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RESEARCH

Predictive Factors for Lymph Node Metastasis in Solitary Papillary Thyroid Carcinomas: A Retrospective Study

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Abstract Identifying risk factors for neck lymph node metastasis (LNM) in papillary thyroid carcinoma (PTC) is important for patient prognosis establishment. We conducted a retrospective study among 317 patients with solitary PTC. Factors associated with clinically evident LNM were evaluated. LNM were identified in 69 (21.7 %) patients. Central compartment (17.3 %) and lateral compartment (9.4 %) were involved. Thyroid capsule invasion and extrathyroidal extension were found to be independent risk factors for both central and lateral compartment metastasis in multivariate analysis. Larger diameter was associated with central compartment metastasis in logistic regression model, whereas male gender only with lateral compartment metastasis. As closer tumors were positioned in relation to glandular capsule we expected rising rates of nodal spread. It was unlikely to find clinically evident neck LNM among patients with centrally located tumors.

Keywords Thyroid gland · Thyroid neoplasms · Carcinoma · Papillary · Lymphatic metastasis

Introduction

Thyroid cancer is the most frequent endocrine malignancy, accounting for approximately 1 % of all malignant tumors in the United States [1]. Papillary thyroid carcinoma (PTC) represents the most common type, with incidence increasing each year [2]. Patient age, tumor subtype, extrathyroidal extension and neck lymph node metastasis (LNM), are known risk factors associated with increased recurrence of PTC [3, 4]. There is a pending discussion about the prognostic significance of central compartment lymph node metastasis in PTC, especially among patients with subclinical disease [5–7]. However there are strong evidences of worse outcomes among patients with clinically evident LNM [8–10]. Lateral neck node metastases are also closely related to tumor recurrence and poor prognosis in patients with PTC [11]. Precise preoperative evaluation for neck node metastasis is helpful in planning decisions regarding the extent of surgery. Among preoperative imaging methods, neck ultrasound (US) is a sensitive tool for evaluation of thyroid lesions, as well as lateral neck nodes. Computed tomography (CT) can also be used for comprehensive and objective evaluation of the neck, regardless of the operator's skills [12]. However both imaging techniques show low sensitivity for central compartment metastasis [13] and few studies have reported the diagnostic accuracy of preoperative CT [14].

Patients with neck LNM at the time of surgery should undergo neck dissection and consider high dose iodine therapy, even though it can lower the patient's quality of life. Elective central or lateral neck dissections in thyroid papillary carcinoma management are still controversial. Though in experienced hands complications related to neck lymphadenectomies are uncommon, some studies reported raised surgical morbidity and increased risk of transient and permanent hypoparathyroidism when routine central or lateral neck dissections was performed [15, 16]. Therefore, there is a need for precise methods for prediction of neck LNM, especially for cases whose metastases may impact in patient's prognosis. We designed the current study to evaluate risk factors associated with LNM in a sample whose lymphadenectomies were performed according to clinically

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suspicious neck lymph nodes, focused on the pathological features, especially distance of tumor from the glandular capsule.

Methods

This study was approved by our institutional review board. A total of 317 cases of PTC patients initially treated in the head and neck surgery department of our institution between June 2000 and December 2010 were included in the study. All patients had no history of neck irradiation and underwent preoperative ultrasonography. Pertinent cases were submitted to US-guided fine needle aspiration biopsy (FNAB). Total thyroidectomy was the procedure of choice in 89.9 % of cases. In 32 patients, all of them presenting with microcarcinomas, a lobectomy or istmo-lobectomy was performed. Neck dissection was performed only in cases with suspicious lymph node disease in preoperative or trans-operative examination, including image exams, clinical findings, lymph node cytology or trans-operative frozen section results. Elective or prophylactic central or lateral neck dissection is not routinely performed in our service. Patients presenting with tumor histology other than PTC (71 cases), cases with collision thyroid neoplasms (7 cases, represented by cases with more than one histology in the same gland; for example, a papillary and a follicular carcinoma in the same case), unresectable tumors (8 cases), multifocal tumors (202 cases) and those with no information about tumor diameter and position of tumors in relation to the glandular capsule (10 cases) were excluded from the study.

