Application of Ultrasonography in the Diagnosis and Management of Papillary Thyroid Microcarcinoma

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Abstract: Thyroid carcinoma is the most common malignant tumor of the endocrine system. Nearly 90% of thyroid carcinomas are papillary type, of which many are thyroid papillary microcarcinoma (PTMC) with a maximum diameter ≤1 cm. High-resolution ultrasound imaging plays an important role in evaluating PTMC and guiding biopsy for pathology as well as appropriate treatment. This review paper discusses the ultrasonography features of PTMC and explores the clinical value of ultrasonography with gene testing in the diagnosis and management of PTMC.

Key words: Thyroid; Papillary thyroid microcarcinoma; Ultrasonography; Gene; Diagnosis; Treatment

Introduction

Thyroid carcinoma is the most common malignant tumor of the endocrine system. An increase in incidence in recent years has garnered the attention of clinicians and researchers. Currently, thyroid carcinoma has outpaced all malignant tumors in terms of high morbidity [1]. The soaring rate of thyroid carcinoma is primarily due to papillary carcinoma, especially in its earliest stages (i.e., microcarcinoma) [2]. According to the latest Surveillance, Epidemiology, and End Results (SEER) data, nearly 90% of thyroid carcinomas are papillary type [3]. Thus, research aimed at thyroid papillary microcarcinoma (PTMC) is of utmost importance. Metastasis of PTMC to cervical lymph nodes reportedly ranges from 30%-70% [4-6]. Some patients experience early postsurgical local recurrences or even present with distant metastases to lungs or bone [7, 8].

Surgery for PTMC is controversial. However, metastasis of PTMC is often metastasize to the lymph nodal. For example, central lymph node metastasis alone ranges from 24%-64% and is associated with recurrence and death [9, 10]. Surgical treatment of PTMC with metastasis is routinely recommended by thyroid specialists. Unfortunately, the diagnostic accuracy of lymph node metastasis of PTMC is low, and the choice of treatment methods is not clear. This review paper will discuss the ultrasonography features of PTMC and explore the clinical value of ultrasonography in the diagnosis and treatment of PTMC.

Common Diagnostic Methods of PTMC and Their Clinical Values

As defined by the World Health Organization (WHO), PTMC is any papillary carcinoma of the thyroid with a maximum diameter ≤1 cm [11, 12]. In addition, in the 2004 edition of the Tumor Pathology and Genetics of Endocrine Organs by WHO, microcarcinoma is a subtype of thyroid carcinoma, and thyroid microcarcinoma is only referred to as a PTMC.

At present, common methods diagnosing PTMC mainly include gray-scale and color Doppler ultrasonography (GS-CD-US), contrast-enhanced ultrasonography (CE-US), and US-guided FNA (US-FNA) along with related BRAF V600E gene testing.
Other imaging modalities such as CT, MRI, ECT, and positron emission tomography-computed tomography (PET-CT) are not often used for evaluation of PTMC in general. This article only addresses diagnostic methods related to ultrasonography, such as GS-CD-US, CE-US, and US-FNA along with BRAF V600E gene testing.

**GS-CD-US**

GS-CD-US is the first choice for the diagnosis of PTMC and is also the most available examination tool in various hospitals around the world. To evaluate the benign and malignant of thyroid nodules, subjects are scanned in the supine position to determine the location, size, number, border, morphology, internal echo, attenuation, elasticity modulus value, presence or absent of cystic component, microcalcification, aspect ratios of the lesion, and blood flow type of thyroid nodules. GS-CD-US is a convenient and quick non-invasive examination method, with 74.2% accuracy for the diagnosis of PTMC [13], which is not high and results in many missed diagnoses and misdiagnoses by young doctors or less experienced doctors. To improve the diagnostic accuracy of PTMC, many scholars investigated the benign and malignant ultrasonography features of thyroid nodules. Hou et al.[14] used logistic regression analysis to show that independent risk factors of PTMC included an aspect ratio > 1, unclear border, apparent hypoechogenicity, and microcalcification (Fig. 1, 2). Similarly, Ma et al.[15] found that predictors of PTMC included an aspect ratio > 1, apparent hypoechogenicity, and unclear border, with the aspect ratio > 1 being the most predictive. Huang et al.[16] found that the anteroposterior diameter of thyroid nodules > 0.7 cm was statistically significant for differentiation of benign and malignant nodules. Therefore, the apparent hypoechogenicity, unclear border, an aspect ratio > 1, microcalcification and anteroposterior diameter > 0.7 cm are all characteristics that are related to PTMC. If the apparent hypoechogenicity, aspect ratio > 1, and anteroposterior diameter > 0.7 cm present together, the clinical value of GS-CD-US for the diagnosis of PTMC is greater. Wang et al.[17] demonstrated that grayscale image features-based learning effectively improved inter-observer agreement for beginners in evaluating thyroid nodule with ultrasound.

