European Review for Medical and Pharmacological Sciences 2016; 20: 3972-3979

The impact of the multifocality and subtypes of papillary thyroid carcinoma on central compartment lymph node metastasis

L. SOYLU[1], O.U. AYDIN[1], S. OZBAS[1], B. BILEZIKCI[2], S. ILGAN[3], A. GURSOY[4], S. KOCAK[1]

Departments of [1]Endocrine Surgery, [2]Pathology, [3]Nuclear Medicine, and [4]Endocrinology; Ankara Guven Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: Papillary thyroid carcinoma (PTC) may often appear as multifocal disease. Few studies demonstrated a higher rate of central compartment lymph node metastasis (CCLNM) in multifocal PTC patients. Therefore, the effect of different histological subtypes of multifocal PTC on CCLNM is another subject for further examination. The aim of the present study is to evaluate the rate of central lymph node positivity in multifocal PTC as compared to unifocal disease, and to identify the role of different histologic subtypes of PTC on central neck lymph node positivity.

PATIENTS AND METHODS: Patients with PTC who underwent total thyroidectomy (TT) + central cervical lymph node dissection (CCLND) at authors' institution between January 2012 and June 2016 were included (n=274). Independent Samples t-test, Mann-Whitney U test and Chi-square tests were used to determine univariate associations, and multivariate analysis was conducted by logistic regression.

RESULTS: The rate of CCLND positivity in multifocal PTC is higher than unifocal tumors and the difference is significant ($p < 0.05$). The univariate analysis demonstrated significant relation with male sex, lymphovascular invasion and size of dominant nodule > 10 mm regarding of CCLND positivity in multifocal PTC patients. The comparison between solitary and mixed histologic subtype of multifocal PTC is also significant ($p < 0.05$).

CONCLUSIONS: Multifocality is an important risk factor for CCLNM. Male sex, dominant tumor size >10 mm and mixed histological subtype in multifocal PTC may play an important role in CCLND positivity.

Key Words:

Multifocality, Central compartment lymph node dissection, Metastasis, Papillary thyroid carcinoma.

Introduction

The most common malignant tumor of the thyroid gland is papillary thyroid cancer (PTC), constituting 80-85% of all thyroid malignancies[1]. The disease is characterized by a good prognosis with surgery as the primary treatment option[2,3]. Nevertheless, it is likely that PTC spreads to regional lymph nodes, and lymphatic involvement primarily occurs in the central neck compartment (20%-90% of patients). Current knowledge suggests that central lymph node metastasis is the most crucial variable to increase the risk of local recurrence and overall survival[4-6].

Some scholars recommend routine central neck lymph node dissection (CCLND) in order to prevent a future recurrence, citing the high risk of positive lymph nodes, the accuracy of staging, better outcomes, reduced postoperative thyroglobulin (Tg) levels, and a lower morbidity rate associated with the first operation[7-10], whereas others suggest that this procedure increases the rate of complications, without any demonstrable benefits in terms of long-term survival[7,10-13].

PTC usually occurs with unilateral or bilateral multifocal tumors. It has been shown by histopathological analysis that the individual glands in PTC host multifocal noncontiguous tumor foci, accompanied by dominant tumor and multifocal additional smaller foci of microcarcinomas[14]. Multiple tumor foci were earlier thought to be the consequence of intraglandular metastasis of a single primary tumor through intraglandular lymphatics. Yet, this view has changed with the introduction of modern molecular techniques, and it has been reported that independent clones result in

Corresponding Author: Lutfi Soylu, MD; e-mail: lutfisoylu@hotmail.com

multiple synchronous primary tumors, which define the multifocal PTCs[15-17]. It has been suggested that multifocal characteristics of PTC present a significant risk factor for central compartment lymph node metastasis (CCLNM)[18-21].

WHO classification suggests 15 different pathological variants for PTC[22]. Several histopathological PTC variants involving growth patterns, stromal changes and combination of cell types have been discovered[23]. This indicates that the same case may involve different histological subtype of PTCs. In addition, the variants might have different clinical behavior, and prediction of the prognosis might be facilitated by classifying these variants[24].

