



Ill-defined Edge on Ultrasonographic Examination Can Be a Marker of Aggressive Characteristic of Papillary Thyroid Microcarcinoma

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Abstract. We have previously demonstrated that, although most papillary thyroid microcarcinomas (PMC) do not grow or grow only slowly, cases showing lateral node metastasis diagnosed by ultrasonography (US) show an aggressive characteristic associated with poor disease-free survival. In this study, we focused on two prominent US features: tumor, edge definition and strong echoes. We investigated whether these findings reflect aggressive characteristics of PMC in a series of 155 cases. Poor edge definition was observed in 21.5% of patients, all of who showed worse disease-free survival ($p = 0.0477$) than those with a well-defined edge. Furthermore, this finding was directly linked to US-diagnosed lateral node metastasis ($p = 0.0001$). Strong echoes were observed in 63.9% of the cases, and fine strong echoes were seen in 25.2%. Cases demonstrating fine strong echoes tended to frequently show recurrence ($p = 0.0902$), and this finding was also significantly linked to US-diagnosed lateral node metastasis ($p = 0.0494$). These findings suggest that an ill-defined tumor edge is an important US feature of biologically aggressive PMC. We should carefully follow such patients, regardless of the therapeutic strategy, observation, or surgical treatment chosen.

Introduction

Papillary carcinoma is the most common histological type of malignancy originating in the thyroid. This tumor generally displays slow growth and shows a good prognosis if competently resected. Recent establishment of the technique of ultrasonography (US)-guided fine-needle aspiration biopsy (FNAB) has facilitated detection and diagnosis, even of small papillary carcinoma measuring 10 mm or less in maximal diameter. Such tumors are defined as papillary microcarcinoma (PMC), according to the World Health Organization (WHO) [1]. To date, there have been two therapeutic options for PMC. One is thyroidectomy with lymph node dissection; similar to larger papillary carcinoma lesions, PMC has been associated with lymph node metastasis as well as multiple tumor formation (intrathyroidal metastasis) in high incidences [2–5]. Another therapeutic option is observation without immediate surgical treatment [6]. Observation has been

proposed based on autopsy findings that PMC is frequently found to be a harmless occult carcinoma [7–9]. To date, we have applied this therapy option to cases without any of the following unfavorable features: (1) tumors located adjacent to the trachea, (2) tumors possibly invading the recurrent laryngeal nerve, (3) FNAB findings suggesting high-grade malignancy, (4) lymph nodes highly suggestive of metastasis (or confirmed as metastatic by FNAB). Uncomplicated PMC detected by US generally have been found to grow slowly or not at all. [6]. For both diagnosis and evaluation of the biological characteristics of PMC, US is the most useful tool.

We recently demonstrated that patients with PMC demonstrating lymph node metastasis in the lateral compartment on preoperative US examination have significantly worse disease-free survival (DFS), even if therapeutic modified radical neck dissection (MRND) is performed [10]. These results suggest that US-diagnosed (but not pathologically confirmed) lateral metastasis predicts a poor prognosis in PMC patients and that preoperative US evaluation of lateral node metastasis is one of the most important factors in selecting the appropriate surgical treatment [10, 11].

We then studied the relationships between US findings of the primary tumors and US-diagnosed lateral node metastasis. Tumors with multiple intrathyroidal metastasis and/or that occupy the upper region of the thyroid on US examination more frequently demonstrated US-diagnosed lateral node metastasis [11]. These findings suggest that, for such cases, evaluation of lateral node metastasis on US should be carefully performed. In addition, when observation is the treatment chosen for patients without US-diagnosed lateral metastasis, such observation should proceed with particular care because lateral metastasis may be more likely to develop.

Since around 2000, the accuracy of US has increased, making it possible to obtain more information about the tumors, as revealed by the status of the border and characteristic of the internal echoes. However, little is known about whether and how the US features of PMC reflect biologically aggressive phenotypes. In this study, we therefore focused on two representative US features of the tumor, edge definition and strong echoes. As the first step in

the study, we investigated the relationships between these findings and DFS of patients, as well as US-diagnosed lateral node metastasis, a known characteristic that definitely indicates the biological aggressiveness of PMC [10, 11].

