ATA), American Association of Endocrine Surgeons (AACE/AAES), and the National Comprehensive Cancer Network (NCCN) guidelines, do not suggest prophylactic CND in low risk patients [4-6]. The European Thyroid Association

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(ETA) has underlined that prophylactic CND could be beneficial in the evaluation of pathological N staging which would help direct treatment and follow-up [7]. Due to debates regarding central neck dissection in patients with papillary thyroid cancer, we aimed to study the relationship between the size of the nodule and presence of lymph node metastasis in CCLN negative (according to clinical findings and imaging modalities) patients, whose selection of treatment is controversial.

Materials and Methods

Between April 2014 and December 2017, a total of 204 patients who underwent total thyroidectomy with the diagnosis of papillary thyroid carcinoma were included in this study. All cases were performed by a single endocrine surgeon, and prophylactic central neck dissection was performed routinely in all cases. All patients were operated under general anesthesia and they were intubated with EMG endotracheal tubes, and NIM system was used for monitoring (Medtronic Inc., Jacksonville, USA).

The patients were divided into two study groups according to the tumor size of >5 mm and ≤5 mm. Patient demographics, tumor properties, lymph node metastasis, preoperative neck ultrasonography findings and surgical outcomes were analyzed.

Statistical Analysis

Data were retrospectively extracted from the institutional database and patients' charts. SPSS 18 (IBM Corp. Armonk, NY) software was used to perform t-test, chi-square, and univariate regression analysis. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were compared with Fisher's exact test or Chi-square test. Statistical significance was defined as $p < 0.05$.

Results

A total of 204 patients were enrolled into the study with a female to male ratio of 1.48 (122/82). The mean age of the patients was 42.9 years. Tumors were mostly located at the right lobe in 98 patients (48.1%), at the left lobe in 62 patients (30.4%) and at both lobes in 44 patients (21.5%). Multifocality was observed in 68 patients (33.3%) while, multicentricity was observed in 44 patients (21.6%). The median tumor size was 11.9 mm (range: 3-41mm). Patients were allocated into two distinct groups with tumor size >5 mm (group 1, n=152, 74.5%) and with tumor size ≤5 mm (group 2, n=41, 25.5%). Preoperative neck ultrasonography showed clinically suspicious lymph nodes at the central compartment in 25 patients (12.3%). Central neck dissection pathology interpretations revealed lymph node metastasis in 56 patients (27.5%) in group 1 and 3 patients (1.4%) in group 2 (p=0.002). Statistical analyses also showed significant relationship between increase in the tumor size and central lymph node metastasis (p=0.004). Multifocal tumors (n=68, 33.3%) are presented with metastasis in the central neck compartment in 29 patients (14.2%) (p=0.02). Tumor capsule invasion, multicentricity and lymphovascular invasion did not show any significant difference with central lymph node metastasis. In terms of complications, only 6 patients (2.9%) had transient vocal cord palsy and 8 patients (3.9%) had transient hypoparathyroidism. The clinical and demographic variables of the patients and subgroups were presented in the Table I.

Table I - *Clinical and pathological characteristics of 204 patients with PTC*

	No. of patients	%
Total Number	204	
Gender		
Female	122	59.8
Male	82	40.2
Mean age	42.9	
Tumor location		
Left	62	30.4
Right	98	48.1
Bilateral	44	21.5
Number of nodules		
Multiple (≥2)	108	52.9
Single nodule	96	47.1
Nodule Size		
>5 mm	152	74.5
≤5 mm	52	25.5
>10 mm	119	58.3
≤10 mm	85	41.7
Radioactive iodine treatment		
Yes	75	36.8
No	129	63.2
Extracapsular invasion		
Yes	37	18.1
No	167	81.9
Multifocality		
Yes	68	33.3
No	136	66.7
Multicentricity		
Yes	44	21.6
No	160	78.4
Complications		
Transient vocal cord palsy	6	2.9
Transient hypoparathyroidism	8	3.9
Pre-operative USG Lymph Node		
Positive	25	12.3
Negative	179	87.7
Metastasis to lymph node		
Group 1 (>5 mm)	56	27.5
Group 2 (≤5 mm)	3	1.4

Discussion

Even though PTC has a good prognosis, it has been known that central neck lymph node metastases occur more than 30-60% of the cases [3,8,9]. Due to the increased locoregional recurrence rate in patients with PTC, the guidelines recommend therapeutic CND with evidence of lymph node metastases. Although there is no scoring system that determines the patients who may underwent prophylactic CND, many reports in the literature note the factors associated with occult metastases as tumor size, aggressive histology and extrathyroidal extension.