The aim of the study is to determine the occurrence of CCLND positivity in multifocal PTC and the impact of different histological subtypes of PTC and other tumor characteristics on CCLNM.

Patients and Methods

We analyzed the data of 274 patients with PTC collected prospectively from January 2012 to June 2016 in our Endocrine Surgery Department in Ankara Guven Hospital. All patients with pathologically proven PTC were treated with total thyroidectomy (TT) + CCLND. Total thyroidectomy was performed by extracapsular dissection to remove both thyroid and pyramidal lobes in all cases. Bilateral CCLND involves removal of pre laryngeal, pretracheal and both the left and the right paratracheal nodal basins. All procedures were performed by two senior endocrine surgeons (SO and SK). Multifocal disease was defined as the presence of two or more foci of PTC. The presence of PTC foci in both right and left lobes or isthmus was called as bilateral disease. Coexistence of lymphocytic thyroiditis, lymphovascular invasion (LVI), and extrathyroidal extension (ETE) were considered positive if recorded as such for any of the foci in the pathology report. Histological subtypes of PTC foci were documented for every case and all the information was kept in a database for evaluation.

Histopathological Examination

Microscopic examinations were done by the same experienced pathologist (BB). Lymph nodes were dissected by manual palpation in the CCLND specimen, and rest of the fibro-adipose tissue was submitted for a pathological process for possible microscopic lymph nodes. All specimens were fixed in 10% formalin solution and preserved in paraffin blocks, which were cut serially in sections of 3 μm thickness, and deparaffinized sections were stained with hematoxylin-eosin. Lymph nodes were assessed by routine histological examination, and no additional techniques were used. The number of microscopic lymph nodes was assessed according to Parkash et al[25]. Assessment of the histopathological types of PTC was based on the World Health Organization's (WHO) published recommendations with a few important alterations based on subsequently published studies[26].

Statistical Analysis

The data were analyzed through IBM SPSS 23.0 statistical software package (SPSS Inc., Chicago, IL, USA). Apart from the use of descriptive statistical methods (frequency, percentage, median, min-max values) in the evaluation of the data, chi-square (c^2) test was also used in comparing the qualitative data. The compliance of the data with normal distribution was evaluated through Kolmogorov-Smirnov and Shapiro-Wilk tests. Independent Samples *t*-test was used for comparison between groups in terms of the variables with normal distribution, while Mann-Whitney U test was used for the variables without normal distribution. The values with a probability (p) smaller than a=0.05 were considered significant, showing the difference between the groups, while greater values were considered insignificant, showing no difference between the groups.

Power Analysis

Power analysis was conducted using G*Power 3.1.9.2 statistical software package, and the power was found $(1-\beta)=0.98$ with the values $n_1=119$, $n_2=155$, $\alpha=0.05$, Effect Size d=0.5.

Results

A total of 274 PTC patients were included in this study. All patients had TT+CCLND as the primary operation. Also, lateral cervical lymph node dissection was performed in 36 of these patients. The average age was 40.9 years, and 220 of them (80.3%) were female. Eight patients had a family history of PTC in their first-degree relatives. Nearly half of the patients had papillary

thyroid microcarcinoma (47.5%-131/274). The rate of CCLND positivity was 43.1% (118/274). Among patients with positive central neck disease, the average number of lymph nodes harvested was 7.7 (range 1-35; median 7). The mean number of positive lymph nodes was 3.4 (range 1-12; median 4). Unifocal and multifocal PTCs were encountered in 155/274 (56.6%) and 119/274 (43.4%) of the patients, respectively. Two hundred and thirty-seven (86.5%) patients had a single pathological subtype of PTC; however, the remaining 37 (13.5%) patients had more than one subtype of PTC. Lymphocytic thyroiditis was also present in 122/274 (44.5%) patients. The extrathyroidal extension was reported in 92/274 (33.6%) patients, and LVI was seen in 72/274 (23.3%) patients (Table I).