**GS-CE-US**

The real time CE-US imaging offers an enhanced mode of GS-CD-US, which have used for assessment of vascularity of thyroid nodules [18]. Microbubble-based contrast medium (1-1.5 mL, SonoVue; Bracco Diagnostics, Milan, Italy) is injected as a bolus via ulnar vein, followed by 3 min of continuous observation, in which the blood perfusion of normal tissues and diseased tissues can be observed to obtain the flow information of the lesions for diagnosis. In gauging benign and malignant thyroid nodes by CE-US, heterogeneous enhancement or hypoenhancement signals malignancy while uniform hyperenhancement or isoenhancement considers as benign [19-21](Fig. 3, 4). According to this reference, studies have shown that the diagnostic accuracy of CE-US was 81.65%, the specificity was 88.00%, and the sensitivity was 88.00% [22]. Similarly, a meta-analyses found that the sensitivity of CE-US was 85% to 90% [23, 24]. Ma et al. found that heterogeneous enhancement had a positive predictive value for PTMC of 88.0% and an accuracy of 83.7% [15]. However, when GS-CD-US was combined with CE-US, the sensitivity and specificity of PTMC diagnosis improved to 88.6% and 94.6%, respectively [15]. Hong et al. reported that the hypoenhancement of PTMC indicated that the tumor tissue had less blood supply than the surrounding thyroid tissue, and isoenhancement or hyperenhancement indicated that the tumor tissue had equal or more blood supply than the surrounding thyroid tissue [25].
However, CE-US has certain limitations. Chen et al. [26] believed that nodules (maximum diameter < 0.5 cm) were not suitable for CE-US, mainly because they had no tumor vascular bed and the arteriovenous network lacked sufficient blood supply, which would decrease the diagnostic accuracy of PTMC. Likewise, nodules with predominantly cystic degeneration and coarse calcification were not suitable for CE-US and would also decrease in the diagnostic accuracy of PTMC.

![Figure 3](image)

**Figure 3** PTMC shown in pathology. CE-US showed heterogeneous enhancement and hypoenhancement mode.

![Figure 4](image)

**Figure 4** (A) Nodular goiter shown in pathology. (B) CE-US showed uniform isoenhancement mode.

**US-FNA and Gene Testing**

Benign and malignant judgments of thyroid nodules can also be evaluated by US-FNA and gene testing. The tissue sample for gene test requests US-guided FNA. Although these tests are invasive and not available at all hospitals, it is expended rapidly to response clinical demands. The reason for choosing gene testing is that many thyroid carcinomas, mainly follicular cell-derived thyroid carcinomas, are caused by genetic mutations, through effects on molecular signaling pathways like MAPK and PI3K/AKT. The most common mutant genes include BRAF, H-RAS, K-RAS, N-RAS, and PTEN. The BRAF V600E mutation is the most common in papillary thyroid carcinoma (PTC) [27], corresponding to 28%–83% of all gene mutations observed and accounting for about 90% of all BRAF mutations [11, 28]. This mutation has not been found in normal thyroid tissue and benign lesions [29-31]. Therefore, many hospitals provide BRAF V600E gene testing. The sensitivity of the BRAF V600E gene testing is very low, reaching only 45%, but the specificity is very high, reaching 99.5% [10, 32]. Hyun et al. reported that the diagnostic specificity of nodules with BRAF V600E alone was 100%, sensitivity was 58.3%, accuracy was 89.9%, positive predictive value was 100%, and negative predictive value was 88.1% [33]. The low sensitivity of gene testing also requires us to find new methods to improve it, and to fully use of its high specificity to diagnose the benign and malignant thyroid nodules. Chen et al. found that BRAF V600E was positively associated with PTMC lymph node metastasis and with multifocality and aspect ratio >1 [34]. However, Sun et al. found that BRAF V600E mutation was weakly negatively correlated with PTMC neck and distant metastasis in 101 patients [35]. Zheng et al. found no significant correlation in univariate analysis between BRAF V600E mutation and central lymph node metastasis (CLNM), lateral cervical lymph node metastasis (LLNM), multifocality, and extracapsular infiltration [36]. There was no significant correlation between PTMC recurrence and BRAF V600E in patients who were followed up for 40 to 72 months [36]. Although there is some debate about their correlation between BRAF V600E positive and the metastasis and
recurrence of PTMC, most scholars believe that BRAF V600E positive is associated with metastasis of PTMC, and BRAF V600E testing is a useful supplement to improve the accuracy of PTMC.