The following variables were used to analyze risk factors for LNM: gender, age at diagnosis, final pathological results, primary tumor size, tumor histological variants, extrathyroidal extension, capsule invasion, tumor distance from the glandular capsule, concomitance with Hashimoto's thyroiditis, lymphovascular invasion signs and T stage. Pathological analysis was performed in 93.6 % of cases by the same pathologist (Barra MB), one with special dedication to thyroid and head and neck tumor pathology. Pathological staging was applied according to the seventh edition of *American Joint Committee on Cancer pTNM staging system* [17]. Tumors located at 1 mm from the glandular capsule, without invading it, were described as tangents to the capsule. Lymph node status and extrathyroidal extension were defined based on microscopic examination findings. Neck compartments were defined according to Memorial Sloan-Kettering Cancer Center's classification of neck lymph node regions [18]. Thyroid specimens were routinely submitted to total inclusion, with slice thickness of 2 mm, cutting the gland from the surface to the center, as "book sheets". The number of slices varied according to the gland and tumor volume. Diameter was used as synonym of major axis, independent if it is longitudinal, latero-lateral or antero-posterior axis.

Frequencies and distribution of each selected variable were calculated. We used mean (standard deviation), absolute frequencies, percentages, and medians (with minimum and maximum values) as appropriated. For the differences between groups, we used chi-square tests for categorical variables. Continuous variables were analyzed with the Student's *t*-test and ANOVA or Mann–Whitney *U* test and Kruskal-Wallis test, according to the result of the Kolmogorov–Smirnov test for normal distribution. We employed two stepwise logistic regressions to identify factors independently associated with LNM (dependent variable). The first model included distance of tumors from the glandular capsule and overall rates of LNM; the second one was similar to the first, but analyzed frequencies of LNM according to level affected (only central metastasis; and only lateral metastasis). The level of statistical significance was set at 5 %. Analysis was performed with SPSS version 15.0 (SPSS Inc., Chicago, IL).

Results

A total of 317 patients consisted of 260 women and 57 men with a mean age of 47.77 (14.58) years (range, 13–84 years). The median size of the primary thyroid cancer was 1.1 cm (range, 0.04–9 cm). In 144 (45.4 %) cases major diameter was ≤1 cm. Capsule invasion was found in 161 patients (50.7 %), but extrathyroidal extension in only 71 cases (22.3 %). In 109 (34.3 %) cases the lesions were located at 0.1 cm from the glandular capsule. The remaining group, 47 (14.8 %) cases, was represented by tumors at least 0.2 cm far from the glandular capsule. One hundred and seventy eight (56.1 %) cases were classified as T1 staging, 35 (11.0 %) as T2, 98 (30.9 %) as T3 and 6 (1.8 %) as T4 staging. Neck dissections were performed in 130 (41.0 %) cases, all with suspicion of LNM. Overall, 39 (12.3 %), 14 (4.4 %) and 16 (5.0 %) had involvement of only central, only lateral and both central and lateral compartments, respectively. Table 1 shows differences among groups according to distance of tumor from the glandular capsule. It is clear that as the lesions came closer to the capsule, rates of LNM also increased (See table 1). We found only one case of LNM among patients with tumors at ≥0.2 cm from the glandular capsule: a solitary PTC, 0.4 cm distant from the glandular capsule, with central compartment metastasis. Univariate analysis showed LNM was significantly more frequent in patients whose tumors showed extrathyroidal extension ($p \leq 0.001$) or capsule invasion signs ($p \leq 0.001$), in patients with signs of lymphovascular invasion ($p = 0.009$), in larger tumors ($p \leq 0.001$) and in those with advanced T stage ($p \leq 0.001$). Besides differences in relative and absolute values, we could find only marginal significance among tumors tangent to the capsule (See Table 2). We found neck dissection was significantly more frequent in the group with capsule invasion tumors ($p = 0.0028$), which may reflects nothing but