Patients and Methods

Patients

When we find micronodules suggestive of malignancy by such US findings as low echoic signals and a jagged border, we perform FNAB to diagnose the micronodules as benign or malignant. We do not routinely perform FNAB for micronodules without such features. The positive predictive value of FNAB is around 99% for papillary carcinoma, as previously described [6].

This study enrolled 155 patients, who were diagnosed as having PMC by FNAB and who underwent surgery in our hospital between October 1999 and August 2001. Before surgical treatment, all patients underwent US to evaluate the form, location, and number of tumors and the presence of lymph node metastasis. On the basis of these findings, the surgeon determined the range of thyroidectomy and lymph node dissection. For US examination in our hospital, an ultrasonic real-time electronic scanner (Aloka SSD-5500, Tokyo, Japan) and a search unit of the mechanical sector model of 10 MHz and 13 MHz have been used since 1999. All patients in the present series were examined using this equipment. In addition all cases were pathologically confirmed as papillary carcinoma after surgery.

Based on the records of US findings and photographs, two examiners (Y. I. and K. K.) reviewed whether the tumor edge was ill-defined or well-defined and whether strong echoes, if present, were fine or coarse in each case. The term "fine strong echoes" indicates multiple dot-like high echoic spots (microcalcification), whereas "coarse strong echoes" indicates apparently detectable calcification in nodules with acoustic shadow. In the cases of multiple lesions, we judged the lesions as ill-defined and/or having fine strong echoes, when at least one of the tumors demonstrated these findings.

We considered nodes metastatic when the US findings met the criteria proposed by Antonelli et al. [12]: (1) diameter of 1 cm or greater; (2) clear hypoechoic pattern or dyshomogeneous pattern, with alternating hypoechoic and hyperechoic areas; (3) irregular cystic appearance; (4) presence of internal calcification; (5) rounded or bulging shape with increased antero-posterior diameter; and (6) shorter/longer diameter ratio greater than 0.7. Twenty patients, who were diagnosed as having lateral node metastasis on preoperative US examination, underwent therapeutic modified radical neck dissection (MRND). Of the remaining 135 patients without US-diagnosed lateral metastasis, 43 underwent prophylactic MRND, and the remaining 92 underwent central node dissection only.

Postoperative Follow-up

After surgical treatment, we followed the patients by US and chest roentgenogram to determine whether local recurrence or distant metastasis had developed. Follow-up periods averaged 37.3 ± 11.1 months (range: 2–58 months). To date, three patients have shown recurrence in the remnant thyroid or lymph node. One patient with ill-defined edge and coarse strong echoes demonstrated lung metastasis at surgery, and was omitted

from the analysis of DFS. This patient remains alive after ^{131}I ablation following total thyroidectomy with MRND. To date, distant metastases have not been detected postoperatively in any patient, and none of the patients have died of papillary carcinoma.

Statistical Analyses

Fisher's exact test was used to compare the clinicopathological variables. The Kaplan-Meier method was adopted to evaluate DFS of the patients. A p value < 0.05 was regarded as significant, and p values between 0.05 and 0.1 was regarded as indicating borderline significance.

Results

US-diagnosed Lateral Node Metastasis

Of the 155 PMCs, lateral node metastasis was detected by preoperative US examination in 20 cases (Fig. 1-a). Table 1 demonstrates the accuracy of US-diagnosed lateral metastasis by comparing pathological findings for 63 patients undergoing therapeutic or prophylactic MRND. Of the 20 cases showing US-diagnosed lateral metastasis, all but two were confirmed as having metastasis by postoperative pathological examination, and the positive predictive value reached 90%. However, US could not detect metastasis in 14 of 32 cases with pathologically confirmed lateral node metastasis, indicating that the sensitivity was only 56.3%. Furthermore, of 43 cases without US-diagnosed lateral node metastasis, 14 (32.6%) had pathologically confirmed metastasis. These incidences are similar to those reported in our previous study, which reported a larger series [11].

Edge Definition

Of the 155 PMC cases the present in series, we could not determine edge definition in 11 cases because of the wide range of acoustic shadows from large and coarse high echoes. These 11 cases were therefore omitted from this analysis. Of the 144 informative cases, edges in 31 (21.5%) were classified as ill-defined and those in the remaining 113 (78.5%) as well-defined (Fig. 1-b, 1-c; Table 1). Figure 2 indicates the DFS of patients with ill-defined and well-defined edges, Patients with an ill-defined edge had a higher incidence of recurrence than those with a well-defined edge ($p = 0.0477$).