Examination with FNA can distinguish the benign and malignant nodules by cytopathological analysis. The accuracy of FNA results mainly depends on the level of examination of the pathologist and the adequacy of the specimens. US-FNA has limited utility in sub-cm nodules due to insufficient cytological specimens and false positive results, especially for nodules (maximum diameter $< 0.5\text{cm}$) [14]. Overall, the accuracy of FNA is not 100%, with studies showing that FNA has a specificity of 100%, sensitivity of 83.3%, accuracy of 95.9%, positive predictive value of 100%, and negative predictive value of 94.9% [33]. When the results of BRAF V600E were combined with cytopathology, specificity was 100%, sensitivity was 91.7%, accuracy was 98.0%, positive predictive value was 100%, and negative predictive value was 97.4% [33], indicating that the combination of gene testing and cytopathology is a good choice. The combination of the two improves the accuracy of FNA by nearly 10%, which greatly solves the drawbacks of FNA and which indicates that in clinical work, we should combine gene testing with FNA to achieve higher diagnostic accuracy of PTMC.

**Correlation between Lymph Node Metastasis of PTMC, Ultrasonography Features and Selection of Surgical Methods**

The treatment of PTMC is mainly based on surgery, supplemented by ablation, and some cases are observed dynamically. However, which method to choose depends on the specific conditions of PTMC patients. Studies have shown that PTMC with lymph node metastasis requires surgical treatment. Only PTMC with central lymph node metastasis requires thyroidectomy/total thyroidectomy + central lymph node dissection, with minimal surgical trauma. PTMC with lateral cervical lymph node metastasis needs thyroidectomy/total thyroidectomy + lateral cervical lymph node dissection, with bigger surgical trauma. Therefore, it is important to predict the metastatic site of lymph nodes. In patients with obvious lymph node metastasis, the decision can be made easily to perform thyroidectomy/total thyroidectomy + lymph node dissection. However, some lymph node metastasis of PTMC was mainly occult metastasis that was not found through GS-CD-US, and postoperative pathology suggested metastasis.

Many experts have researched the correlation between ultrasonography features and lymph node metastasis of PTMC. Hong et al. [25] confirmed that PTMC with age $\leq 45$, irregular morphology, and microcalcification was more likely to have CLNM. Pyo et al. [37] found that multifocality in PTMC was significantly associated with aggressive behavior of the tumor. Jeon et al. [38] found that male patients $< 50$ years of age, tumors located in the upper or subcapsular, and microcalcification had a higher risk of LLNM (Fig. 5). Xi et al. [39] confirmed that being male and having a tumor located in the upper pole and tumor diameter $\geq 0.7\text{cm}$ were predictors of LLNM in unilateral PTMC. Back et al. [40] found that male, CLNM, and tumor located in the upper pole were risk factors for LLNM. Li et al. [11, 41] reported a close association of BRAF V600E mutation with extracapsular infiltration of PTC, lymph node metastasis, and high TNM stage of tumor, and a subsequent higher capsular invasion rate [42]. BRAF V600E-variant PTC was found to have a greater risk of invasion, to invade the tissues surrounding the thyroid gland, and to often present in an advanced clinical stage [41, 43] and exhibit a worse prognosis [43, 44]. In conclusion, age $< 45$, microcalcification, and irregular morphology have all been associated with CLNM and PTMC, with above features requiring thyroidectomy/total thyroidectomy + central lymph node dissection; meanwhile age, gender, multifocality, the anteroposterior diameter $\geq 0.7\text{cm}$,
nodule site, microcalcification and gene positivity have been found to be risk factors for LLNM. Such nodules are treated with thyroidectomy/total thyroidectomy + lateral cervical lymph node dissection. PTMC that does not meet the above characteristics and does not have obvious lymph node metastasis can be ablated or dynamically observed.