Table I. Clinicopathologic characteristic of the PTC patients (n=274).

Variables		n	%
Age	40.9 ± 10.4		
Sex	Female	220	80.3
	Male	54	19.7
Family history		8	3.2
Microcarcinoma		131	47.8
CCLND positivity		118	43.1
Lymphocytic thyroiditis		122	44.5
Focality	Multifocal	119	43.4
	Unifocal	155	56.6
LVI		72	26.3
ETE		92	33.6
Mix subtype PTC		37	12.8

CCLND: Central compartment lymph node dissection, LVI: Lymphovascular invasion, ETE: Exthyroidal extension.

The comparison of the clinicopathological characteristics between the multifocal group and the unifocal group is presented in Table II. There is statistically significant difference in terms of age, CCLND positivity and LVI ($p<0.05$). Sixty-two out of 119 (52.1%) patients with multifocal PTC had positive central neck lymph nodes compared with fifty-six out of 155 (36.1%) patients with unifocal disease, showing a significant association between multifocality and CCLNM ($p<0.05$). However, the comparison of sex, family history, the presence of lymphocytic thyroiditis, dominant tumor size, and ETE are not significant between these groups.

Univariate analysis of the risk factors associated with CCLND positivity in multifocal PTC patients is presented in Table III. Male sex is a significant risk factor in this group ($p<0.05$). In patients who have a dominant nodule <10 mm had a CCLND positivity of 38.9% (21/54); however those with a dominant nodule of >10 mm had 63.1% (41/65), and the difference is statistically significant ($p<0.05$). The effect of the number of PTC foci on central neck metastasis was further examined. The CCLND positivity rate in multifocal PTC patients was 47.7% (31/65), 56.9% (29/51) and 66.7% (2/3) in patients who had two foci, between three and nine foci, and 10 or more foci, respectively ($p>0.05$). Laterality is another important risk factor in some published series. However, in our study bilateral multifocal PTC and unilateral multifocal disease rates were identified as 51.3% (20/39) and 52.5% (42/80), respectively. Laterality, the presence of lymphocytic thyroiditis, ETE and number of foci were not significant

Table II. Comparison of clinicopathological characteristics between multifocal and unifocal groups (n=274).

Variables		Multifocal (n=119)	Unifocal (n=155)	p
Age		43.3 ± 11.3	39.0 ± 9.3	**0.001**
Sex	Female	92 (77.3%)	128 (82.6%)	0.350
	Male	27 (22.7%)	27 (17.4%)	
Family history		4 (3.4%)	4 (2.6%)	0.730
CCLND positivity		62 (52.1%)	56 (36.1%)	**0.008**
Lymphocytic thyroiditis		56 (47.1%)	66 (42.6%)	0.460
Dominant tumor size				
	0-10 mm	54 (45.4%)	84 (54.2%)	0.343
	11-20 mm	54 (45.4%)	58 (37.4%)	
	>20 mm	11 (9.2%)	13 (8.4%)	
LVI		39 (32.8%)	33 (21.3%)	**0.032**
ETE		47 (39.5%)	45 (29.0%)	0.069

CCLND: Central compartment lymph node dissection, LVI: Lymphovascular invasion, ETE: Exthyroidal extension.

Table III. Univariate analysis of factors associated with CCLND positivity in multifocal PTC patients.

Variable	CCLN pozitivity / total (%)		p
Dominant tumor size	0-10 mm	21/54 (38.9%)	
	>10 mm	41/65 (63.1%)	**0.009**
Sex			
	Female	40/92 (43.5%)	**0.001**
	Male	22/27 (81.5%)	
Laterality			
	Unilateral	20/39 (51.3%)	
	Bilateral	42/80 (52.5%)	1.000
Lymphocytic thyroiditis		25/56 (44.6%)	0.125
LVI		32/39 (82.1%)	**0.000**
ETE		26/47 (55.3%)	0.704
Number of foci	2 foci	31/65 (47.7%)	
	3-9 foci	29/51 (56.9%)	0.542
	≥10 foci	2/3 (66.7%)	

CCLND: Central compartment lymph node dissection, LVI: Lymphovascular invasion, ETE: Exthyroidal extension

parameters for CCLND positivity (p>0.05) (Table III).