Of the 31 US studies showing an ill-defined edge, lateral node metastasis was detected by preoperative US examination in 13 (41.9%), while such metastasis was found only in 4 of 113 cases showing a well-defined edge (3.7%) (Table 2). There was a significant difference between the two diagnoses ($p < 0.0001$).

Strong Echoes

Of the 155 cases in this series, fine strong echoes were detected in 39 (25.2%), while 60 (38.7%) demonstrated coarse strong echoes (Fig. 1-c, 1-d). There were no strong echoes found in the remaining 56 cases (36.1%). We compared the DFS of patients showing fine strong echoes with that of those showing coarse or no strong echoes (Fig. 3). Patients with fine strong echoes tended to show recurrence more frequently than those with coarse or no strong echoes ($p = 0.0902$).

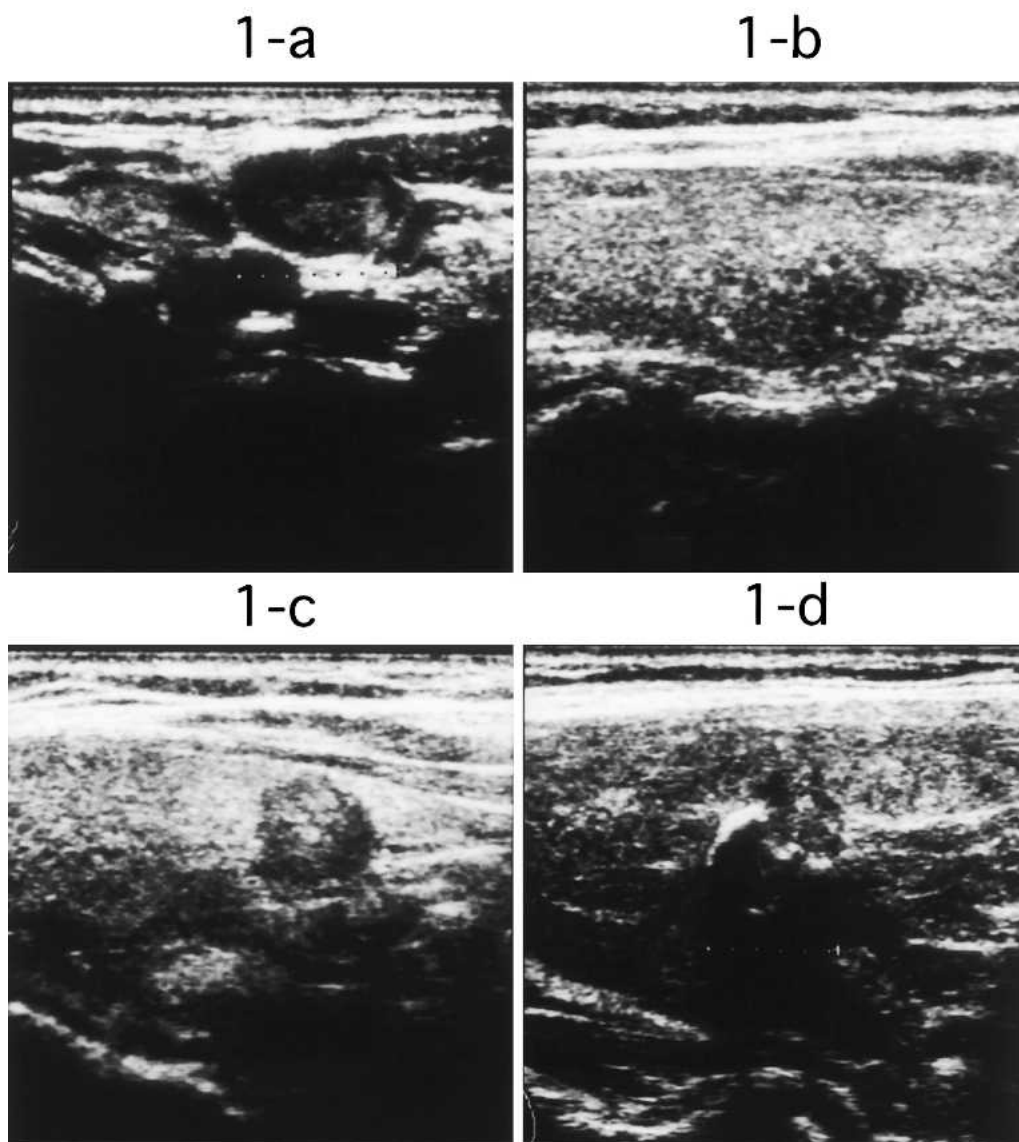


Fig. 1. 1-a. Ultrasound (US) photograph of a metastatic node in the lateral compartment. 1-b. US photograph of a papillary thyroid microcarcinoma (PMC) with an ill-defined edge and fine strong echoes. 1-c. US photograph of a PMC with a well-defined edge. 1-d. US photograph of a PMC with coarse strong echoes. We could not determine edge definition in this case.

Table 3 shows the relationship between the presence of strong echoes and US-diagnosed lateral metastasis. Cases showing fine strong echoes more frequently showed US-diagnosed lateral metastasis ($p = 0.0494$). There was no significant difference in the rate of US-diagnosed lateral metastasis between cases showing coarse strong echoes and those without strong echoes.

Discussion

To date, several groups have studied the US findings of thyroid carcinoma. Chang et al. reported that papillary carcinoma lesions manifested as well-limited, heterogeneous, and hypoechoic nodules, and that cystic degenerations and/or discrete particles could be present [13]. Thereafter, Khoo et al. reported that the risk of malignancy is high when calcification is noted within a solitary

