



GUIDELINE

2016 Chinese expert consensus and guidelines for the diagnosis and treatment of papillary thyroid microcarcinoma

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The incidence of papillary thyroid carcinoma (PTC) has exponentially increased in recent years. Papillary thyroid microcarcinoma (PTMC) accounts for the majority of the reported cases of PTC. The debates and crucial issues in PTMC management have received researchers' attention. To further improve the clinical management of PTMC in China,

the Chinese Association of Thyroid Oncology thus presents "2016 Chinese expert consensus and guidelines for the diagnosis and treatment of papillary thyroid microcarcinoma" based on current practices. The consensus provides 23 rated recommendations for thyroid surgery, pathology, imaging, endocrinology, and nuclear medicine. Given the limited available literature on thyroid research in China, particularly prospective thyroid cancer studies, certain areas might be overlooked. We expect comments and suggestions to improve revising the consensus. The rating system and the rated recommendations are listed in **Tables 1 and 2**.

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Table 1 Strength of recommendations

Rating	Definition
A	Strongly recommends. The recommendation is based on good evidence that the service or intervention can improve important health outcomes.
B	Recommends. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes.
C	Recommends. The recommendation is based on expert opinion.
D	Recommends against. The recommendation is based on expert opinion.
E	Recommends against. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or else its harms outweigh its benefits.
F	Strongly recommends against. The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or its harms outweigh its benefits.
I	Recommends neither for nor against. The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention. There is insufficient evidence that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. Therefore, the balance of benefits and harms cannot be determined.

Epidemiology of PTMC

PTMC is defined by the World Health Organization (WHO) as PTCs with a maximum diameter ≤ 10 mm. The SEER database indicated that the prevalence of thyroid carcinoma has significantly increased in recent years. In particular, the prevalence of PTMC has increased faster than other types of PTCs. However, the mortality rate associated with PTMC has not significantly increased. The 2014 World Cancer Report stated that among the new cases of thyroid carcinoma, >50% are PTMC. Therefore, PTMC has become the focus of research in domestic and international medical centers¹⁻⁶.

Recommendation:

(1) Given that the prevalence of PTMC has increased significantly, PTMC should be considered in the diagnosis and treatment of thyroid carcinoma. Recommendation rating: A.

Imaging diagnosis of PTMC

High-frequency ultrasonography is the first-line imaging procedure for the diagnosis of PTMC. Given that CT, MRI, and positron emission tomography/computed tomography (PET/CT) are less sensitive than ultrasound, these procedures are not recommended as routine diagnostic procedures for PTMC. High-frequency ultrasonography (grey-scale ultrasound) is recommended to describe the location and number of thyroid nodules for the quantity and quality diagnosis of PTMC. Additionally, sonography is used to detect lymph node status in PTMC. If large metastasis or suspicious invasion of surrounding tissue were detected by PTMC, CT, or MRI should be considered for further assessment.

More recently, the thyroid imaging reporting and data system (TI-RADS) has been used in numerous centers in China. The reporting system should be standardized to improve PTMC diagnosis (**Table 3**). Moreover, ultrasound-guided fine-needle aspiration biopsy (FNAB) can be performed and combined with molecular biomarker testing to assist diagnosis. Contrast-enhanced ultrasonography (CEUS) and ultrasonographic elastography (USE) are available for more difficult PTMC cases. These methods should be considered as complementary, but not routine, diagnostic methods for PTMC.

Recommendations:

(2) High-frequency ultrasonography is recommended as the first-line imaging modality for the diagnosis of PTMC. Recommendation rating: A.

(3) Ultrasound-guided FNAB is recommended for the further diagnosis of PTMC. Recommendation rating: B.

(4) CEUS and USE are recommended as complementary, but not routine, diagnostic modalities for PTMC. Recommendation rating: D.

(5) Enhanced CT and MRI are recommended as valuable tools for the diagnosis of large metastasis and the suspicious invasion of surrounding tissue in PTMC. Recommendation rating: B.