Table 1 Comparative analysis of clinic and histopathological factors among papillary thyroid carcinoma cases according to distance of tumor from the glandular capsule

	Distance of tumor from the glandular capsule *										
	− 0.1 cm Mean(SD)		0 cm Mean(SD)		0.1 cm Mean(SD)		≥0.2 cm Mean(SD)		Total Mean(SD)		*p* value
Age	47.23(17.97)		45.03(14.02)		49.66(13.55)		49.46(11.46)		47.77(14.58)		0.12
Diameter	3.00(1.99)		1.57(1.23)		1.67(1.72)		0.53(0.66)		1.77(1.72)		
	Median (min - max)		Median (min - max)		Median (min - max)		Median (min - max)		Median (min - max)		
Diameter	2(1.1–9)		1.05(0.1–6.5)***		1(0.04–7)***		0.4(0.1–4.3)		1.1(0.04–9)		<0.001
	N=71	% (22.3)	*N*=90	% (28.3)	*N*=109	% (34.3)	*N*=47	% (14.8)	*N*=317	% (100)	
M/F	15/56	21.1/78.8	16/74	17.7/82.2	18/91	16.5/83.4	8/39	17.0/82.9	57/260	17.9/82.0	0.881
More aggressive variants**	7	9.8	5	5.5	6	5.5	1	2.1	19	5.9	0.361
Hashimoto's thyroiditis	15	21.1	26	28.8	41	37.6	14	29.7	96	30.2	0.128
Neuro-vascular or lymphatic invasion	9	12.6	6	6.6	5	4.5	0	0	20	6.3	0.035
T1-2/T3-4	0/71	0/100	71/19	78.8/21.1	96/13	88.0/11.9	46/1	97.8/2.1	213/104	67.1/32.8	<0.001
Neck lymph node metastasis	32	45.0	26	28.8	10	9.1	1	2.1	69	21.7	<0.001

N: absolute frequency; %: Relative frequency; *SD* Standard Deviation, Min-Max: Variation betweeen Minimum and Maximum; Age in years; Diameter in centimeters (cm); *M/F* Male/Female,− 0.1 cm: tumors with extrathyroidal extension; 0 cm: tumors invading glandular capsule but restricted to it; 0.1 cm: tumors at 0.1 cm from the glandular capsule; ≥0.2 cm: tumors at 0.2 cm or more from the glandular capsule; **Considered more agressive variants: Tall Cell Variant, Columnar Variant, Diffuse Sclerosing Variant and Solid Variant; *** Underlined values do not differ between themselves in Kruskal-Wallis Test (p=0,271); T: T Staging; F: ANOVA coefficient test; *H*: Kruskal-Wallis coefficient test; $\chi 2$: chi-square coefficient test; *p* value: level of significance utilized

Table 2 Comparative analysis of clinic and histopathological factors among papillary thyroid carcinoma cases with or without neck lymph node metastasis at initial presentation

	Absence of neck Lymph node metastasis		Presence of neck Lymph node metastasis		Total		*p* value
	Mean(SD)		Mean(SD)		Mean(SD)		
Age	48.40(13.92)		45.53(16.66)		47.77(14.58)		0.148
Diameter	1.55(1.66)		2.55(1.71)		1.77(1.72)		
	Median (min - max)		Median (min - max)		Median (min - max)		
Diameter	0.9(0.04–9)		2(0.4–8)		1.1(0.04–9)		<0.001
	N=248	% (78.2)	*N*=69	% (21.7)	*N*=317	% (100)	
M/F	40/208	16.1/83.8	17/52	24.6/75.3	57/260	17.9/82.0	0.104
More aggressive variants*	12	4.8	6	8.6	18	5.6	0.221
Hashimoto's thyroiditis	81	32.6	15	21.7	96	30.2	0.810
Neuro-vascular or lymphatic invasion	11	4.4	9	13.0	20	6.3	0.009
Relation to glandular capsule**							<0.001
− 0.1 cm	39	15.7	32	46.3	71	22.3	<0.001
0 cm	64	25.8	26	37.6	90	28.3	<0.001
0.1 cm	99	39.9	10	14.4	109	34.3	0.053
≥0.2 cm	46	18.5	1	1.4	47	14.8	
T1-2/T3-4	182/66	73.3/26.6	31/38	44.9/55.0	213/104	67.1/32.8	<0.001