nodule [14]. Koike et al. analyzed US findings for a large number of thyroid nodules and showed that the malignancy of nonfollicular neoplasms can be predicted on US by analyzing five US features: margin, shape, US structure, echogenicity, and calcification [15]. According to Chan et al., US findings in papillary carcinoma demonstrate a broad spectrum, and US features atypical of papillary carcinoma can be seen in half of all lesions [16]. To date, however, there have not been any studies focusing on the US features of PMC.

To our knowledge, this is the first study investigating the US features of PMC tumors. This is because, before 1999, the lack of accuracy in US findings precluded investigation of the US features of tumors in detail. We found an ill-defined edge in 21.5% of PMC, and such cases showed a worse DPS rate than those with a well-defined edge, although the follow-up period remains rather short, 37.3 months on average. This finding indicates that ill-de-

Table 1. Relationship between ultrasound (US)-diagnosed and pathologically confirmed lateral node metastasis in papillary thyroid microcarcinoma.

	Pathologically confirmed lateral metastasis		
	Absent	Present	Total
US-diagnosed lateral metastasis			
Absent	29	14	43
Present	2	18	20
Total	31	32	63

Positive predictive value (PPV) 90.0%.
Sensitivity 56.3%.

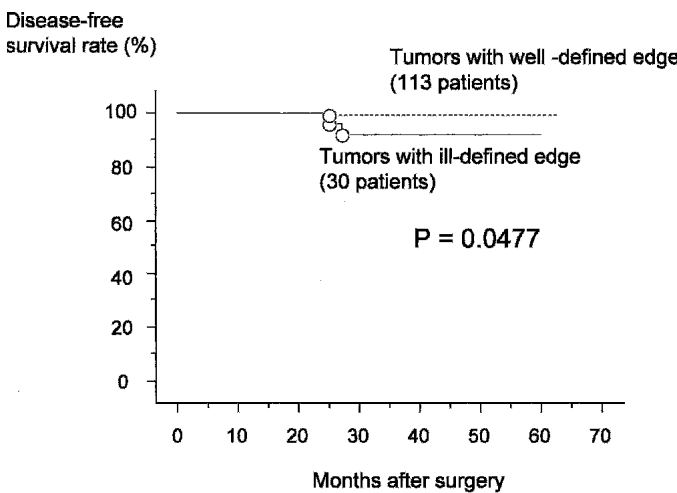


Fig. 2. The Kaplan-Meier curve of patients with PMC with an ill-defined edge and those with a well-defined edge.

Table 2. Relationship between edge definition and US-diagnosed lateral node metastasis in PMC.