(6) MRI and PET/CT are not recommended as routine diagnostic modalities for PTMC. Recommendation rating: E.

Pathologic diagnosis of PTMC

Cytology diagnosis of PTMC

The diameter criterion for PTMC FNAB remains

Table 2 Recommendations for the diagnosis and management of PTMC

Items	Recommendations	Rating
1	Given that the prevalence of PTMC has increased significantly, PTMC should be considered in the diagnosis and treatment of thyroid carcinoma.	A
2	High-frequency ultrasonography is recommended as the first-line imaging modality for the diagnosis of PTMC.	A
3	Ultrasound-guided FNAB is recommended for the further diagnosis of PTMC.	B
4	CEUS and USE are recommended as complementary, but not routine, diagnostic modalities for PTMC.	D
5	Enhanced CT and MRI are recommended as valuable tools for the diagnosis of large metastases and the suspicious invasion of surrounding tissue in PTMC.	B
6	MRI and PET/CT are not recommended as routine diagnostic modalities for PTMC.	E
7	FNAB could be performed to diagnose PTMC when tumor diameter ≥ 5 mm. The Bethesda system is recommended for malignancy risk classification.	B
8	Testing with auxiliary molecular markers could further improve the accuracy rate of PTMC preoperative diagnosis.	C
9	In the evaluation of suspicious cervical lymph nodes in patients with PTMC, FNA-Tg washout fluid could be selectively tested as an auxiliary diagnostic method but is not recommended as a routine diagnostic method.	I
10	PTMC variants should be reported in the final diagnosis.	C
11	Surgical treatment is recommended for PTMC patients with high-risk factors.	B
12	Close follow-up observation for PTMC patients with low-risk factors could be considered upon the strict selection of indications and the adequate consideration of the patient's preferences.	C
13	Clinical observations should be strictly time limited and documented. High-resolution ultrasound imaging is preferred in follow-up review.	B
14	Thyroid lobectomy+ thymectomy or total/near-total thyroidectomy is selected depending on the clinical situation and the evaluation of recurrence risk.	A
15	The protection of the recurrent laryngeal nerve, superior laryngeal nerve, and parathyroid gland must be emphasized.	A
16	cN+PTMC patients need lymph node resection.	A
17	Prophylactic central lymph node dissection is recommended for cN0 PTMC patients.	B
18	Prophylactic lateral neck lymph node dissection is not recommended for PTMC patients.	E
19	^{131}I radioablation is not recommended as a routine procedure after PTMC surgery.	E
20	Radioactive iodine (RAI) treatment should be applied individually in accordance with the patient's specific condition.	B
21	The dosage and the principles of RAI in PTMC are basically the same as those for PTC patients.	A
22	PTMC still requires TSH suppression therapy after surgery, and individualized treatment should be implemented based on the risk of tumor recurrence and the risk of the adverse effects of suppression therapy.	B
23	Long-term follow-up is needed for PTMC patients regardless of surgical or nonsurgical treatment.	A

unstandardized. According to domestic and international researches, FNAB could be performed in PTMC with diameter ≥ 5 mm. FNAB should be performed under ultrasound guidance because blind puncturing tends to have low accuracy. The Bethesda system, which is commonly used as a reference for the classification of FNAB specimens from the thyroid, recognizes six diagnostic categories: 1) nondiagnostic/unsatisfactory, 2) benign, 3) atypia of undetermined significance/follicular lesion of undetermined significance, 4) follicular neoplasm/suspicious for follicular neoplasm, 5) suspicious for malignancy, and 6) malignant. The necessity for a 3-month waiting period for repeated

FNAB is recommended for patients of Bethesda I, II, and IV after the first FNAB without a definitive diagnosis⁷⁻¹².

