Papillary Microcarcinoma and Microtumor of the Thyroid Gland

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Abstract

Debate continues on what is the best choice of treatment for well-differentiated papillary microcarcinoma (PMC) in patients with very low-risk: observation, lobectomy alone, or total thyroidectomy. Some surgeons recommend total thyroidectomy, followed by radioactive iodine (RAI) ablation for all patients with papillary thyroid carcinoma to avoid missing the very rare cases that may develop distant metastasis, while other surgeons may explain some more options to the patient with PMC, such as observation or lobectomy alone (without RAI ablation) to avoid operation-related complications and RAI-related second primary malignancy. Presence of this debate is because we do not have reliable methods to identify the rare aggressive tumors from the vast majority of very low-grade tumors. Under these circumstances, total thyroidectomy with neck dissection followed by RAI ablation should be applied only to the high-risk PMC patients who have gross lymph node metastasis, extrathyroid involvement, or distant metastasis at presentation, because these treatments have no prognostic benefits to the patients with incidental PMC. A thyroid function-conserving approach, lobectomy alone, may be a sufficient treatment for low-risk, unifocal, and intrathyroidal PMCs (T1N0M0, less than 1 cm in diameter, no lymph node metastasis, no extrathyroid invasion, and no distant metastasis). Even if any adverse events appear during the observation period, patients can still be managed with surgical treatment without increased risk of recurrence. Molecular analysis using samples obtained from aspiration cytology may help to identify the high-risk tumors that are required for immediate operation in the future.

Keywords: Thyroid, papillary carcinoma, microcarcinoma, precursor lesion, borderline malignancy

Introduction

Papillary microcarcinoma (PMC) is a small papillary thyroid carcinoma (PTC) measuring 1 cm or less in diameter (1). In the last few decades, the frequency of PTC has dramatically increased in many countries, with PMC exhibiting the highest rate of increase. Most researchers have concluded that this increased incidence of PTC reflects an increase in the detection of subclinical diseases such as small and low-risk carcinomas with ultrasonography (US) and fine needle aspiration cytology (FNA) (1-7). As a result, PMC has become the most common variant of PTC, accounting for nearly half of all surgically treated thyroid carcinomas (2-9). PMC is a malignant tumor that has been shown to have a rate of lymph node metastasis up to 50%, but it is a very low-grade malignancy with a 10-year cause-specific mortality rate being less than 1% (2, 3, 6-11). These small foci of carcinoma are often found as intrathyroid metastases or as multifocal PMCs in the thyroid gland outside of the index nodule and in the opposite lobe in patients with thyroid carcinoma. In a series of 105 patients with PTC, intrathyroidal metastases in the opposite lobe were found in 61% of the patients (12). This extremely high incidence of intraglandular metastasis and multifocal PMCs in the residual thyroid tissue in patients treated for PTC justifies surgeons applying total thyroidectomy instead of lobectomy (4-15). It is natural to assume that the risk of recurrence might therefore be reduced by more extensive surgery than lobectomy. However, in a large patient series from the Mayo Clinic, the recurrence rates did not differ significantly between the patients treated with unilateral lobectomy and those treated with bilateral resection (8). In a report from the iodine-sufficient country Finland, PMC was found in more than one-third of the autopsy patients and PMC could be regarded as a normal finding in adult populations, which should not be treated when incidentally found (16-19). To avoid unnecessary operations, it has been suggested by Harach et al. that incidentally found small PMCs (less than 5 mm) should be called occult papillary tumors rather than carcinoma, a malignant terminology, and in a similar proposal by expert pathologists, PMCs (intrathyroidal and less than 1 cm in diameter) in adult patients have been termed papillary microtumors (19, 20). Furthermore, our group proposed a new classification of thyroid tumors in which we have suggested to class intrathyroidal PMCs (T1N0M0 and less than 1 cm) into borderline malignancy (21).

Against this background, a question arises: are all PMCs malignant tumors? This review tries to answer this question and to find practical solutions to identify high-risk PMC patients who require radical treatments in order to establish personalized treatment for patients with PMC. Majority of the patients with this very low-risk thyroid tumor can be followed closely without immediate surgery, and we believe that this approach also makes it possible to save patients from unnecessary operation-related complications without sacrificing prognostic benefit (6-8, 11, 21-29).

