Annals of Diagnostic Pathology 48 (2020) 151592

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Tumor border pattern and size help predict lymph node status in papillary microcarcinoma: A clinicopathologic study

Orhun Çığ Taşkın[a,*], Ayşe Armutlu[a], Orhan Ağcaoğlu[b], Önder Peker[c], Tarık Terzioğlu[d], Mehmet Onur Demirkol[e], Serdar Tezelman[b], Yersu Kapran[a]

[a] Department of Pathology, Koç University Hospital, Turkey
[b] Department of Surgery, Koç University Hospital, Turkey
[c] Department of Pathology, VKV American Hospital, Turkey
[d] Department of Surgery, VKV American Hospital, Turkey
[e] Nuclear Medicine and Radionuclide Therapy, Koç University Hospital, Turkey

ARTICLE INFO

Keywords:
Thyroid
Microcarcinoma
Lymph node metastasis
Size
Encapsulation
Lymphovascular invasion

ABSTRACT

Objective: Lymph node metastasis occurs in a subset of papillary microcarcinoma patients. We aimed to analyze the differences between metastatic and non-metastatic papillary microcarcinomas in order to identify a high-risk subgroup that is likely to require more aggressive treatment.

Materials and methods: 126 thyroidectomies with lymph node dissections (central ± lateral), diagnosed as papillary microcarcinoma, were reviewed.

Results: Mean age of 126 patients (F/M = 3.3) was 42 years. Mean size of the largest tumor was 7 mm. Classical was the most frequently (89%) encountered subtype. Multiple histologic subtypes co-occurred in 19%. Lymphovascular invasion was present in 16% (n = 20). 55 (44%) and 71 (56%) cases were unifocal and multifocal, respectively. 90 cases (71%) were non-encapsulated with overall infiltrative tumor borders, whereas in 36 cases (29%), the tumor had a well-defined capsule. Among those, 23 (64%) had tumor capsule invasion. 47 (37%) cases had metastasis in lymph nodes. In univariate analysis, metastasis was associated with tumor size of > 5 mm ($p = 0.02$), tumor burden of > 5 mm ($p = 0.03$), lymphovascular invasion ($p = 0.02$) and non-encapsulation ($p = 0.01$). No associations were found regarding sex, age, histologic subtype, lymphocytic thyroiditis, tumor capsule invasion (in capsulated tumors), laterality and multifocality ($p > 0.05$). In multivariate analysis, lymphovascular invasion ($p = 0.01$, OR = 3.97, 95% CI 1.35–11.67), tumor size > 0.5 cm ($p = 0.031$, OR = 2.92, 95% CI 1.10–7.71) and non-encapsulation ($p = 0.033$, OR = 2.85, 95% CI 1.08–7.51) were independent risk factors.

Conclusion: Size (largest tumor or sum of all foci) of > 5 mm, non-encapsulation and lymphovascular invasion were independent predictors of LNM in PMs. Unifocal tumors metastasize the same as multifocal tumors, suggestive of the contribution of other factors. Patients with sporadically resected microcarcinomas should be carefully followed-up, especially those that harbor risk factors in histology.

1. Introduction

Papillary thyroid carcinoma is the most common malignancy of the thyroid gland, accounting for around 1–2% of all malignancies [1,2]. Papillary microcarcinoma (PM) is defined as a papillary thyroid carcinoma that measures equal to or less than 10 mm [3]. PMs are frequently encountered, approximately in a third of thyroid glands. They can be encountered incidentally in thyroidectomies performed for other causes, or non-incidentally when the tumor is clinically detected [4]. Over the last decades, the incidence of papillary thyroid carcinomas, especially PMs have been rising, mostly due to advances in the imaging technology that have led to increased detection of smaller nodules [5-7].