Male sex and LVI were also found to be significant risk factors in the multivariate analysis concerning of CCLND positivity in multifocal PTC. The odds ratio (OR) for CCLND positivity was determined by logistic regression. There was a significantly increased OR for sex and LVI (Table IV).

The rate of CCLND positivity based on multifocal PTC histological subtypes is presented in Table V. CCLND positivity in patients who have a solitary histological subtype of PTC, and 2 or more subtypes was 45.1% (37/82) and 67.6% (26/37), respectively. The difference between these groups is statistically significant (p<0.05).

All the histological subtypes of PTC found in the pathology specimens are presented in Table VI. The most common subtype is classical PTC and the second one is follicular variant PTC. Most of the multifocal patients with a mixed histological subtype of PTC have classic and follicular variants as part of the pathology.

Table IV. Multivariate analysis of association of CCLND positivity with multifocal PTC.

Risk Factors	OR (Odds Ratio)	%95 GA	p
Sex	7.74	2.490-24.038	**0.000**
LVI	9.49	3.528-25.516	**0.000**

LVI: Lymphovascular invasion.

Discussion

PTCs often arise as multiple tumor foci in the thyroid gland. Multifocal PTCs can be synchronous tumors or the metastatic foci of the largest primary tumor. Multifocality is known to be associated with higher rates of lymph node metastasis, persistent local disease after initial treatment, regional recurrence and poorer prognosis compared with unifocal disease[20,27-30].

Multifocal PTC has an incidence ranging from 18% to 87% in published series[22,31-33]. It was found by Bansal et al[34] that distinct molecular alterations cause the development of minimum 30% of multifocal PTCs, while approximately 60% might be multiple synchronous primary tumors. 119 patients out of 274 (43.4%) in our study population had multifocal PTC. It has been recently shown that multifocality also plays a role as a risk factor for CCLNM[18,20,21,35].

Differentiated PTC highly tends to spread to regional lymph nodes. It is acknowledged that lymph node metastasis in PTC increases the likelihood of local disease recurrence[4,12,36,37] as well as

Table V. The rate of CCLND positivity based on PTC histologic subtype in multifocal disease.

	CCLND positivity (n - %)	p
Soliter	37/82 (45.1%)	0.038
Mixt	25/37 (67.6%)	
Total	62/119 (52.1%)	

Table VI. Histologic subtypes of PTC according to unifocal and multifocal disease.

Histologic subtypes	Unifocal	Multifocal	
		Soliter	Mixt
Classic type	105 (28.3%)	45 (12.4%)	32 (8.6%)
Follicular variant type	41 (13.1%)	37 (11.8%)	34 (10.8%)
Warthin like type	3 (1.0%)	--	3 (1.0%)
Cystic papillary type	1 (0.3%)	--	1 (0.3%)
Solid type	--	--	1 (0.3%)
Oncocytic type	3 (1.0%)	--	1 (0.3%)
Diffuse sclerosing type	1 (0.3%)	--	--
Cribriform morular type	1 (0.3%)	--	--
Total	**155 (49.4%)**	**82 (26.1%)**	**77 (24.5%)**

causing a poor prognostic factor for PTC[1,11,20]. Nevertheless, this finding is disputed since other studies conclude that long-term patient prognosis is not affected by central neck lymph node positivity due to the indolent nature[38]. Cervical neck lymph node metastases are widespread with an incidence rate among PTC patients ranging from 20 to 50%[12,13,39-41]. In a previous study conducted by our group, we found a CCLND positivity rate of 38% in pT1, clinic N0 PTC patients. Therefore, performing CCLND with total thyroidectomy poses no additional risk of injury to the recurrent laryngeal nerve or of permanent hypocalcemia[42].