Diagnostic criteria for small PTC

The nuclear features of papillary thyroid carcinoma (PTC-N) are among the most important diagnostic criteria of thyroid tumors, and PTC-N is a gold standard for the diagnosis of PTC, similar to papillary structure and invasive growth (1, 16-21, 26-32). The arbitrary evaluation of PTC-N enables pathologists to diagnose microscopic foci with PTC-N as PMC, even if they are less than 1 mm in diameter (1, 16-21). PTC belongs to the low-grade malignant category, and its biological characteristics and clinical stage at diagnosis largely determine its clinical behavior; as a result, most PMCs limited to the thyroid gland have an excellent outcome as if they were benign (6-8, 16-25). Changes in the diagnostic approach to thyroid nodules on US and US-guided FNA may have resulted in the increase in the apparent incidence of thyroid cancer, particularly that of PMCs (2-9).

Precursor lesions of papillary thyroid carcinoma

From the definition and description in the WHO classification of thyroid tumors, there are no known precursor lesions of papillary thyroid carcinoma (1). Mori et al., from our group, analyzed 1044 cases of thyroid specimens and identified 20 cases (7%) of incidental PMCs in 277 cases with benign nodular lesions. They reported that small early PTC may be found in two different situations: in normal thyroid parenchyma (de novo cancer) or within thyroid nodule (cancer in adenoma) (30). PMC is usually applied to a small PTC in normal thyroid parenchyma or in non-neoplastic thyroid lesions such as Hashimoto's disease. Focal PTC-N in nodular thyroid lesions usually excludes PMC because the whole nodule is traditionally diagnosed as encapsulated papillary carcinoma (either common type or follicular variant) (31-33) or so-called well-differentiated tumor of uncertain malignant potential (WDT-UMP) (29, 34). Therefore, PMCs, small tumors with PTC-N in non-nodular thyroid gland, could be an early phase of PTC or precursor lesions of PTC (precancerous, borderline lesion or grey zone lesion) leading to clinical PTC. In conclusion, PMC is one of the candidates of precursor lesions of PTC and not a well developed clinical cancer or genuine cancer with high mortality rate. An observation trial of PMCs with cytological evidence of PTC-type morphology may help to resolve this issue in the near future (22-25).

Prognosis of PMC after surgical treatment

Noguchi et al. analyzed 2070 cases of PMC (43%) among 4840 cases treated for PTC, the largest series of PMCs with a long-term follow-up in the literature; they found that PMC has a very good prognosis in general (7). In this study, PMCs recurred in only 73 patients (3.5%) over a 35-year follow-up period and larger PMCs (6-10 mm) recurred in 14% versus 3.3% for the smaller PMCs (<5 mm) within 35 years. Of the 2070 patients who were followed up for 16.5 ± 7.3 years, only 12 patients (0.6%) died of thyroid cancer (7). Hay et al. analyzed 900 cases with PMC and emphasized that patients with PMC had an excellent prognosis; only three patients (0.3%) died of the disease and none of the 892 patients with initial complete tumor resection developed metastatic spread during 20 postoperative years (8). The 20-year and 40-year tumor recurrence rates were 6% and 8%, respectively. Higher recurrence rates were seen in patients with multifocal tumors ($P = 0.004$) and in patients with positive nodes ($P < 0.001$) (8).

Occasionally, PMC as an occult carcinoma represents the primary tumor for a large cervical lymph node metastasis and rare cases of PMC develop distant metastases and result in cancer death (6-11, 13-15, 35). PMC is a heterogeneous disease in terms of prognosis and most reports on the outcome after surgical treatment have proved its very low-grade malignancy (6-11, 35). Davies and Welch have pointed out that cancer mortality has been stable over several decades, while the incidence of thyroid cancer has increased dramatically, suggesting that the increase in the incidence of thyroid cancer is largely due to the very low-grade malignancy that may not contribute to mortality (3).