Despite the usual indolent behavior and good prognosis of PMs, a subset of cases are associated with metastasis to lymph nodes or distant sites, and rarely, disease related death [8]. Considering the fact that non-invasive management strategies like active surveillance are also available for patients [9], a risk stratification system is crucial to accurately select the patients that are more likely to metastasize, thus may need more aggressive treatment options such as surgery and additional

* Corresponding author at: Koç University Hospital, Department of Pathology, Davutpasa Caddesi No: 4, 34010 Topkapi, Istanbul, Turkey.
E-mail address: otaskin@kuh.ku.edu.tr (O.Ç. Taşkın).

https://doi.org/10.1016/j.anndiagpath.2020.151592

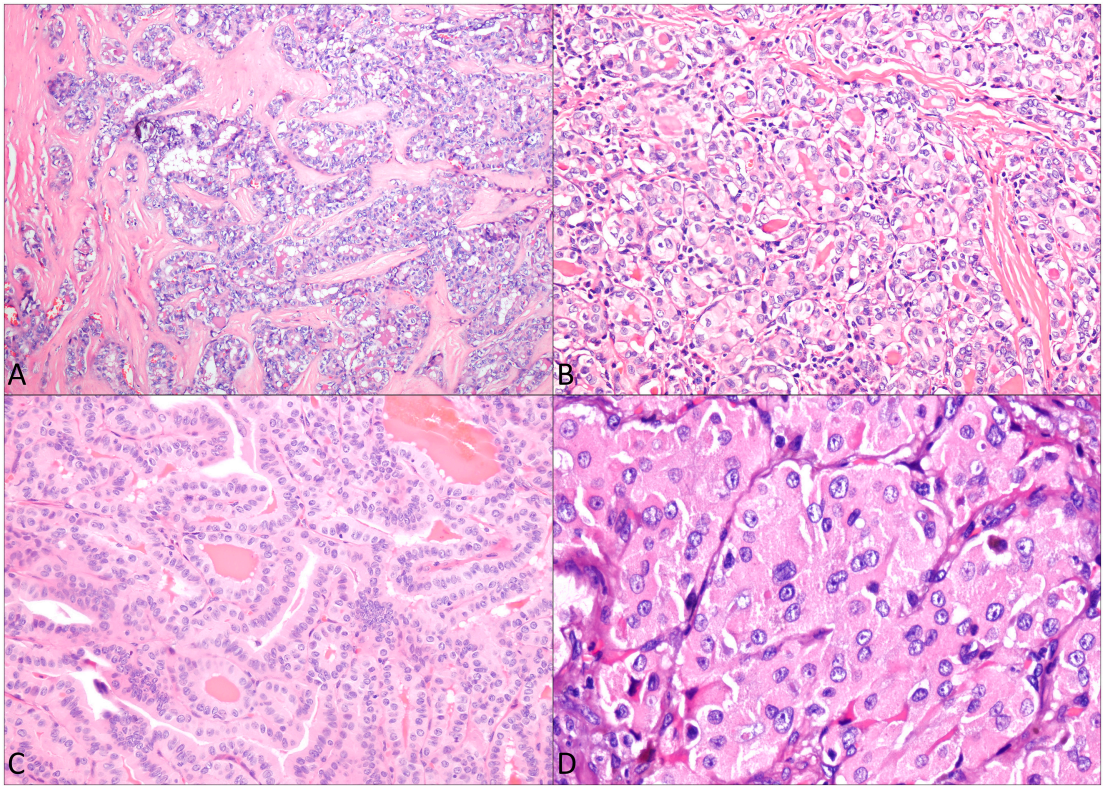

Fig. 1. (A) Classic (conventional) variant of papillary microcarcinoma; complex, branching papillae in sclerotic background and psammoma bodies (H&E, 100×). (B) Follicular variant of papillary microcarcinoma; neoplastic cells arranged as microfollicular architecture (H&E, 200×). (C) Tall cell variant of papillary microcarcinoma; closely packed papillary growth pattern with tall cells which have 2–3 times of cell width (H&E, 200×). (D) Oncocytic variant of papillary microcarcinoma; tumor cells with abundant eosinophilic cytoplasm and typical nuclear features (H&E, 400×).

radioiodine treatment.

The aim of this study was to analyze the differences between metastatic and non-metastatic PMs, by retrospectively analyzing our series of thyroidectomies and dissected lymph nodes, in order to identify useful histopathologic associations of lymph node metastasis (LNM), which is considered a predictor for recurrence [10]. In the light of our findings, our goal was to contribute to the knowledge and hopefully recognize and identify a high-risk group of PMs that is likely to require more aggressive treatment.

2. Materials and methods

2.1. Ethics statement

This study was approved by the institutional review board.

2.2. Case selection, inclusion and exclusion criteria

In the digital archives of the pathology department, a retrospective search was conducted for cases diagnosed as papillary thyroid microcarcinoma between 2015 and 2020. Among those, cases with lymph node dissection (central ± lateral) of at least 5 lymph nodes were included in the study. Cases with additional tumors that measured > 1 cm and cases with dissections of less than 5 lymph nodes were excluded [11].