N: absolute frequency; %: Relative frequency; *SD* Standard Deviation, Min-Max: Variation betweeen Minimum and Maximum; Age in years; Diameter in centimeters (cm); *M/F*: Male/− 0.1 cm: tumors with extrathyroidal extension; 0 cm: tumors invading glandular capsule but restricted to it; 0.1 cm: tumors at 0.1 cm from the glandular capsule; ≥0.2 cm: tumors at 0.2 cm or more from the glandular capsule; **Considered more agressive variants: Tall Cell Variant, Columnar Variant, Diffuse Sclerosing Variant and Solid Variant; T: T Staging; *t*: *t* Student test coefficient; U: Mann–Whitney coefficient test; $\chi 2$: chi-square coefficient test; *p* value: level of significance utilized the routine of performing neck dissections only when suspicious or confirmed LNM.

Stepwise regression analysis was used to assess the independent factors related to LNM. Table 3 summarizes the odds ratios and confidence intervals of the factors which showed statistical significance in multivariate analysis. The set included all variables analyzed. Cases with tumors at least 0.2 cm far from the glandular capsule were used as parameter in relation to the variable distance. Distance of tumors from the glandular capsule was found to be an independent risk factor for neck LNM by logistic regression analysis, though we have found statistically significant results only for tumors with capsule invasion signs. Cases with extrathyroidal extension were 24.89 times more likely to show LNM (Exp(B)=24.890; p=0.002). Patients with tumors with only capsule invasion, without signs of extrathyroidal extension, were 15.61 times more likely to have LNM (Exp(B)=15.614; p=0.008). Meanwhile cases whose tumors were tangent to the capsule were 3.7 times more likely to evidence LNM at clinical presentation (Exp(B)=3.707; p=0.222). Each additional centimeter to tumor diameter added 18.6 % in overall chances (Exp(B)=1.186; p=0.05) of presenting LNM. When restricting analysis to cases with only central compartment metastasis, distance from the glandular capsule and tumor diameter maintained statistical significance. We observed no cases of lateral compartment metastasis among patients with tumors at least 0.2 cm distant from the glandular capsule. Among patients with only lateral compartment metastasis, glandular capsule invasion, extrathyroidal extension and gender showed significance in logistic regression model (See Table 3).

Discussion

PTC is a common finding in general population [19]. Similarly, the prevalence of occult LNM among cases of PTC is also high [5]. Despite the presence of metastatic lymph nodes being associated with higher rates of recurrence [20], elective central and lateral compartment neck dissection is still controversial, since its impact on survival and neck recurrence is not clear [21, 22]. Wada et al. found discrepancy between the high frequency of pathologic lymph node involvement and the rareness of clinical lymph node recurrence in the prophylactic dissection group. One may attribute this low rate of lymph node recurrence to the efficacy of the node dissection, but this cannot be, since the nodal recurrence rate was also low in those who did not undergo neck node dissection [10].