Molecular diagnosis of PTMC

Testing with auxiliary molecular markers could further improve the accuracy of preoperative PTMC diagnosis. The combined detection of molecular markers, such as BRAF, RAS, TERT, RET/PTC, Pax8-PPAR, and Galectin-3, is recommended for patients with indeterminate FNAB cytology results. Previous studies have confirmed that preoperative BRAF testing is crucial in guiding surgical

Table 3 Grading of TI-RADS

Grade	Explanation
Grade 0	No completed imaging evaluation. Necessary for further assessment.
Grade 1	Negative
Grade 2	Positive
Grade 3	Suspicious benign (<5%)
Grade 4	
4a	Low-risk suspicious malignancy (5%–45%)
4b	Intermediate-risk suspicious malignancy (45%–75%)
4c	High-risk suspicious malignancy (75%–95%)
Grade 5	High-risk suspicious malignancy (≥95%)
Grade 6	Malignancy (to be proved by biopsy)

extent and is clinically valuable for determining recurrence and in follow-up¹³⁻²⁰.

In the evaluation of suspicious cervical lymph nodes in patients with PTMC, FNA-Tg washout fluid testing could be selectively performed as an auxiliary diagnostic method.

Surgical pathology diagnosis of PTMC

The pathologic diagnosis in PTMC is the same as in PTC and can also be divided into many variants based on morphological features: follicular, solid, encapsulated, diffuse sclerosing, tall cell, columnar cell, and oncocyctic variants. Follicular, encapsulated, columnar cell, oncocyctic, and diffuse sclerosing variants are the most common variants. Immunohistochemical staining is important and has a certain auxiliary function in finalizing PTMC diagnosis. Cytokeratin (CK), thyroglobulin (Tg), and thyroid transcription factor-1 (TTF-1) are positively expressed in thyroid neoplastic follicular epithelium. In addition, the expression levels of CK19, galectin-3, and HBME-1 are higher in PTMC.

Recommendations:

(7) FNAB could be performed to diagnose PTMC when tumor diameter ≥ 5 mm. The Bethesda system is recommended for malignant risk classification. Recommendation rating: B

(8) Testing with auxiliary molecular markers could further improve the accuracy rate of PTMC preoperative diagnosis. Recommendation rating: C

(9) In the evaluation of suspicious cervical lymph nodes in patients with PTMC, FNA-Tg washout fluid could be

selectively tested as an auxiliary diagnostic method but is not recommended as a routine diagnostic method. Recommendation rating: I

(10) PTMC variants should be reported in the final diagnosis. Recommendation rating: C

Surgical treatment of PTMC

Currently, the treatment of PTMC remains unstandardized. Domestic and international controversies mainly focus on the necessity and the extent of surgery for PTMC. Although PTMC has favorable outcomes, not all PTMC are slow-growing lesions without any progression. All cases of advanced PTC progressed from PTMC. Some PTMC can combine with highly aggressive histological variants and even exhibit early-localized invasion or lymph node and distant metastasis. Furthermore, therapy has positive effects on PTMC, and the majority of PTMC patients can be cured with surgical treatment. Therefore, surgical treatment should focus on thoroughness and adhere to standards to effectively decrease the rate of recurrence and metastasis. Some PTMC are static and rarely develop into clinically significant thyroid carcinoma. Some patients are asymptomatic even for life. PTMC has limited impact on survival even though some cases present with clinical symptoms or cervical lymph node metastasis. Therefore, PTMC without any metastasis and symptoms should be closely observed without any treatment. Experts agree that the need of surgical treatment for PTMC should be considered comprehensively with risk assessment, the imaging features of two-dimensional ultrasound, histological characteristics of the tumor (invasion, multifocal, and lymph node metastasis) and the patient's appropriate participation and compliance.

The controversy surrounding the requirement of surgery for PTMC mainly focuses on the extent of operation for the primary tumor and cervical lymph nodes. Experts agree that the surgical procedures for the primary tumor should be a reasonable balance between lobectomy+isthmusectomy and total/near-total thyroidectomy. The extent of dissection for secondary lesions (cervical lymph nodes) should follow the principle of individualized treatment. Central-compartment neck dissection is generally recommended. Lateral neck compartmental lymph nodes should be reasonably and selectively dissected²¹⁻²⁸.