2.3. Clinicopathologic analysis

Patient demographics were obtained from pathology reports. Largest diameter(s) of the tumor(s), histologic subtypes, tumor border pattern (as encapsulated with/without invasion, or non-encapsulated/overall infiltrative pattern), lymphovascular invasion, multifocality (and number of tumor foci), laterality, metastatic status and the presence of lymphocytic thyroiditis were documented. “Tumor burden” was designated as the sum of all tumors' diameters in a given case.

2.4. Statistical analysis

Descriptive statistics were presented to define continuous variables. The normality of continuous variables was investigated by Shapiro-Wilk's test. For comparison of two non-normally distributed groups Mann Whitney *U* test was used. The χ^2 test was used for categorical variables along with Fisher Exact test, when applicable. Logistic regression was used to evaluate the effect of risk factors on the occurrence of metastasis. Statistical significance was accepted when p value was lower than 0.05. Statistical analysis was performed using the IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

3. Results

3.1. Patient information

126 cases that matched the inclusion criteria were retrieved. The mean age of patients (97 females and 29 males, F/M = 3.3) was 42 years (range: 17–71 years). Among those, 100 patients underwent bilateral total thyroidectomy and 26 had hemithyroidectomy. For the latter group, the imaging of the contralateral lobe was normal. Central lymph node dissection was performed in all cases, along with lateral neck dissection in 6.

3.2. Pathology

- *Tumor size*: Mean size of the largest tumor was 7 mm (range:

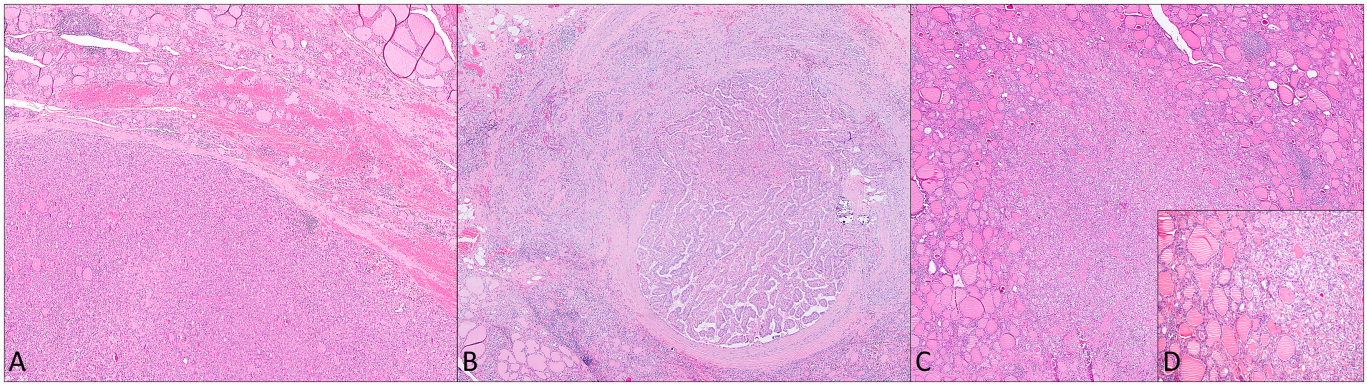

Fig. 2. (A) Follicular variant of papillary microcarcinoma with well-defined capsule (H&E, 10×). (B) Classic variant papillary microcarcinoma with encapsulation and overt capsule infiltration (H&E, 10×). (C–D) Non-encapsulated follicular variant papillary microcarcinoma with infiltrative tumor borders (H&E, 10× and 100×).

1–10 mm).