In this study population, we found that the ratio of CCLND positivity was 43.1% (118/274), 36.1% (52/155) and 52.1% (62/119) in overall PTC patients, in the unifocal disease and in the multifocal group, respectively. Therefore, the difference between the multifocal and the unifocal group is statistically significant ($p<0.05$), showing a significant association between multifocality and CCLNM as reported in the literature. In a study by Kuo et al[27], higher rates of regional lymph node metastases, extrathyroidal invasion, and distant metastases were detected at the time of diagnosis in a series of 2418 PTC patients. As the tumor number increased, central lymph node metastasis also increased. Kim et al[43] reported that the number of tumor foci independently predicted regional lymph node metastasis and an increase in the number of tumor foci was strongly associated with older age at diagnosis, CCLND positivity, and advanced TNM stage of PTC. The effect of multifocality on prognosis in patients having one, two, or three or more PTC foci undergoing thyroidectomy has been investigated by Qu et al[20]. The researchers found that the likelihood of recurrence and death was significantly increased by the presence of several foci, particularly three or more. Another study[30] found that patients with multifocal tumors had a significantly higher extrathyroidal extension, CCLNM, and advanced TNM stage.

A meta-analysis conducted with the inclusion of 20 studies and 9084 patients who had had a thyroidectomy and prophylactic CCLND largely concentrated on the risk factors for central lymph node metastasis in patients who had negative central compartment lymph nodes revealed by clinical examination[44]. The researchers found that the increased risk was associated with factors such as male sex, age < 45 years, multifocality, tumor size > 2 cm for PTC and > 0.5 cm for papillary microcarcinoma, location of primary tumor in the central area and low lobe, LVI, capsular invasion and ETE. Yet, there was no relationship between increased risk of CCLND positivity in these patients and bilateral tumors and lymphocytic thyroiditis. The authors concluded that these factors should guide the application of prophylactic CCLND in patients with clinically negative central compartment lymph nodes. In a more recent study, Afif et al[35] looked into the relationship between number of tumors and central lymph node metastasis, and they also reported a similar rate of metastasis in patients having one and two foci. But, the rate was two times higher in the presence of 3-9 tumors, and 4 times higher when there were ten or more. Similar studies[15,18,45] have shown that tumor multifocality is significantly associated with lymph node metastasis, which is consistent with our results. In our study group, not only CCLND positivity but also older age and LVI were also statistically significant risk factors between multifocal and unifocal PTC patients.

In our study, CCLNM rate in the multifocal group is 47.7%, 56.9%, and 66,7% in patients who have two foci, from 3 to 9 foci, and 10 or

more foci, respectively. These data showed no significance between the number of foci and CCLND positivity unlike the other published series above ($p>0.05$).

Univariate analysis of multifocal PTC patients demonstrated increasing size of dominant tumor (>10 mm), LVI and sex as significant predictors of CCLND positivity in our study population. However, the multivariate analysis further showed that LVI presented the most significantly increased OR for central neck metastasis.

WHO classification suggests 15 histological subtypes for PTC[22]. Classical and follicular variant PTCs (FVPTC) appear as the most frequent subtypes. PTC histological variants might exhibit different biological behaviors compared to classical PTC[46]. Ito et al[24] observed follicular, tall cell, and oncocytic variants in 6.6%, 3.9%, and 1.9% of the cases, respectively.

Kelli et al[47] found in their study that patients with conventional PTC, rather than those with FVPTC, had malignant lymph nodes with high frequency. Whether or not to conduct elective CCLND in patients with FVPTC is to be confirmed by additional studies. There is a gap in the literature about the occurrence of multifocal PTC and CCLND positivity as solitary and mixed types. In our study, the relation between CCLND positivity and PTC histological variants are statistically significant between solitary and mixed tumors. CCLND positivity in patients who have a solitary histological subtype of PTC, and 2 or more subtypes was 45.1% (37/82) and 67.6% (26/37), respectively. The difference between these groups is statistically significant ($p<0.05$). However, the aggressive variants of PTC are few in our study group and it is difficult to explain the significance between solitary and mixed groups as most of the histologic subtypes are classical and FVPTCs in both groups. All histological subtypes of PTC found in the pathology specimens of multifocal PTC patients are presented in Table VI.