Identification of high-risk patients with PMC

A high prevalence (about 45–52%) of RET/PTC rearrangements has been reported not only in clinical PTCs but also in PMCs (36, 37), suggesting that the activation of this oncogene (RET/PTC) plays a role in the early stage in PTC development, however this finding does not seem to be a sign of cancer aggressiveness (37). BRAFV600E mutation, the most common genetic alteration in PTC, is present in many PMCs with extrathyroidal extension and lymph node metastasis (38-43). Lee et al. studied the clinico-pathological characteristics and the BRAFV600E mutation in 64 cases of PMC and they detected the mutation in 37.5% of the PMCs (43). The mutation-positive PMCs exhibited significantly more features of aggressiveness (advanced disease stages, extrathyroidal extension and nodal metastasis) than mutation-negative PMCs, indicating that BRAFV600E mutation may be a marker of tumor aggressiveness and progression from PMC to PTC (43). Niemeier et al. detected BRAFV600E mutation in 77% of the aggressive and 32% of the non-aggressive PMCs, suggesting that the BRAFV600E mutation may be a marker of invasiveness and, together with histopathologic features of aggressiveness, it may allow clinical risk stratification of PMCs (40). Soares and Sobrinho-Simoes recently suggested that genetic screening of the BRAFV600E mutation might help assess risk stratification and manage patients with PMC (39). PMCs without BRAFV600E may be conservatively managed unless other molecular markers or clinical risk stratification of poor prognosis indicates a more aggressive nature (38-43).

Sugitani et al. analyzed 190 patients with PMC, including 34 patients with gross metastatic lymphadenopathy, and they concluded that high Ki-67 labeling index and positive immunohistochemistry for TGFbeta3 in cancer cells were potential indicators of aggressive PMC (22). Khoo et al. reported that more than 90% of the metastasized PMCs expressed cyclin D1, which was higher than the rates reported previously for clinical PTCs (44). They demonstrated overexpression of cyclin D1 and underexpression of p27/Kip in the PMC with gross metastatic disease (44).

Scoring systems and TNM stage classification system for thyroid carcinoma can also be adapted to PMC to identify high-risk patients. Hay et al. have stated that PMC represents a life-threatening condition in only a tiny minority of patients, and those few patients can usually be identified at the time of diagnosis (8). Of the three patients who succumbed to thyroid cancer, one had evidence of distant metastases at the time of diagnosis; the other two fatal cases occurred in men who presented with extensive regional nodal metastases and developed widespread metastatic disease more than 25 years later (8). Sugitani et al. divided PMCs into three types clinically: Type I comprises incidentally detected PMC without any symptoms, which is harmless and the lowest-risk cancer. Conservative follow-up with US every 6 or 12 months is feasible in these cases. Type II involves the early stage of the usual low-risk papillary carcinoma. This type can be treated with lobectomy when an increase in size is noted during conservative follow-up. Type III comprises clinically symptomatic PMC,

representing high-risk cancers. For these cases, immediate wide resection followed by radioiodine treatment and suppression of thyroid-stimulating hormone is recommended (24).

Multifocality and nodal metastasis of PMC

PTC is often multiple and bilateral in the thyroid and PMC is often found in the thyroid at a high incidence from patients with any thyroid surgery. In the series of PTC patients reported by Katoh et al., small foci of PTC have been found to distribute around the primary lesions and also frequently (61.0%) in the opposite lobe as bilateral disease (12). The investigators concluded that multiple involvements (intraglandular metastases and multiple PMCs) could be regarded as one of the most important biological characteristics of PTC (12). In the PMC patient series reported by Hay et al. from Mayo Clinic, multiple foci of PMC have been found in 23% of patients. At initial surgery, 273 patients (30%) had cervical lymph node involvement and only three patients (0.3%) had distant metastases at the time of initial presentation (8). Both multifocality and nodal involvement increased the risk of later nodal recurrence, with 11% of multifocal tumors exhibiting recurrence, compared with only 4% of unifocal tumors presenting recurrence. Higher recurrence rates were seen in the patients with multifocal tumors ($P = 0.004$) and in the patients with positive nodes ($P < 0.001$) (8). A literature review on PMC by Roti et al. summarized that bilateral and multiple foci were observed in 2.9% to 48% and 7.1% to 56.8% of cases with PMC, respectively (9).