- *Histologic subtype*: Classical was the most frequent (n = 112), followed by follicular (n = 12), oncocytic (n = 11), solid (n = 1) and warthin-like (n = 1) subtypes. 6 cases had tall cell component. In 24 cases, more than one histologic subtype was present. See Fig. 1 for histologic subtypes.
- *Lymphovascular invasion*: Lymphovascular invasion was present in 20 (16%) cases.
- *Laterality*: Tumors were unilateral and bilateral in 80 (63%) and 46 (37%) cases, respectively.
- *Multifocality*: 55 (44%) cases had solitary tumor, whereas 71 cases (56%) had multifocal microcarcinoma. Among multifocal cases, mean number of tumor foci was 3.2 (rage: 2–10).
- *Tumor border pattern*: In 36 cases (29%), the tumor had a well-defined capsule. 90 cases (71%) were non-encapsulated with infiltrative tumor borders (see Fig. 2).
- *Tumor capsule invasion*: Among encapsulated cases (n = 36), 23 (64%) had tumor capsule invasion.
- *Tumor burden*: The mean tumor burden was 10.2 mm (range: 1–40).
- *Lymph nodes and metastatic status*: Mean number of total dissected lymph nodes was 10.4 (range: 5–75). Mean numbers of lymph nodes dissected for central and lateral neck were 8.8 and 42, respectfully. 47 (37%) cases had at least one metastatic lymph node. 5 out of 6 cases with lateral neck dissection were metastatic. In cases with metastasis, the mean number of metastatic lymph nodes was 2.9 (range: 1–20). Mean size of metastasis was 5.1 mm (range: 0,1–52). Extranodal invasion was present in 8 cases.
- *Extrathyroidal extension* was present in only one case.

3.3. Correlations between metastatic status and different histopathologic parameters

In univariate analysis, LNM was found to be associated with tumor size larger than 5 mm (size of the biggest tumor in multifocal cases) ($p = 0.02$), tumor burden of > 5 mm ($p = 0.03$), lymphovascular invasion ($p = 0.02$) and non-encapsulation ($p = 0.01$). No associations were found between LNM and sex, age, histologic subtype, lymphocytic thyroiditis, tumor capsule invasion (in capsulated tumors), laterality and multifocality ($p > 0.05$).

Multivariate analysis showed that lymphovascular invasion ($p = 0.01$, OR = 3.97, 95% CI 1.35–11.67), tumor size > 0.5 cm (size of the biggest tumor in multifocal cases) ($p = 0.031$, OR = 2.92, 95% CI 1.10–7.71) and non-encapsulation ($p = 0.033$, OR = 2.85, 95% CI 1.08–7.51) were independent risk factors for LNM.

See Table 1 for the summary of clinicopathologic features.

Table 1
Clinicopathologic features of papillary microcarcinomas and univariate analysis.

	All cases	LNM (+)	LNM (−)	*p* value
Number of cases	126	47 (37%)	79 (63%)	
Age				
- Mean (years)	42 (17–71)	40 (17–67)	44 (17–71)	$p = 0.30$
- < 45 years	69 (55%)	29 (62%)	40 (51%)	
- ≥ 45 years	57 (45%)	18 (38%)	39 (49%)	
Sex				
- Female	97 (77%)	34 (72%)	63 (80%)	$p = 0.46$
- Male	29 (23%)	13 (28%)	16 (20%)	
Multifocality				
- Unifocal	55 (44%)	18 (38%)	37 (47%)	$p = 0.45$
- Multifocal	71 (56%)	29 (62%)	42 (53%)	
Size of the largest tumor (mean)	7 mm	7.3 mm	6.8 mm	$p = 0.28$
Size of the largest tumor focus				
- ≤ 5 mm	35 (28%)	7 (15%)	28 (35%)	**$p = 0.02$**
- > 5 mm	91 (72%)	40 (85%)	51 (65%)	
Tumor burden (mean)	10.2 mm (range: 1–40)	10.9 mm (range: 5–40)	9.7 mm (range: 1–32)	$p = 0.15$
Tumor burden				
- ≤ 5 mm	21 (17%)	3 (6%)	18 (23%)	**$p = 0.03$**
- > 5 mm	105 (83%)	44 (94%)	61 (77%)	
Lymphatic invasion	20 (16%)	14 (30%)	6 (%7)	**$p = 0.02$**
Laterality				
- Unilateral	80 (63%)	31 (66%)	49 (62%)	$p = 0.8$
- Bilateral	46 (37%)	16 (34%)	30 (38%)	
Histologic subtype				
- Classic (conventional)	112 (89%)	43 (91%)	69 (87%)	$p = 0.67$
- Non-classic	14 (11%)	4 (9%)	10 (13%)	
Tumor capsule				
- Non-encapsulated	90 (71%)	40 (85%)	50 (63%)	**$p = 0.01$**
- Encapsulated	36 (29%)	7 (15%)	29 (37%)	
Tumor capsule infiltration (% among encapsulated tumors)				
- Absent	13 (36%)	1 (15%)	12 (41%)	$p = 0.38$
- Present	23 (64%)	6 (85%)	17 (59%)	
Lymphocytic infiltration in the non-tumoral parenchyma	71 (56%)	21 (45%)	50 (63%)	$p = 0.06$

p values of < 0.05 are bold.