Conclusions

We showed that multifocality increases the CCLND positivity in PTC. In those patients, male sex, size of dominant tumor >10 mm and LVI are also related with CCLNM. However, its impact on patient survival is still unknown. The impact of the histologic subtype of multifocal PTC is a subject to be further investigated. Some mixed subtypes of multifocal PTC may be associated with more aggressive metastasis in the central neck but our patient sample size is not enough to make a proper comment on this subject.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer 2006; 106: 524-531.
2) Sciuto R, Romano L, Rea S, Marandino F, Sperduti I, Maini CL. Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. Ann Oncol 2009; 20: 1728-1735.
3) Toniato A, Boschin I, Casara D, Mazzarotto R, Rubello D, Pelizzo M. Papillary thyroid carcinoma: factors influencing recurrence and survival. Ann Surg Oncol 2008; 15: 1518-1522.
4) Wang Q, Chu B, Zhu J, Zhang S, Liu Y, Zhuang M, Yang Y. Clinical analysis of prophylactic central neck dissection for papillary thyroid carcinoma. Clin Transl Oncol 2014; 16: 44-48.
5) Pelizzo MR, Boschin IM, Toniato A, Piotto A, Pagetta C, Gross MD, Al-Nahhas A, Rubello D. Papillary thyroid carcinoma: 35-year outcome and prognostic factors in 1858 patients. Clin Nucl Med 2007; 32: 440-444.
6) Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery 2008; 144: 1070-1077.
7) Docimo G, Tolone S, Ruggiero R, Gubitosi A, Pasquali D, De Bellis A, Limongelli P, DelGenio G, Docimo L, Conzo G. Total thyroidectomy without prophylactic central neck dissection combined with routine oral calcium and vitamin D supplements: is it a good option to achieve a low recurrence rate avoiding hypocalcemia? A retrospective study. Minerva Chir 2013; 68: 321-328.
8) Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, Barbieri V. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1,087 patients and review of the literature. Thyroid 2012; 22: 911-917.
9) Nixon IJ, Ganly I, PatelSG, MorrisLG, Palmer FL, ThomasD, Tuttle RM, Shah JP, Shaha AR. Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. Surgery 2013; 154: 1166-1173.
10) Conzo G, Docimo G, Mauriello C, Gambardella C, Esposito D, Cavallo F, Tartaglia E, Napolitano S, Santini L. The current status of lymph node dis-

section in the treatment of papillary thyroid cancer. A literature review. Clin Ter 2013; 164: 343-346.

11) Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. Thyroid 2009; 19: 683-689.

12) Barczynnski M, Konturek A, Stopa M, Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. Br J Surg 2013; 100: 410-418.

13) Conzo G, Pasquali D, Bellastella G, Esposito K, Carella C, De BellisA, Docimo G, Klain M, Iorio S, Napolitano S, Palazzo A, Pizza A, Sinisi AA, Zampella E, Bellastella A, Santini L. Total thyroidectomy, without prophylactic central lymph node dissection, in the treatment of differentiated thyroid cancer. Clinical retrospective study on 221 cases. Endocrine 2013; 44: 419-425.

14) De Matos PS, Ferreira AP, Ward LS. Prevalence of papillary microcarcinoma of the thyroid in Brazilian autopsy and surgic series. Endocr Pathol 2006; 17: 165-173.

15) Park SY, Park YJ, Lee YJ, Lee HS, Choi SH, Choe G, Jang HC, Park SH, Park DJ, Cho BY. Analysis of differential BRAF(V600E) mutational status in multifocal papillary thyroid carcinoma: evidence of independent clonal origin in distinct tumor foci. Cancer 2006; 107: 1831-1838.