Though discrepancies between studies, there are strong evidences of worse outcomes among patients with clinically evident LNM [8–10]. In our study, univariate and multivariate analysis were used to evaluate the risk factors for LNM in a sample whose neck dissections were performed only when clinical suspicion was present. We found that extrathyroidal extension and capsular invasion were risk factors in multivariate analysis for both central and lateral compartment LNM. Increased diameter and male gender were also risk factors for central and lateral compartment disease, respectively. Our results are in agreement with previous reports, when male gender was a risk factor for LNM [5, 23]. Jeong et al. also found association between male sex, larger tumor size and LNM rate in multivariate analysis [24]. Gülben et al. found both multifocality and capsule invasion to be isolated risk

Table 3 Independent factors associated to the presence of neck lymph node metastasis after multiple regression

Neck Lymph Node Metastasis (Central and Lateral Compartment)						
Variables	β	SE	*p* value	OR	95 % CI	
					Lower	Upper
Extrathyroidal extension	3.578	1.159	0.002	35.804	3.695	346.951
Capsular invasion only	2.759	1.047	0.008	15.779	2.028	122.754
Neck Lymph Node Metastasis (Central Compartment Only)						
Variables	β	SE	*p* value	OR	95 % CI	
					Lower	Upper
Extrathyroidal extension	2.932	1.067	0.006	18.758	2.318	151.788
Capsular invasion only	2.388	1.05	0.023	10.892	1.392	85.213
Diameter	0.211	0.091	0.02	1.235	1.033	1.476
Neck Lymph Node Metastasis (Lateral Compartment Only)						
Variables	β	SE	*p* value	OR	95 % CI	
					Lower	Upper
Male Gender	1.052	0.453	0.02	2.862	1.177	6.962
Extrathyroidal extension	2.961	0.66	<0.001	19.309	5.301	70.334
Capsular invasion only	2.117	0.672	0.002	8.304	2.223	31.024

β: Coefficient of determination, *SE* Standard Error; *p* value: level of significance utilized, *OR* Odds Ratio value, *CI* Confidence Interval factors for clinically evident LNM by logistic regression analysis [25]. Choi et al. reported that degree of tumor lymphangiogenesis may be related to the risk of lateral LNM, though extrathyroidal extension showed no significance in multivariate analysis [26]. Hunt et al. found that patients with lateral compartment metastasis were significantly more likely to be younger, to have extrathyroidal extension, histological characteristics of a conventional variant of PTC and tumors involving the superior aspect of the thyroid lobe [27]. Zhang et al., working with solitary tumors, also found association between upper pole tumors and lateral compartment LNM, besides lower third lesions were associated with central compartment disease [28]. However even those authors agree they can not exclude that the proximity of the lesions to the gland periphery may lead to tumors reaching the thyroid capsule more quickly, leading to earlier lymphatic spread of tumors even with small-volume disease [27].

Multiple studies recognized capsule invasion and extrathyroidal disease as important factors in relation to LNM [29, 30]. Niemeier et al. observed not only that extrathyroidal extension was associated with aggressive features of papillary thyroid microcarcinomas but also that the simple presence of tumor located at the surface of the thyroid gland had a strong correlation with LNM [31]. Though the authors did not discriminate capsular invasive tumors from those lesions only tangent to the capsule, it is likely that superficial tumor location may have facilitated tumor spread into lymphatic channels and regional lymph nodes. Kim et al. also observed a significant difference in univariate analysis when studying central LNM and the state of contact of tumors with the glandular capsule in ultrasonographic examinations of ≤2 cm PTC patients [32]. Moreover, animal studies suggested that vascular and lymphatic network appears denser in the subcapsular region, which could explain a predisposition of LNM in groups with peripherally located tumors [33, 34]. In our study we did not find an association of tumors tangent to the glandular capsule with LNM, but we could observe a type of scale which as closer tumors were positioned in relation to the capsule rising rates of LNM may be expected, being unfeasible to find neck metastasis among patients with solitary nodules distant from the glandular capsule (See Table 1). It seems cases with a centrally located solitary PTC represent a subpopulation with low risk of neck metastasis, which could be benefited from a conservative neck approach.