Extent of surgery for PMC

A high incidence of nodal metastasis at surgery and multiplicity of PMCs prompted most surgeons to apply total thyroidectomy with prophylactic neck dissection followed by RAI ablation to patients with PMC. This radical treatment was once recommended for the treatment of PMC, with strongly supportive evidence in major clinical guidelines (6, 45-48). Mazzaferri et al. concluded that a near-total thyroidectomy followed by RAI ablation plus thyroid hormone therapy confers a distinct outcome advantage and this therapy reduces tumor recurrence and mortality in the patients with PTC (13, 14). This therapy may be one of the factors that contribute the low recurrence rate and low mortality rate in the patients surgically treated for PTC (6, 9, 10, 13-15). However, this extremely successful prognostic schema can also be achievable with thyroid function-conserving surgery (such as lobectomy alone), which has been reported by several other authors (6-8, 11, 22-25, 48-50). However, there is no consensus on the management of PMC, resulting in a wide spectrum of responses for this condition, ranging from observation to total thyroidectomy plus RAI treatment (6-11, 13-15, 22-25, 45-54).

In a series of 403 patients with PMC studied by Pelizzo et al., although no significant prognostic factors were found with uni- and multivariate analyses, the authors commented that it was noteworthy that, in patients with a larger primary tumor (size ≥5 mm) and treated by partial thyroidectomy alone, the prevalence of recurrent disease was higher than that in patients treated by total thyroidectomy and RAI administration (15). Their conclusion has been that it appears reasonable to perform total thyroidectomy (possibly associated with central compartment node dissection), RAI whole body scan (followed by RAI therapy when necessary), and TSH-suppressive hormonal therapy in patients with PMC (15). Roti et al. meta-analyzed the extent of surgery in 9259 patients

with PMC in the literature, showing that 72% of the surgery were total/near-total thyroidectomy, 11% were subtotal thyroidectomy, and 17% were lobectomy (9).

However, in a large patient series from the Mayo Clinic, recurrence rates did not differ statistically between patients treated with unilateral lobectomy and those treated with bilateral resection, as long as complete tumor resection was achieved (8) and this observation has been confirmed by several other authors (6, 7, 11, 45-53). Noguchi et al. analyzed 2070 (43%) cases of PMC among 4840 cases of PTC and found that PMC had a very good prognosis in general. Tumor recurred in only 73 patients (3.5%) over a 35-year time span. Of the 2070 patients who were followed up for 16.5 ± 7.3 years, only 12 patients (0.6%) died of thyroid cancer. They concluded that thyroid lobectomy or subtotal thyroidectomy without RAI ablation is sufficient if unifocal PMC is established (7). Davies and Welch, through analysis of the treatment data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program in the USA, stated that PTCs of any size that are limited to the thyroid gland (no extraglandular extension or lymph node metastases at presentation) have favorable outcomes whether or not they are treated in the first year after diagnosis and whether they are treated by lobectomy alone or total thyroidectomy (3).

Recent modification of the guidelines, published in 2009 by the American Thyroid Association and others, has recommended that lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroid PTC (6, 45-48) and this recommendation is expanded to the larger (less than 4 cm) intrathyroidal (T1N0M0 and T2N0M0) PTC in the Japanese Clinical Guideline (48). It is assumed that multiple small papillary lesions (undetectable by US) in the contralateral lobe are mostly dormant lesions and do not become clinical carcinoma in most instances. At present, we have no reliable methods to distinguish the minority of aggressive PMC from the majority of dormant lesions clinically. Molecular analysis using FNA samples may help to identify the aggressive type in the future. Until that time comes, less differentiated cytological features, extrathyroid invasion by US image, and clinically apparent metastasis should be the most reliable landmarks for the application of total thyroidectomy with neck dissection, which could feasibly reduce overtreatment and unnecessary complications among patients with low-risk PMC.

Does RAI ablation reduce recurrence and increase risk of second primary malignancy?