16) Giannini R, Ugolini C, Lupi C, Proietti A, Elisei R, Salvatore G, Berti P, Materazzi G, Miccoli P, Santoro M, Basolo F. The heterogeneous distribution of BRAF mutation supports the independent clonal origin of distinct tumor foci in multifocal papillary thyroid carcinoma. J Clin Endocrinol Metab 2007; 92: 3511-3516.

17) Frank R, Baloch ZW, Gentile C, Watt CD, LiVolsi VA. Multifocal fibrosing thyroiditis and its association with papillary thyroid carcinoma using BRAF pyrosequencing. Endocr Pathol 2014; 25: 236-240.

18) Tam AA, Özdemir D, Çuhaci N, Ba er H, Aydin C, Yazgan AK, Ersoy R, Çakir B. Association of multifocality, tumor number, and total tumor diameter with clinicopathological features in papillary thyroid cancer. Endocrine 2016 53: 774-783.

19) So YK, Kim MW, Son YI. Multifocality and bilaterality of papillary thyroid microcarcinoma. Clin Exp Otorhinolaryngol 2015; 8: 174-178.

20) Qu N, Zhang L, Ji QH, Zhu YX, Wang ZY, Shen Q, Wang Y, Li DS. Number of tumor foci predicts prognosis in papillary thyroid cancer. BMC Cancer 2014;14: 914.

21) Huang G, Tian X, Li Y, Ji F. Clinical Characteristics and Surgical Resection of Multifocal Papillary Thyroid Carcinoma: 168 Cases. Int J Clin Exp Med 2014; 15: 5802-5807.

22) Malloy MK, Cunnane FM. Pathology and cytologic features of thyroid neoplasms. Surg Oncol Clin N Am 2008; 17: 57-70.

23) DeLellis RA. Pathology and genetics of thyroid carcinoma. J Surg Oncol 2006; 94: 662-669.

24) Ito Y, Hirokawa M, Uruno T, Kihara M, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A. Prevalence and biological behaviour of variants of papillary thyroid carcinoma: experience at a single institute. Pathology 2008; 40: 617-622.

25) Parkash V, Bifulco C, Feinn R, Concato J, Jain D. To count and how to count. That is the question. Interobserver and intraobserver variability among pathologists in lymph node counting. Am J Clin Pathol 2010; 134: 42-49.

26) DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. Pathology and Genetics of Tumours of the Endocrine Organs. Lyon, France: IARC Press, 2004.

27) Kuo SF, Lin SF, Chao TC, Hsueh C, Lin KJ, Lin JD. Prognosis of multifocal papillary thyroid carcinoma. Int J Endocrinol 2013; 2013: 809382.

28) Liu Z, Wang L, Yi P, Wang CY, Huang T. Risk factors for central lymph node metastasis of patients with papillary thyroid microcarcinoma: a meta-analysis. Int J Clin Expt Pathol 2014; 7: 932-937.

29) Iacobone M, Jansson S, Barczynski M, Goretzki P. Multifocal papillary thyroid carcinoma: a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbecks Arch Surg 2014; 399: 141-154.

30) Kim HJ, Sohn SY, Jang HW, Kim SW, Chung JH. Multifocality, but not bilaterality, is a predictor of disease recurrence/persistence of papillary thyroid carcinoma. World J Surg 2013; 37: 376–384.

31) Singhal S, Sippel RS, Chen H, Schneider DF. Distinguishing classical papillary thyroid microcancers from follicular-variant microcancers. J Surg Res 2014; 190: 151-156.

32) Ahn HY, Chung YJ, Kim BS, Kang KH, Seok JW, Kim HS, Park SJ, Cho BY. Clinical significance of the BRAF V600E mutation in multifocal papillary thyroid carcinoma in Korea. Surgery 2014; 155: 689-695.