	Edge defined		
	Ill-defined	Well-defined	Total
US-diagnosed lateral metastasis			
Absent	18	109	127
Present	13	4	17
Total	31	113	144

$p < 0.0001$

finer edge reflects the aggressive character of PMC. Furthermore, tumors with an ill-defined edge more frequently demonstrated US-diagnosed lateral node metastasis. This finding does not provide direct evidence that an ill-defined edge is a marker of the aggressiveness of PMC, but, because US-diagnosed lateral metastasis is a strong indicator of worse DFS, an ill-defined edge may indirectly indicate that such tumors tend to be biologically aggressive. Furthermore, for cases managed by observation without immediate surgical treatment, careful US evaluation to screen for metastasis is required at every follow-up to determine whether to proceed to surgery. It is important to consider that

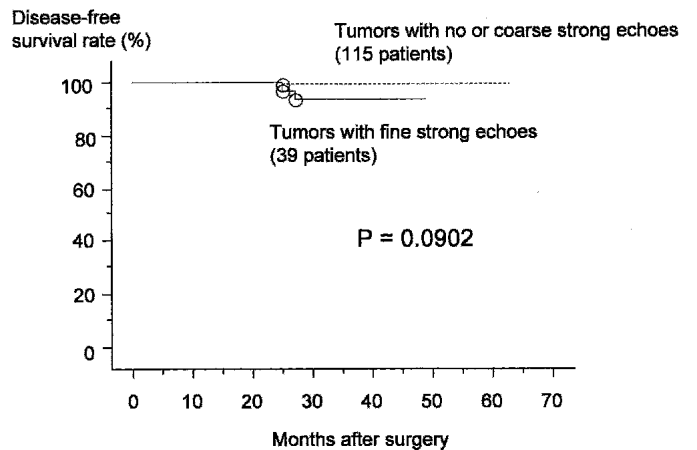


Fig. 3. The Kaplan-Meier curve comparing patients with PMC with fine strong echoes and those with coarse or no strong echoes.

Table 3. Relationship between the presence of strong echoes and US-diagnosed lateral node metastasis in PMC.

	Strong echoes			Total
	None	Coarse	Fine	
US-diagnosed lateral metastasis				
Absent	51	54	30	135
Present	5	6	9	20
Total	56	60	39	155

$p = 0.0494$ (fine vs none and coarse).

US-diagnosed lateral metastasis may be more likely to occur in patients with PMC with an ill-defined edge.

Koike et al. demonstrated that ill-defined margin could be observed in 56.1% of nonfollicular malignant nodules [15]. Chan et al. also reported a similar incidence of this feature, 53%, in papillary carcinoma [16]. The incidences were greater than that presented in this study, perhaps because their series included all sizes of tumors. Because tumor size is one of the prognostic factors of papillary carcinoma [17], it seems reasonable that the incidence of ill-defined edge in PMC would be lower than that reported in larger tumors.

Fine strong echoes were observed in 25.2% of our US studies, which is similar to the incidence reported in a previous study of nonfollicular malignant nodules but less frequent than that in another study of papillary carcinoma [15, 16]. This phenomenon is thought to historically represent psammoma bodies, small crystalline calcific deposits in the epithelium [18, 19]. This type of strong echo signal can be observed not only in primary tumors but also in metastatic nodes [20]. Although the significance of fine strong echoes has not been confirmed, this pattern of strong echoes is accepted as a radiological sign of papillary carcinoma. By comparison coarse strong echoes mostly correlate with amorphous and dense calcifications and have less diagnostic value [13]. The clinical, as well as physiological significance of fine strong echoes remains to be clarified.

Previous studies demonstrated that the prognosis of the diffuse sclerosing variant of papillary carcinoma with abundant psam-

moma bodies does not significantly differ from that of the more common type [21, 22]. In PMC, the DFS rates of patients with tumors showing fine strong echoes tended to be worse, but the difference did not reach significance. Therefore, we can not accurately assess whether fine strong echoes can be considered a marker of aggressive character of PMC. Nevertheless, because we have found that tumors with fine strong echoes are more likely to be associated with US-diagnosed lateral metastasis, careful US evaluation for node metastasis is an essential aspect of patient management when observation has been chosen as the treatment plan.

In summary, we have demonstrated that, in PMC, the presence of an ill-defined tumor edge may be a marker of aggressive characteristics. Also, fine strong echoes, may potentially reflect the biological aggressiveness of a lesion. Further studies over a longer follow-up are necessary to determine with greater certainty the clinical significance of this finding in PMC.