4. Discussion

PMs constitute a specific subgroup of papillary thyroid carcinoma that is defined by size (≤ 10 mm) rather than histopathology which shares features similar to their larger counterparts [3]. With increasing frequency over the last decades [5-7], they are among the most

commonly encountered thyroid malignancies [4,7]. The vast majority of PMs have an innocuous clinical course, as supported by their occurrence in up to 35% of autopsy series of patients who died of unrelated causes [12-14]. In fact, several proposals were made in order to avoid the term "carcinoma" for the nomenclature of these tumors [12,15,16]. However, despite the overall excellent prognosis, it is well known that a subset of patients have adverse outcomes including recurrence, metastasis, and very rarely, disease related death [8].

As mentioned in the introduction, PMs are incidentally diagnosed in thyroidectomies performed for non-neoplastic reasons, or clinically detected, diagnosed and treated accordingly. Recently, some authors stated the difference in behavior between incidental vs. non-incidental tumors, suggesting the adoption of different treatment protocols [17,18], meanwhile long term prognosis was found similar between the two groups in a study by Ruiz et al. [19]. Those being mentioned, we believe that the clinical setup in which a tumor is defined as "incidental" depends heavily on the amount and quality of pre-operative clinical workup, creating a selection bias. In order to eliminate that and to consequently focus on histopathologic features, our cohort comprised of PMs with lymph node dissections, regardless of their clinical presentation. Nevertheless, we acknowledge that the presence of lymph node dissection -especially of the lateral neck-, usually implies the clinical suspicion for metastasis.

In our series, the overall ratio of LNM was 37%, supporting the high metastatic potential of these tumors. In the literature, numbers as high as 69.5% have been reported in studies with routine central lymph node dissection [20-23]. Together, these data not only promote the execution of central lymph node dissection, but also create curiosity towards the undetermined metastatic status of patients with incidental PMs, for whom dissection is not generally performed [24]. Overall, we believe that despite the commonly believed "indolent" nature of these tumors, patients without lymph node dissections should be closely followed-up in the post-operative period. In addition, these patients are perhaps the ones that should benefit the most from the pathologic examination, since their metastatic status is left undetermined, and they can be offered additional treatment based on the risk-factors determined by histology.

Associations of LNM in PMs have been subjected in a number of studies, in which, several clinicopathologic factors, including male gender, young age, tumor size, laterality, capsular invasion and extrathyroidal extension were found to be connected with LNM [25,26]. *BRAF* mutations are also known to contribute, although opposing results exist [26-29]. In the pre-operative period, patients without designated high-risk factors are offered less invasive treatment options like active surveillance in some institutions [30,31]. However, nearly a third of candidates for active surveillance were found to be at risk of recurrence due to the limitations of pre-operative analyses [32].

In the literature, multifocality is reported in up to a third of PMs [33,34]. Together with laterality, multifocality was frequently reported to be associated with LNM [8,25,35,36]. Although 56% and 36% of our cohort comprised of multifocal and bilateral cases respectively, we did not find any significant associations between LNM and multifocality or laterality. This supports the assumption that unifocal PMs also metastasize similar to multifocal tumors (in our study, 33% vs. 41%, respectively), suggesting the contribution of additional factors affecting their biology: The vast majority (89%) of our cohort had conventional (classical) histology, which was reported as an independent predictor of LNM [37], although we failed to demonstrate this association, probably due to small number of cases harboring non-conventional histology. Of note, we also encountered 6 cases with tall cell component, which is known to be an aggressive histologic subtype, and 2 of those (33%) were metastatic.

The relationship of tumor size and LNM has been analyzed in several studies. Although the cut-off point differs, it appears that larger PMs are more inclined to metastasize [21,25,38]. Additionally, in multifocal tumors, the total tumor diameter (sum of all tumors' diameters in a given case, designated as "tumor burden" in our study) was also found associated with LNM [39]. Similarly, in our study, tumor burden of > 5 mm was associated with LNM in univariate analysis, meaning that small (< 5 mm) tumor foci, whose total sum of diameter is larger than 5 mm, are also at risk for metastasis. Additionally, the largest tumor's size of > 5 mm was an independent risk factor for LNM.