Our study did have some limitations. We did not exclude from the analysis cases with occasionally found thyroid cancers. Also we cannot exclude the possibility of peripherally located tumors being associated to a major suspicion of malignancy, which may influence on neck dissection decisions. However, as commented above, our routine is to undergo neck dissections only when patients show clinical or imaging signs concerning for nodal disease. The only way to reinforce our results is to conduct a longitudinal study, analyzing lymph node recurrence rates between peripherally and centrally located carcinomas. Our hypothesis will be sustained if our observations direct to a major prevalence of recurrences among individuals previously reported as presenting neck metastasis at initial presentation. Finally we also did not subclassify PTC extrathyroidal extension in “minimal extension” or “massive extension”, an important sight when analyzing prognosis and relapse free survival, as demonstrated by Ito et al. [35].

In conclusion, when the results of neck preoperative diagnostic evaluation are not definitive or are inadequate, clinical and pathological characteristics may help to predict neck LNM. Based on this retrospective study, patients with nodules distant at least 2 mm from the glandular capsule rarely present with neck metastasis at initial presentation and could be managed conservatively in relation to neck lymph nodes, as far as clinically unsuspected. The definition of nodule positioning in relation to the glandular capsule must to be explored in other studies. As commented above, long-term follow-up studies are needed to determine the rates of lymph node relapse in that subpopulation.

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Conflicts of Interest None.

References

1. Sherman SI (2003) Thyroid carcinoma. Lancet 361(9356):501–11
2. Davies L, Welch HG (2006) Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 295(18):2164–7
3. Baek SK, Jung KY, Kang SM, Kwon SY, Woo JS, Cho SH et al (2010) Clinical risk factors associated with cervical lymph node recurrence in papillary thyroid carcinoma. Thyroid 20(2):147–52
4. Beasley NJ, Lee J, Eski S, Walfsh P, Witterick I (2002) Impact of nodal metastases on prognosis in patients with well-differentiated thyroid cancer. Arch Otolaryngol Head Neck Surg 128(7):825–8
5. So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS et al (2010) Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. Surgery 148(3):526–31
6. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fugimoto Y (2010) Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: Our treatment strategies and outcomes. World J Surg 34(6):1222–31
7. Roti E, degli Uberti EC, Bondanelli M, Braverman LE (2008) Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. Eur J Endocrinol 159(6):659–73
8. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K et al (2004) Papillary microcarcinoma of the thyroid: how should it be treated? World J Surg 28(11):1115–21
9. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K et al (2004) Preoperative ultrasonographic examination for lymph node metastasis: usefulness when designing lymph node dissection for papillary microcarcinoma of the thyroid. World J Surg 28(5):498–501
10. Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T et al (2003) Lymph node metastasis from 259 papillary thyroid