One of the main debates regarding the performance of prophylactic CND is increased risk of postoperative complications [10]. While some reports have shown approximately 6% temporary hypoparathyroidism, other authors have reported up to 12% when CND was performed [11,12]. Our data also shows similar results to those studies which support no difference in terms of complications and may also be considered acceptable compared to literature. Even though in a recent large series, Monacelli et al. have reported 1.5% unilateral permanent palsy, and 4.4% of permanent hypoparathyroidism, we did not encounter any permanent morbidity [13].

Regarding the detection of metastatic central neck lymph nodes in preoperative period, ultrasonography is still the gold standard diagnostic tool which help to identify the CCLN metastases, however, there are many reports showing the low sensitivity of detecting central neck metastases [14,15]. Similarly, in our study the preoperative ultrasonography was only able to reveal 64% of the metastatic lymph nodes.

The large series in literature generally shows a positive correlation with increased tumor size and central compartment metastases. In these studies, using multivariate analysis, Roh et al. showed that the tumor size of equal or larger than 1 cm was an independent factor for lymph node metastases, moreover, in another study, Koo et al. has obtained similar outcomes in tumors larger than 1cm in size [16-18]. However, contrary to these studies, Kutler et al. [19] showed no statistical significance for tumor size in correlation with central compartment metastases. When the tumor cutoff value is taken as 5 mm in size, our results were similar to the general data in the literature which supports the positive correlation of tumor size and increased incidence of metastatic lymph nodes [16-18]. However, our subanalysis with the cutoff value taken as 10 mm, revealed no statistical significance as parallel to the Kutler et al.'s study [19]. Therefore, we postulate that tumor sizes between 5 to 10 mm should be thoroughly evaluated for prophylactic CND. Previously it was showed that the multifocality was a risk factor for persistence and recurrence of the disease [20]. Moreover, the result of this study also showed that multifocality of the tumor in one lobe leads to a higher incidence of metastasis compared to tumors on both thyroid lobes.

Furthermore, prophylactic CND may lead to clarify the staging of the patient after surgery and explicit benefits of guiding the adjuvant therapy of radio-iodine therapy and TSH suppression therapy. To date, there are also other techniques for determining the postoperative period and advancement of the disease as analysis of the BRAF V600E mutation which may also help to determine the aggressive histology of PTC. However, this was also one of our limitations in this study in addition to not being a prospective randomized study.

Conclusion

The results of this study showed that patients with nodules larger than 5 mm or patients with multifocal tumors should undergo prophylactic CND. Thus, in order to understand the efficiency of prophylactic CND in terms of disease-free survival and overall survival, controlled randomized studies and large series are needed to be performed.

Riassunto

Nel carcinoma papillare della tiroide (PTC) sono comuni le metastasi ai linfonodi cervicali (LN), in particolare se il nodulo è di dimensioni superiori a 1 cm. Nel trattamento chirurgico solitamente si preferisce l'esecuzione della dissezione del collo centrale e omolaterale (CND) anche in assenza di LN palpabile. Con questo studio ci si propone di chiarire l'incidenza e i fattori predittivi per metastasi LN omolaterali occulte in questi pazienti e la gestione di pazienti senza evidenza clinica di metastasi linfonodale.

Sono stati studiati 204 pazienti affetti da PTC. I pazienti sono stati divisi in due in base alla dimensione del tumore di ≤5mm o superiore. Sono stati analizzati i dati demografici dei pazienti, le proprietà dei tumori, le metastasi LN, i risultati dell'ecografia del collo preoperatoria e gli esiti chirurgici.

152 pazienti erano presenti nel gruppo di studio 1 (nodulo> 5 mm) e 52 pazienti nel gruppo 2 (nodulo ≤ 5 mm). La dimensione media del tumore era di 11,9 mm. Nel complesso, l'ecografia del collo preoperatoria ha mostrato LN centrali nel collo in 25 casi (12,3%), ma lo studio anatomo-patologico definitivo ha rivelato l'esistenza di un LN metastatico al compartimento centrale in 59 pazienti (28,9%). Nel gruppo 1 si sono dimostrati 56 pazienti con metastasi (27,5%) rispetto a 3 (1,4%) nel gruppo 2.

In conclusione la CND di profilassi è consigliabile in caso di PTC per la riduzione della recidiva nel compartimento centrale. Tuttavia, nei tumori inferiori a 5 mm senza evidenti metastasi a LN nel compartimento centrale all'ecografia preoperatoria del collo, non sono state osservate metastasi, e potrebbero non aver necessità di una CND.

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