Similar to other thyroid tumors [40], infiltration of tumor capsule is a known parameter affecting LNM in PMs [26]. Between encapsulated tumors, we did not find any difference between cases with and without capsule invasion. However, that being said, our analysis revealed that the tumor border pattern was an independent predictor of LNM. Tumors that were non-encapsulated with overall infiltrative borders were much more likely to metastasize than encapsulated/well defined tumors.

Lymphovascular space invasion is accepted as a tumor's introduction to local lymphatic/vascular system, virtually leading to metastasis. It is mostly undetectable in pre-operative workup and detected in histological examination. Although controversies exist regarding its definition and recognition [41], lymphovascular invasion is often acknowledged among the risk factors for LNM in thyroid carcinomas, including PMs [42,43]. In accordance, we found lymphovascular invasion to be an independent predictor for LNM in our series.

Another aspect, perhaps a limitation worth mentioning is that our series did not include any cases with distant metastasis or disease related death, detaining us from analyzing the prognosis. Although we demonstrated –in accordance with the literature– that these tumors frequently metastasize to local lymph nodes, it is highlighted in the literature that disease related mortality is very rare, thus the prognosis remains unaffectedly good [10]. Nevertheless, the effect of the LNM on the actual prognosis should be investigated in larger series with enough events to evaluate the survival.

In conclusion, size (largest tumor or sum of all tumor foci) of > 5 mm, non-encapsulation /overall infiltrative pattern and lymphovascular invasion were independent predictors of LNM in PMs. Unifocal tumors metastasize the same as multifocal tumors, suggestive of the contribution of other factors. Patients with sporadically resected PMs should be carefully followed-up and screened for LNM, especially those that harbor the abovementioned risk factors in histologic examination.

Acknowledgements

Authors have no conflict of interest or funding to declare. Authors would like to thank Dr. Arzu Baygul for her assistance with the statistical analysis.

References

[1] Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic review of trends in the incidence rates of thyroid cancer. Thyroid 2016;26:1541–52. https://doi.org/10.1089/thy.2016.0100.

[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86. https://doi.org/10.1002/ijc.29210.

[3] Lloyd R, Osamura R, Klöppel G, Rosai J. WHO classification of tumours of the endocrine organs. 4th ed. Lyon (France): International Agency for Research on Cancer; 2017.

[4] Piersanti M, Ezzat S, Asa SL. Controversies in papillary microcarcinoma of the thyroid. Endocr Pathol 2003;14:183–91. https://doi.org/10.1385/EP:14:3:183.

[5] Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 2006;295:2164–7. https://doi.org/10.1001/jama.295.18.2164.

[6] Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. Cancer Epidemiol Biomarkers Prev 2009;18:784–91. https://doi.org/10.1158/1055-9965.EPI-08-0960.

[7] Yildiz SY, Berkem H, Yuksel BC, Ozel H, Kendirci M, Hengirmen S. The rising trend of papillary carcinoma in thyroidectomies: 14-years of experience in a referral center of Turkey. World J Surg Oncol 2014:12. https://doi.org/10.1186/1477-7819-12-34.

[8] Chow SM, Law SCK, Chan JKC, Au SK, Yau S, Lau WH. Papillary microcarcinoma of