Microcarcinomas: Frequency, Pattern of Occurrence and Recurrence, and Optimal Strategy for Neck Dissection. Ann Surg 237(3):399–407
11. Hughes CJ, Shaha AR, Shah JP, Loree TR (1996) Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. Head Neck 18(2):127–32
12. Sarvanan K, Bapuraj JR, Sharma SC, Radotra BD, Khandelwal N, Suri S (2002) Computed tomography and ultrasonographic evaluation of metastatic cervical lymph nodes with surgicoclinicopathologic correlation. J Laryngol Otol 116(3):194–9
13. Lee DW, Ji YB, Sung ES, Park JS, Lee YJ, Park DW et al (2013) Roles of ultrasonography and computed tomography in the surgical management of cervical lymph node metastases in papillary thyroid carcinoma. Eur J Surg Oncol 39(2):191–6
14. Jeong HS, Baek CH, Son YI, Choi JY, Kim HJ, Ko YH et al (2006) Integrated 18 F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. Clin Endocrinol (Oxf) 65(3):402–7
15. Henry JF, Gramatica L, Denizot A, Kvachenyuk A, Puccini M, Defechereux T (1998) Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Arch Surg 383(2):167–9
16. Pereira JA, Jimeno J, Miquel J, Iglesias M, Munne A, Sancho JJ et al (2005) Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery 138(6):1095–100
17. Edge SE, Byrd DR, Carducci MA, Compton CA (2010) AJCC cancer staging manual. Springer, New York
18. Shah JP (1990) Cervical lymph node metastases—diagnostic, therapeutic, and prognostic implications. Oncology (Williston Park) 4(10): 61–9
19. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ et al (2009) Revised american thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19(11):1167–214
20. Cho JK, Kim JY, Jeong CY, Jung EJ, Park ST, Jeong SH et al (2012) Clinical features and prognostic factors in papillary thyroid microcarcinoma depends on age. J Korean Surg Soc 82(5):281–7
21. Choi SJ, Kim TY, Lee JC, Shong YK, Cho KJ, Ryu JS et al (2008) Is routine central neck dissection necessary for the treatment of papillary thyroid microcarcinoma? Clin Exp Otorhinolaryngol 1(1):41–5
22. Zuniga S, Sanabria A (2009) Prophylactic central neck dissection in stage N0 papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 135(11):1087–91
23. Nam IC, Park JO, Joo YH, Cho KJ, Kim MS (2013) Pattern and predictive factors of regional lymph node metastasis in papillary thyroid carcinoma: A prospective study. Head Neck 35(1):40–45
24. Jeong JJ, Lee YS, Lee SC, Kang SW, Chung WY, Chang HS et al (2011) A scoring system for prediction of lateral neck node metastasis from papillary thyroid cancer. J Korean Med Sci 26(8): 996–1000
25. Gülben K, Berberoğlu U, Çelen O, Mersin HH (2008) Incidental papillary microcarcinoma of the thyroid - factors affecting lymph node metastasis. Langenbecks Arch Surg 393(1):25–9
26. Choi Y, Park KJ, Ryu S, Kim DH, Yun J, Kang DK et al (2012) Papillary thyroid carcinoma involving cervical neck lymph nodes: correlations with lymphangiogenesis and ultrasound features. Endocr J 59(10):941–8
27. Hunt JP, Buchmann LO, Wang L, Abraham D (2011) An analysis of factors predicting lateral cervical nodal metastases in papillary carcinoma of the thyroid. Arch Otolaryngol Head Neck Surg 137(11): 1141–5
28. Zhang L, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y et al (2012) Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. J Clin Endocrinol Metab 97(4):1250–7
29. Mirallié E, Sagan C, Hamy A, Paineau J, Kahn X, Le Néel JC et al (1999) Predictive factors for node involvement in papillary thyroid carcinoma. Univariate and multivariate analyses. Eur J Cancer 35(3): 420–3
30. Ortiz S, Rodríguez JM, Soria T, Pérez-Flores D, Piñero A, Moreno J et al (2001) Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study. Otolaryngol Head Neck Surg 124(3):261–5
31. Niemeier LA, Kuffner Akatsu H, Song C, Carty SE, Hodak SP, Yip L et al (2012) A combined molecular-pathologic score improves risk stratification of thyroid papillary microcarcinoma. Cancer 118(8): 2069–77
32. Kim SS, Lee BJ, Lee JC, Kim SJ, Lee SH, Jeon YK et al (2011) Preoperative ultrasonographic tumor characteristics as a predictive factor of tumor stage in papillary thyroid carcinoma. Head Neck 33(12):1719–26
33. Foschini MP, Papotti M, Parmeggiani A, Tallini G, Castaldini L, Meringolo D et al (2004) Three-dimensional reconstruction of vessel distribution in benign and malignant lesions of thyroid. Virchows Arch 445(2):189–98
34. Pissas A, Papamiltiades M (1981) Our experience on anatomical injections of the lymphatic vessels. Lymphology 14(4): 145–8
35. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K et al (2006) Minimal extrathyroid extension does Not affect the relapse-free survival of patients with papillary thyroid carcinoma measuring 4 cm or less over the Age of 45 years. Surg Today 36(1):12–8