33) Zhao Q, Ming J, Liu C, Shi L, Xu X, Nie X, Huang TL. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. Ann Surg Oncol 2013; 20: 746-752.

34) Bansal M, Gandhi M, Ferris RL, Nikiforova MN, Yip L, Carty S, Nikiforov YE. Molecular and histopathologic characteristics of multifocal papillary thyroid carcinoma. Am J Surg Pathol 2013; 37: 1586-1591.

35) Al Afif A, Williams BA, Rigby MH, Bullock MJ, Taylor SM, Trites J, Hart RD. Multifocal papillary thyroid cancer increases the risk of central lymph node metastasis. Thyroid 2015; 25: 1008-1012.

36) Conzo G, Tartaglia E, Avenia N, Calò PG, de Bellis A, Esposito K, Gambardella C, Iorio S, Pasquali D, Santini L, Sinisi MA, Sinisi AA, Testini M, Polistena A, Bellastella G. Role of prophylactic central compartment lymph node dissection in clinically N0 differentiated thyroid cancer patients: analysis of risk factors and review of modern trends. World J Surg Oncol 2016; 14: 149.

37) Raffaelli M, De Crea C, Sessa L, Giustacchini P, Bellantone R, Lombardi CP. Can intraoperative frozen section influence the extension of central neck dissection in cN0 papillary thyroid carcinoma? Langenbecks Arch Surg 2013; 398: 383-388.

38) Riss JC, Peyrottes I, Chamorey E, Haudebourg J, Sudaka A, Benisvy D, Marcy PY, Nao EEM, Demard F, Vallicioni J, Poissonnet G, Dassonville O, Santini J, Bozec A. Prognostic impact of tumour multifocality in thyroid papillary microcarcinoma based on a series of 160 cases. Eur Ann Otorhinolaryngol Head Neck Dis 2012; 129: 175-178.

39) Wang W, Gu J, Shang J, Wang K. Correlation analysis on central lymph node metastasis in 276 patients with cN0 papillary thyroid carcinoma. Int J Clin Exp Pathol 2013; 6: 510-515.

40) Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. Ann Surg Oncol 2013; 20: 3477-3483.

41) White ML, Doherty GM. Level VI lymph node dissection for papillary thyroid cancer. Minerva Chir 2007; 62: 383-393.

42) Aydin OU, Soylu L, Ozbas S, Ilgan S, Bilezikci B, Gursoy A, Sengezer T, Kocak S. The risk of hypoparathyroidism after central compartment lymph node dissection in the surgical treatment of pT1, N0 thyroid papillary carcinoma. Eur Rev Med Pharmacol Sci 2016; 20: 1781-1787.

43) Kim HJ, Park HK, Byun DW, Suh K, Yoo MH, Min YK, Kim SW, Chung JH. Number of tumor foci as predictor of lateral lymph node metastasis in papillary thyroid carcinoma. Head Neck 2015; 37: 650-654.

44) Sun W, Lan X, Zhang H, Dong W, Wang Z, He L, Zhang T, Liu S. Risk Factors for central lymph node metastasis in CN0 papillary thyroid carcinoma: a systematic review and meta-analysis. PLoS One 2015; 10: e0139021.

45) Kim HJ, Kim NK, Choi JH, Kim SW, Jin SM, Suh S, Bae JC, Min YK, Chung JH, Kim SW. Radioactive iodine ablation does not prevent recurrences in patients with papillary thyroid microcarcinoma. Clin Endocrinol (Oxf) 2013; 78: 614-620.

46 Lin JD, Hsueh C, Huang BY. Papillary thyroid carcinoma with different histological patterns. Chang Gung Med J 2011; 34: 23-34.

47) Salter KD, Andersen PE, Cohen JI, Schuff KG, Lester L, Shindo ML, Sauer D, Gross ND. Central nodal metastases in papillary thyroid carcinoma based on tumor histologic type and focality. Arch Otolaryngol Head Neck Surg 2010; 136: 692-696.