the thyroid - prognostic significance of lymph node metastasis and multifocality. Cancer 2003;98:31–40. https://doi.org/10.1002/cncr.11442.
[9] Sugitani I, Ito Y, Miyauchi A, Imai T, Suzuki S. Active surveillance versus immediate surgery: questionnaire survey on the current treatment strategy for adult patients with low-risk papillary thyroid microcarcinoma in Japan. Thyroid 2019;29:1563–71. https://doi.org/10.1089/thy.2019.0211.
[10] Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery 2008;144:980–8. https://doi.org/10.1016/j.surg.2008.08.035.
[11] Sung TY, Yoon JH, Song DE, Lee Y mi, Kim TY, Chung KW, et al. Prognostic value of the number of retrieved lymph nodes in pathological Nx or N0 classical papillary thyroid carcinoma. World J Surg 2016;40:2043–50. https://doi.org/10.1007/s00268-016-3490-5.
[12] Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A “normal” finding in Finland. A systematic autopsy study. Cancer 1985;56:531–8. https://doi.org/10.1002/1097-0142(19850801)56:3<531::AID-CNCR2820560321>3.0.CO;2-3.
[13] Bondeson L, Ljungberg O. Occult thyroid carcinoma at autopsy in Malmö, Sweden. Cancer 1981;47:319–23. https://doi.org/10.1002/1097-0142(19810115)47:2<319::AID-CNCR2820470218>3.0.CO;2-A.
[14] Sobrinho-Simões MA, Sambade MC, Gonçalves V. Latent thyroid carcinoma at autopsy: a study from Oporto, Portugal. Cancer 1979;43:1702–6. https://doi.org/10.1002/1097-0142(197905)43:5<1702::AID-CNCR2820430521>3.0.CO;2-S.
[15] Rosai J, LiVolsi VA, Sobrinho-Simoes M, Williams ED. Renaming papillary microcarcinoma of the thyroid gland: the Porto proposal. Int J Surg Pathol 2003;11:249–51. https://doi.org/10.1177/106689690301100401.
[16] Hazard JB, Crile G, Dempsey WS. Nonencapsulated sclerosing tumors of the thyroid. J Clin Endocrinol Metab 1949:9. https://doi.org/10.1210/jcem-9-11-1216.
[17] Mehanna H, Al-Maqbili T, Carter B, Martin E, Campain N, Watkinson J, et al. Differences in the recurrence and mortality outcomes rates of incidental and non-incidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up. J Clin Endocrinol Metab 2014;99:2834–43. https://doi.org/10.1210/jc.2013-2118.
[18] Der Lin J, Kuo SF, Chao TC, Hsueh C. Incidental and nonincidental papillary thyroid microcarcinoma. Ann Surg Oncol 2008;15:2287–92. https://doi.org/10.1245/s10434-008-9958-2.
[19] Ruiz J, Ríos A, Rodríguez JM, Paredes M, Soriano V, Oviedo MI, et al. Incidental versus clinical diagnosis of papillary thyroid microcarcinoma. Long-term prognosis. Endocrinol Diabetes y Nutr 2019. https://doi.org/10.1016/j.endinu.2019.09.012.
[20] Wada N, Duh Q-Y, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas. Ann Surg 2003;237:399–407. https://doi.org/10.1097/01.sla.0000055273.58908.19.
[21] Chang YW, Kim HS, Kim HY, Lee JB, Bae JW, Son GS. Should central lymph node dissection be considered for all papillary thyroid microcarcinoma? Asian J Surg 2016;39:197–201. https://doi.org/10.1016/j.asjsur.2015.02.006.
[22] Zheng X, Peng C, Gao M, Zhi J, Hou X, Zhao J, et al. Risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a study of 1,587 patients. Cancer Biol Med 2019;16:121–30. https://doi.org/10.20892/j.issn.2095-3941.2018.0125.
[23] Yazıcı D, Çolakoğlu B, Sağlam B, Sezer H, Kapran Y, Aydın Ö, et al. Effect of prophylactic central neck dissection on the surgical outcomes in papillary thyroid cancer: experience in a single center. Eur Arch Oto-Rhino-Laryngology 2020;277:1491–7. https://doi.org/10.1007/s00405-020-05830-1.
[24] Makay Ö, Özdemir M, Şenyürek YG, Tunca F, Düren M, Uludağ M, et al. Surgical approaches for papillary microcarcinomas: Turkey's perspective. Turkish J Surg 2018;34:89–93. https://doi.org/10.5152/turkjsurg.2018.3596.
[25] Cheng F, Chen YY, Zhu L, Zhou B, Xu Y, Chen YY, et al. Risk factors for cervical lymph node metastasis of papillary thyroid microcarcinoma: a single-center retrospective study. Int J Endocrinol 2019:2019. https://doi.org/10.1155/2019/8579828.