Although Pellegriti et al. and some others have shown the role of RAI ablation in decreasing locoregional and lymph node recurrence of PMCs (6, 13-15, 55), the impact of RAI on reducing recurrence has not been demonstrated in other studies (6, 8, 45, 46, 51, 56). The American Thyroid Association's guidelines currently recommend the selective use of RAI therapy in patients with well-differentiated thyroid cancer (6, 45). Despite these guidelines, RAI ablation has been used routinely in all but the very lowest-risk patients with well differentiated thyroid cancer over the last 30 years in the Western countries. In the literature review by Roti et al., RAI treatment following surgical treatment was found to be carried out from 10.3% to 100%. In total, 1594 (17%) out of the 9379 patients were treated with RAI (9). Based on the SEER database, Iyer et al. analyzed the trends for RAI use over time in the United States (57). Their analysis has shown that the second primary malignancies with significantly elevated risk are salivary

gland malignancies, and the excess risk of leukemia is significantly greater in younger patients (<45 years) than in older ones (57). Lang et al. from Hong Kong analyzed 1,106 patients with well-differentiated thyroid carcinoma; they reported that 92 (8.3%) patients developed second primary malignancy and 40 (3.6%) patients died of second primary malignancy (58). Second primary malignancy accounted for 18.7% of all deaths in well differentiated thyroid carcinoma, but mortality was high (43.5%). For the occurrence of second primary malignancy, age at the diagnosis of well differentiated thyroid carcinoma (≥50 years old), cumulative RAI activity of 3.0-8.9 GBq, and external local radiotherapy were significant risk factors (58). In an analysis of the PTC patients treated in the Memorial Sloan Kettering Cancer Center, Ibrahimpasic et al. concluded that selective low- and intermediate-risk patients who have undetectable thyroglobulin after total thyroidectomy for PTC can be managed safely without adjuvant RAI and with no increase in the risk of recurrence (59). Based on the above publications, the risk of second primary malignancy after RAI treatment is significant and evidence that adjuvant RAI treatment reduces the mortality rate in the PMC patients is not well established (6, 8, 45, 46, 51, 56-60).

References

1. LiVolsi VA, Albores-Saavedra J, Asa SL, Baloch ZW, Sobrinh-Simoes M, Wenig B, DeLellis RA, Cady B, Mazzaferri EL, Hay I, Fagin JA, Weber AL, Caruso P, Voutilainen PE, Franssila KO, Williams ED, Schneider AB, Nikiforov Y, Rabes HM, Akslen L, Ezzat S, Santro M, Eng C, Harach HR. Papillary carcinoma. In WHO classification of tumors. Pathology and genetics. Tumours of endocrine organs, IARC Press, Lyon, France, 2004:pp57-66.

2. Wartofsky L. Increasing world incidence of thyroid cancer. Increased detection or higher radiation exposure? Hormone 2010:9:103-8.

3. Davies L and Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006:295:2164-7.

4. Cronan JJ. Thyroid nodules: is it time to turn off the US machines? Radiol 2008:247:602-4.

5. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer 1998:83:2638-48.

6. Pacini F. Thyroid microcarcinoma, Best Pract Res Clin Endocrinol Meatab 2012:26:381-9.

7. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. World J Surg 2008:32:743-53.

8. Hay I, Hutchison ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, Thompson GB, Sebo TJ, Goellner JR. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surg 2008:144:980-7.

9. Roti E, degli Uberti EC, Bondanelli M, Braverman LE. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. Eur J Endocrinol 2008:159:659-73.

10. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A. Papillary microcarcinoma of the thyroid: how it should be treated? World J Surg 2004:28:1115-21.

11. Ogilvie JB, Patel KN, Heller KS. Impact of 2009 American Thyroid Association guidelines on choice of operation for well-differentiated thyroid microcarcinomas. Surg 2010:148:1222-6.

12. Katoh R, Sasaki J, Kurihara H, Suzuki K, Iida Y, Kawaoi A. Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma. A clinicopathologic study of 105 consecutive patients. Cancer 1992:70:1585-90.

13. Mazzaferri EL and Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994:97:418-28.

14. Mazzaferri EL. Management of low-risk differentiated thyroid cancer. Endocr Pract 2007:5:498-512.

15. Pelizzo MR, Boschin MI, Toniato A, Piotto A, Bernante P, Pagetta C, Rampin L, Rubello D. Papillary thyroid microcarcinoma (PTMC): prognostic factors, management and outcome in 403 patients. Eur J Surg Oncol 2006:32:1144-8.

16. Franssila KO and Harach HR. Occult papillary carcinoma of the thyroid in children and young adults. A systemic autopsy study in Finland. Cancer 1986:58:715-9.

17. Lang W, Borrusch H, Bauer L. Occult carcinoma of the thyroid. Evaluation of 1020 sequential autopsies. Am J Clin Pathol 1988:90:72-6.