PTMC surgery or observation

Surgical resection should be the preferred treatment for PTMC patients who were selected for aggressive treatment.

The experts of the consensus agree that the size of the tumor is not the sole indicator of its invasive and metastatic capability of the tumor. The invasion of the capsule or adjacent vital structures by PTMC is common and includes metastasis to central compartment lymph nodes and even to lateral neck compartment lymph nodes. Therefore, surgical treatment is recommended for PTMC patients who meet any of the following risk factors (surgical indications for PTMC): 1) history of neck exposure to radiation during childhood or adolescence; 2) family history of thyroid carcinoma; 3) identification or suspicion of cervical lymph node metastasis or distant metastasis; 4) invasion of neoplastic foci beyond the lobe, such as the invasion of the recurrent laryngeal nerve, trachea, or esophagus; 5) high-risk histopathologic variants, such as tall-cell, columnar cell, diffuse sclerosing, solid/insular, and Hürthle variants); 6) biopsy specimen positive for BRAF mutation; 7) progressive increase in neoplastic foci within a short period (diameter increased by over 3 mm in 6 months).

The experts of the consensus recommend that the relative surgical indications of PTMC include: 1) foci diameter ≥ 6 mm; 2) multi-foci carcinoma, especially bilateral carcinoma; 3) patients with psychological burden and request for surgery; 4) thyroid stimulating hormone (TSH) level that is persistently higher than normal.

Whether intrathyroidal PTMC within the gland (in particular, diameter ≤ 5 mm) can be closely observed remains controversial. Before fully understanding the clinical biological behavior of PTMC, the clinical decision should be made based on patient's clinical staging, the comprehensive analysis of risk assessment, and full communication with patients and their families. Close follow-up observation may also be considered for PTMC in the following situations: 1) non-high-risk pathological variants, 2) tumor diameter ≤ 5 mm, 3) tumor is distant from the thyroid capsule and has not invaded surrounding tissues, 4) no evidence of lymph node or distant metastasis, 5) no family history of thyroid carcinoma, 6) no history of neck exposure to radiation during childhood or adolescence; 7) patients with low psychological burden who can actively cooperate. Close observation can be recommended to patients who meet all of the above conditions (patients who simultaneously meet recommendations 1–6 are identified as low-risk PTMC patients). The initial observation period can be set from 3 to 6 months and adjusted in accordance with the disease; for example, the observation period may be extended if the patient is in a stable condition. The patients should provide written consent and be observed and documented in accordance with a unified standard. Surgical treatment

should be considered if the following conditions occur during close observation: 1) tumor diameter increased by more than 3 mm, 2) clinical lymph node metastasis is present, 3) patient requests surgery.

Recommendations:

(11) Surgical treatment is recommended for PTMC patients with high-risk factors. Recommendation rating: B

(12) Close follow-up observation for PTMC patients with low-risk factors could be considered upon the strict selection of indications and the adequate consideration of the patient's preferences. Recommendation rating: C

(13) Clinical observations should be strictly time limited and documented. High-resolution ultrasound imaging is preferred in follow-up review. Recommendation rating: B

Resection extent of PTMC

Thyroid lobectomy+isthmusectomy is the recommended initial surgical approach when surgery is considered for PTMC patients. Total thyroidectomy is inappropriate in terms of overtreatment. Decisions regarding the extent of surgery are influenced by several factors, including clinical stage, risk evaluation, complications, and the patient's willingness. Personalized treatment plans are presented in this paper.