[26] Zhang Q, Wang Z, Meng X, Duh QY, Chen G. Predictors for central lymph node metastases in CN0 papillary thyroid microcarcinoma (mPTC): a retrospective analysis of 1304 cases. Asian J Surg 2019;42:571–6. https://doi.org/10.1016/j.asjsur.2018.08.013.
[27] Jin WX, Ye DR, Sun YH, Zhou XF, Wang OC, Zhang XH, et al. Prediction of central lymph node metastasis in papillary thyroid microcarcinoma according to clinicopathologic factors and thyroid nodule sonographic features: a case-control study. Cancer Manag Res 2018;10:3237–43. https://doi.org/10.2147/CMAR.S169741.
[28] Tallini G, De Biase D, Durante C, Acquaviva G, Bisceglia M, Bruno R, et al. BRAF V600E and risk stratification of thyroid microcarcinoma: a multicenter pathological and clinical study. Mod Pathol 2015;28:1343–59. https://doi.org/10.1038/modpathol.2015.92.
[29] Bernstein J, Virk RK, Hui P, Prasad A, Westra WH, Tallini G, et al. Tall cell variant of papillary thyroid microcarcinoma: Clinicopathologic features with BRAFV600E mutational analysis. Thyroid 2013;23:1525–31. https://doi.org/10.1089/thy.2013.0154.
[30] Miyauchi A, Ito Y, Oda H. Insights into the management of papillary microcarcinoma of the thyroid. Thyroid 2018;28:23–31. https://doi.org/10.1089/thy.2017.0227.
[31] Rovira A, Nixon IJ, Simo R. Papillary microcarcinoma of the thyroid gland: current controversies and management. Curr Opin Otolaryngol Head Neck Surg 2019;27:110–6. https://doi.org/10.1097/MOO.0000000000000520.
[32] Rosario PWS, Mourão GF, Oliveira PHL, Silva TH. Are papillary thyroid carcinomas that are candidates for active surveillance in fact classical microcarcinomas restricted to the gland? Eur Thyroid J 2018;7:258–61. https://doi.org/10.1159/000490701.
[33] Mercante G, Frasoldati A, Pedroni C, Formisano D, Renna L, Piana S, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. Thyroid 2009;19:707–16. https://doi.org/10.1089/thy.2008.0270.
[34] Zheng W, Wang K, Wu J, Wang W, Shang J. Multifocality is associated with central neck lymph node metastases in papillary thyroid microcarcinoma. Cancer Manag Res 2018;10:1527–33. https://doi.org/10.2147/CMAR.S163263.
[35] So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. Surgery 2010;148:526–31. https://doi.org/10.1016/j.surg.2010.01.003.
[36] Park JP, Roh JL, Lee JH, Baek JH, Gong G, Cho KJ, et al. Risk factors for central neck lymph node metastasis of clinically noninvasive, node-negative papillary thyroid microcarcinoma. Am J Surg 2014;208:412–8. https://doi.org/10.1016/j.amjsurg.2013.10.032.
[37] Kim SK, Park I, Woo JW, Lee JH, Choe JH, Kim JH, et al. Predictive factors for lymph node metastasis in papillary thyroid microcarcinoma. Ann Surg Oncol 2016;23:2866–73. https://doi.org/10.1245/s10434-016-5225-0.
[38] Agcaoglu O, Sengun B, Ozoran E, Bilgic C, Karabay O, Taskin OC, et al. Should we perform routine prophylactic central neck dissection in patients with thyroid papillary microcarcinoma? Ann Ital Chir 2018;89:485–8.
[39] Liu C, Wang S, Zeng W, Guo Y, Liu Z, Huang T. Total tumour diameter is superior to unifocal diameter as a predictor of papillary thyroid microcarcinoma prognosis. Sci Rep 2017:7. https://doi.org/10.1038/s41598-017-02165-6.
[40] Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LDR, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016;2:1023–9. https://doi.org/10.1001/jamaoncol.2016.0386.
[41] Mete O, Asa SL. Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation. Mod Pathol 2011;24:1545–52. https://doi.org/10.1038/modpathol.2011.119.
[42] Sezer A, Celik M, Bulbul BY, Can N, Tastekin E, Ayturk S, et al. Relationship between lymphovascular invasion and clinicopathological features of papillary thyroid carcinoma. Bosn J Basic Med Sci 2017;17:144–51. https://doi.org/10.17305/bjbms.2017.1924.
[43] Al-Qurayshi Z, Nilubol N, Tufano RP, Kandil E. Wolf in sheep's clothing: papillary thyroid microcarcinoma in the US. J Am Coll Surg 2020;230:484–91. https://doi.org/10.1016/j.jamcollsurg.2019.12.036. Elsevier Inc.