18. Martinez-Tello FJ, Martinez-Cabruja R, Fernandez-Martin J, Lasso-Oria C, Ballestin-Carcavilla C. Occult carcinoma of the thyroid. A systematic autopsy study from Spain of two series performed with two different methods. Cancer 1993:15:4022-9.

19. 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.

20. 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.

21. Kakudo K, Bai Y, Liu Z, Li Y, Ito Y, Ozaki T. Classification of thyroid follicular cell tumors: with special reference to borderline lesions. Endocr J 2012:59:1-12.

22. Sugitani I, Yanagisawa A, Shimizu A, Clinocopathologic and immunohistochemical studies of papillary thyroid microcarcinoma presenting with cervical lymphadenopathy. World J Surg 1998:22:731-7.

23. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, Tomoda C, Takamura Y, Kobayashi K, Miya A. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 2010:34:28-35.

24. Ito Y and Miyauchi A. A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid. Nat Clin Paract Endocrinol Metab 2007:3:240-8.

25. Sugitani I, Toda K, Yamada K Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg 2010:34:1222-31.

26. Kakudo K, Bai Y, Liu Z, Ozaki T. Encapsulated papillary thyroid carcinoma, follicular variant: a misnomer. Pathol Int 2012:62:155-60.

27. Kakudo K, Bai Y, Katayama S Hirokawa M, Ito Y, Miyauchi A, Kuma K. Classification of follicular cell tumors of the thyroid gland: analysis involving Japanese patients from one institute. Pathol Int 2009:59:359-67.

28. Kakudo K, Tang W, Ito Y, Mori I, Nakamura Y, Miyauchi A. Papillary carcinoma of the thyroid in Japan: subclassification of common type and identification of low risk group. J Clin Pathol 2004:57:1041-6.

29. Liu Z, Zhou G, Nakamura M Koike E, Li Y, Ozaki T, Mori I, Taniguchi E, Kakudo K. Encapsulated follicular thyroid tumor with equivocal nuclear changes, so-called well-

differentiated tumor of uncertain malignant potential: a morphological, immunohistochemical, and molecular appraisal. Cancer Sci 2011:102:288-94.

30. Mori I Miyauchi A, Kuma S, Tang W, Kakudo K. Thyroid nodular lesion: Analysis of cancer risk based on Kuma hospital experience. Pathol Int 2003:53:579-83.

31. Baloch ZW and LiVolsi VA. Our approach to follicular-patterned lesions of the thyroid. J Clin Pathol 2007:60:244-50.

32. Liu J, Singh B, Tallini G, Carlson DL, Katabi N, Shaha A, Tuttle RM, Ghossein RA. Follicular variant of papillary carcinoma. A clinicopathologic study of a problematic entity. Cancer 2006:107:1255-64.

33. Zhu Z, Gandhi M, Nikiforova MN, Fischer AH, Nikiforov YE. Molecular profile and clinico-pathologic features of the follicular variant of papillary carcinoma. An usually high prevalence of ras mutations. Am J Clin Pathol 2003:120:71-7.

34. Williams ED. Two proposals regarding the terminology of thyroid tumors. Int J Surg Pathol 2000:8:181-3.

35. Chow S, Law SCK, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid - prognostic significance of lymph node metastasis and multifocality. Cancer 2003:98:31-40.

36. Corvi R, Martinez-Alfaro M, Harach HR, Zini M, Papotti M, Romeo G. Frequent RET rearrangements in thyroid microcarcinoma detected by interphase fluorescence in situ hybridization. Lab Invest 2001:81:1639-45.

37. Tallini G, Santoro M, Helie M, Carlomagno F, Salvatore G, Chiappetta G, Carcangiu ML, Fusco A. RET/PTC oncogene activation define a subset of papillary thyroid carcinomas lacking evidence of progression to poorly or undifferentiated tumor phenotypes. Clin Cancer Res 1998:4:287-94.

38. Xing M. BRAF mutation in papillary thyroid microcarcinoma: the promise of better risk management. Ann Surg Oncol 2009:16:801-3.

39. Soares P and Sobrinho-Simoes M. Cancer: small papillary thyroid cancers - is BRAF of prognostic value? Nat Rev Endocrinol 2011:7: 9-10.