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Invited Commentary

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The article by Ito et al. (DOI:10.1007/s00268-005-7834-9) regarding ultrasonographic evaluation of papillary microcancers is of major interest, and their findings could have an important impact on how we manage patients with papillary thyroid microcancers (PMC), that is tumors 1 cm in greatest diameter.

The authors report the ultrasound characteristics in 155 patients who were diagnosed as PMC by fine-needle aspiration biopsy (FNAB) and confirmed histologically between October 1999 and August 2001 (followup of 37.3 months). Three patients during follow-up have developed recurrence in the remnant thyroid or

lymph nodes. Overall, 63 patients had therapeutic (20 patients) or prophylactic modified radical neck dissections (43 patients).

Of their 155 patients, 144 had definable edges of their occult PMCs; 31 of these nodules (21.5%) had irregular or ill-defined echoes, and 113 (78.5%) had well-defined echoes. Patients with tumors that had ill-defined edges were more likely to have a recurrence than those with tumors with well-defined edges ($p < 0.05$). Ultrasound-identified lateral neck nodes were more common in patients with ill-defined primary tumors (41.9% versus 3.7%; $p < 0.0001$).

Fine calcifications were also an important predictive characteristic of possible cancer in thyroid nodules, whereas coarse calcifications were not, as reported in this and in previous investigations [1–3].

The authors do not state whether the presence of more than one thyroid nodule versus a solitary nodule influenced the risk of cancer, whether any of their patients had familial papillary thyroid cancer, or whether any had been exposed to low-dose therapeutic radiation; the later situations would increase the risk of cancer. Also, the authors do not state why they performed prophylactic thyroid operations in 43 patients or what operation they would recommend as treatment for patients with occult PTC. Knowing the blood thyroglobulin levels among their patients would also be of interest because thyroglobulin levels are a sensitive indicator of persistent or recurrent PTC after total or near-total thyroidectomy [4, 5]. Ultrasound is also a sensitive predictor of nodal metastases in PTC, but as this article demonstrates, it failed to document the presence of metastases in 14 of 43 patients who had prophylactic neck dissection.

It would be interesting to know whether the authors have changed their management of patients with thyroid nodules with irregular borders; that is, are they now recommending total thyroidectomy and prophylactic ipsilateral lateral neck dissection?

One of the major dilemmas regarding nodal metastases in patients with PTC is that, although nodal metastases are associated with a higher recurrence rate, their adverse effect on survival is relatively small [6]. Because of improved sensitivity of ultrasonography and blood thyroglobulin testing, small nodal recurrences are more frequently being identified. There has been a recent multidisciplinary consensus conference regarding this subject [7]. Whether removing these occult nodes that contain

PTC is necessary, because most do not grow, is an important question that has not been answered [8].

Also, current data document that occult nodal metastases in PTC rarely, if ever, progress to distant metastases. Matted nodes and large nodes invading the internal jugular vein are of greater concern [9].

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Response to Commentary

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‘We appreciate Professor Orlo Clarks’ fine commentary. Recent improvement of the sensitivity of ultrasonography (US) has enabled us to diagnose papillary microcarcinoma (PMC) and evaluate its progression. What is most important is that US-detected lateral metastasis significantly affects the disease-free survival (DFS) of PMC patients [10, 11 in the text]. It is true that the sensitivity of US for lateral node metastasis is low, but as we reported in 2004, lateral node metastasis undetectable by US does not need to be dissected [10]. Since the publication of our study, we ourselves have not performed prophylactic lateral neck dissection for PMC without US-detectable metastasis, because we now have evidence that dissection is not necessary in such cases.

For the next step of our study, we have focused on the status of tumor detected by US. It is true that tumors showing multiple tumor formation or locating in the upper lesion of the thyroid are

more likely to have US-detectable lateral node metastasis [11]. In our study, we further investigated the US features of PMC, and showed that an ill-defined tumor edge could be indicative of a PMC with aggressive characteristics. However, it remains an open question whether patients having tumors with an ill-defined edge should undergo prophylactic lateral node dissection. The number of patients in our series is small and the follow-up period after surgery is not long enough. It will take more time to draw a final conclusion. At present, we do not recommend lateral node dissection for such patients.

To our knowledge, US is the most useful tool for the diagnosis and evaluation of progression of thyroid carcinoma, including PMC. Its appropriate application will contribute significantly to establishing the gold standard for treatment of PMC.