**Correlation between Recurrence of PTMC and Ultrasonography Features**

Some patients with PTMC relapse after surgery. Many scholars have completed postoperative follow-up of PTMC patients for several years. Hay [45] followed 900 PTMC patients diagnosed and treated at Mayo Clinic from 1945-2004, with an average follow-up duration of 17.2 years; the 20-year and 40-year tumor recurrence rates were 6% and 8%, respectively. In 281 PTMC patients treated at Gustave-Roussy Institute, 3.9% of cases experienced local recurrence, and 1 case developed pulmonary metastasis [46]. In another study including low-risk thyroid carcinoma patients (stage I or II), the recurrence rate was 8.9% [47-49]. However, Nixon et al.[50] demonstrated that PTMC has an extremely low recurrent rate, i.e., 0.6%. Durante et al.[51] confirmed that none of 312 patients with PTMC T1N0M0 experienced local recurrence during a median 6-year follow-up. In conclusion, the recurrence rate after PTMC is very low overall.

Some experts have also studied the biological behavior of recurrent PTMC. Pedrazzini L et al.[52] showed in multivariate analysis that two parameters predicted local recurrence of PTMC: age (<45 years) and lymph node metastasis. It was also demonstrated that in patients with sporadic PTMC without multifocality, and with invasive or histologically confirmed lymph node metastasis, the risk of recurrence after thyroidectomy was low [52]. Ito et al.[53] confirmed that the proportion of patients with recurrent PTMC is the lower in middle and old age and higher in young people. In multivariate analysis, age was an independent predictor of PTMC progression. Ito et al.[54] confirmed that the presence of clinically significant LLNM (N1b) and being male were independent prognostic factors for disease-free survival. Mazzaferri et al.[55] found multifocality to be an independent risk factor for recurrence [56] (Fig. 6). Wada et al.[57] found that the recurrent rate of patients with LLNM was higher than that of patients with only CLNM, and the difference was statistically significant. The major cause for this is that central lymph nodes are located in the VIa area, the first location of thyroid carcinoma metastasis, while lateral cervical lymph nodes are located at II, III, and IV areas and are usually the second location of metastasis; the lymph drainage generally reaches the second location in the middle and advanced tumor stages. Additionally, patients with LLNM are often at least stage T1N1bM0, and they are more susceptible to recurrence and metastasis than patients with stage T1N1aM0 disease. In conclusion, although the recurrence rate of PTMC is very low, we should also pay attention to the patient characteristics and ultrasonography features for PTMC recurrence, such as male patients, age <45 years old, tumor multifocality and LLNM which are associated with postoperative thyroid recurrence.

**Figure 6** (A) Ultrasonographic features of PTMC showed tumor multifocality. (B) Relapse after 24 months of follow-up, the ultrasonographic features of lymph node showed microcalcification.

**Existing Problems and Prospects of PTMC Diagnosis and Treatment**

Although there are many examination methods for PTMC, the imbalance of medical conditions and the clinical signs of various thyroid lesions limit the accuracy of non-invasive diagnostic approaches and result both missed diagnoses and misdiagnoses. Therefore, a
comprehensive overview of available diagnostic tools is needed. In recent years, the number of diagnosed PTMC cases has increased significantly, resulting in many patients with PTMC being over-treated. However, risky PTMC does need to be treated. CD-US can be used to distinguish the risk of PTMC, choose the appropriate treatment, and reduce the chance of over-treatment.

In conclusion, PTMC has a high incidence and low recurrence rate post-therapy, including certain invasive PTMC. We should diagnose PTMC by combining both ultrasonography and gene testing methods along with clinical data, especially to identify invasive PTMC. We need to move beyond the inertia of postponing medical treatment and dispel the mentality of over-treatment. Appropriately using ultrasound along with gene testing provides a big step forward in improving differential diagnosis of thyroid cancer for clinical management of PTMC.

Conflict of Interest

The authors report no conflict of interest of this research work.

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