40. Niemeier L A, Kuffner Akatsu H, Song C, Carty SE, Hodak SP, Yip L, Ferris RL, Tseng GC, Seethala RR, Lebeau SO, Stang MT, Coyne C, Johnson JT, Stewart AF, Nikiforov YE. A combined molecular-pathologic score improves risk stratification of thyroid papillary microcarcinoma. Cancer 2012:118:2069-77.

41. Nucera C and Pontecorvi A. Clinical outcome, role of BRAF^{V600E}, and molecular pathways in papillary thyroid microcarcinoma: is it an indolent cancer or an early stage of papillary thyroid cancer? Front Endocrinol (Lausanne) 2012:3:33.

42. Rossi ED, Martini M, Capodimonti S, Lombardi CP, Pontecorvi A, Vellone VG, Zannoni GF, Larocca LM, Fadda G. BRAF(V600E) mutation analysis on liquid-based cytology-processed aspiration biopsies predicts bilaterality and lymph node involvement in papillary thyroid microcarcinoma. Cancer Cytopathol 2012:epub ahead of print.

43. Lee X, Gao M, Ji Y, Yu Y, Feng Y, Li Y, Zhang Y, Cheng W, Zhao W. Analysis of differential BRAF(V600E) mutational status in high aggressive papillary thyroid microcarcinoma. Ann Surg Oncol 2009:16:240-5.

44. Khoo MLC, Ezzat S, Freeman JL, Asa SL. Cyclin D1 protein expression predict metastatic behavior in thyroid papillary

microcarcinomas but is not associated with gene amplification. J Clin Endocrinol Metab 2002:87:1810-3.

45. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009:19:1167-214.

46. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006:154:787-803.

47. Franklyn JA. Comparing USA and UK guidelines for the management of differentiated thyroid carcinoma. Thyroid 2006:16:105-7.

48. Takami H, Ito Y, Okamoto T, Yoshida A. Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. World J Surg 2011:35:111-21.

49. Wada N, Duh Q-Y, Sugino K, Iwasaki H, Kameyama K, Mimura T, Ito K, Takami H, Takanashi Y. Lymph node metastasis from 259 papillary thyroid microcarcinomas. Frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003:237:399-407.

50. Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Tuttle RM, Shaha A, Shah JP. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. Surgery 2012:151:571-9.

51. Lo CY, Chan WF, Lang BH, Lam KY, Wan KY. Papillary microcarcinoma: is there any difference between clinically overt and occult tumors? World J Surg 2006:30:759-66.

52. Pazaitou-Panayiotou K, Capezzone M, Pacini F. Clinical features and therapeutic implication of papillary thyroid microcarcinoma. Thyroid 2007:17:1085-92.

53. Arem R, Padayatty SJ, Saliby AH, Sherman SI. Thyroid microcarcinoma: prevalence, prognosis, and management. Endocr Pract 1999:5:148-56.

54. Falvo L, D'Ercole C, Sorrenti S, D'Andrea V, Catania A, Berni A, Grilli P, De Antoni E. Papillary microcarcinoma of the thyroid gland: analysis of prognostic factors including histological subtype. Eur J Surg (suppl) 2003:588: 28-32.

55. Creach KM, Siegel BA, Nussenbaum B, Grigsby PW. Radioactive iodine therapy decreases recurrence in thyroid papillary microcarcinoma. ISRN Endocrinol 2012:epub ahead of print.

56. Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, Stranus S, Goldstein DP: An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am, 37:457-480, 2008.

57. Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I. Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. Cancer 2011:117:4439-46.

58. Lang BH and Wong KP. Risk factors for nonsynchronous second primary malignancy and related death in patients with differentiated thyroid carcinoma. Ann Surg Oncol 2011:18:3559-65.

59. Ibrahimpasic T, Nixon IJ, Palmer FL, Whitcher MM, Tuttle RM, Shaha A, Patel SG, Shah JP, Ganly I. Undetectable thyroglobulin after total thyroidectomy in patients with low- and intermediate-risk papillary thyroid cancer - is there a need for radioactive iodine therapy. Surg 2012:152:1096-105.

60. Sawka AM, Thabane L,Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, Stranus S, Ezzat S,Goldstein DP: Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid, 19:451-457, 2009.