Indications of thyroid lobectomy+isthmusectomy include:

1) Patients without familial thyroid carcinoma, 2) without a history of radiation exposure, 3) no bilateral nodular disease, 4) single encapsulated tumor, 5) low risk, 6) no positive lymph node or metastasis. Some patients may need total/near-total thyroidectomy. The advantages of total/near-total thyroidectomy include: 1) definitive removal of tumor, 2) enabling subsequent ^{131}I treatment, 3) convenient postoperative monitoring, 4) resection of nonpalpable mass. Indications of total/near-total thyroidectomy include: 1) familial thyroid carcinoma, 2) history of radiation exposure, 3) multi-focal tumor, especially bilateral multifocal thyroid cancer, 4) positive bilateral lymph node or metastasis, 5) extrathyroidal invasion of the thyroid cancer that might lead to the incomplete resection of the tumor. In this case, ^{131}I will be needed after operation.

Relative indications of total/near-total thyroidectomy include: 1) clinical metastasis of ipsilateral cervical lymph node; 2) high risk of recurrence; 3) contralateral thyroid nodules; 4) pathological subtypes: tall cell, columnar cell, diffuse sclerosing, insular, and Hurthle cell variants of PTC.

Professional training, standard surgical approach, and skills are recommended. Protecting the recurrent laryngeal nerve, superior laryngeal nerve, and parathyroid gland can

decrease complications³⁴⁻³⁹.

Recommendation:

(14) Thyroid lobectomy thymectomy or total/near-total thyroidectomy is selected depending on the clinical situation and the evaluation of recurrence risk. Recommendation rating: A.

(15) The protection of the recurrent laryngeal nerve, superior laryngeal nerve, and parathyroid gland must be emphasized. Recommendation rating: A.

Neck dissection

patients with lymph node metastasis have a high recurrence rate. The factors for recurrence include age, tumor diameter, and thyroid capsule invasion. Some PTMC patients are found to have lymph node metastasis during initial diagnosis, and some cN0 patients are found to have lymph node metastasis after surgery. The central compartment is the most common site of metastases in PTMC. Recommendations should be combined with preoperative and intraoperative risk assessment. Primary tumor surgery with preventive central lymph node dissection is recommended. Recurrent laryngeal nerve and parathyroid gland protection should be emphasized. Surgeons should pay attention to the difference of the anatomy of left and right laryngeal recurrent nerve. The posterior aspect of the right recurrent laryngeal nerve deep area should be dissected²⁹⁻³⁹.

Prophylactic lateral neck lymph node dissection is generally not recommended except when lateral neck lymph node metastases are present. Relative indications include: 1) central region lymph node, extranodal, or lymph node metastasis number ≥ 3 pieces; 2) tumor is located on the upper thyroid gland and has spread outside of the thyroid.

Recommendations:

(16) cN+PTMC patients need lymph node resection. Recommendation rating: A.

(17) Prophylactic central lymph node dissection is recommended for cN0 PTMC patients. Recommendation rating: B.

(18) Prophylactic lateral neck lymph node dissection is not recommended for PTMC patients. Recommendation rating: E.

¹³¹I therapy for PTMC patients

For most PTMC patients, ¹³¹I ablation is generally not recommended as a routine procedure to eliminate thyroid remnants following thyroidectomy. However, long-term clinical experience, as well as many research articles, has revealed that cervical lymph node metastases from various

forms of PTMC are not uncommon. In rare instances, distant metastases originate from PTMC. For patients with metastatic lesions, especially distant metastasis, ¹³¹I therapy may be helpful in eliminating residual lesions or metastasis that could not be surgically excised, thus decreasing the risks of recurrence or providing significant palliation. Indications for ¹³¹I ablation for PTMC patients following total or near-total thyroidectomy are those with: 1) distant metastasis; 2) unresectable malignant lesion, suspicious lesion, or evident residual lesion after surgery; 3) unexplainable, abnormal, and consistently elevated serum levels of Tg during follow-up. When ¹³¹I therapy is required for PTMC patients with evident metastasis, the treatment methodology, appropriate procedures for radioactive safety, subsequent long term TSH suppressive therapy, and criteria for follow-up and evaluation are basically the same as those for PTC patients⁴⁰⁻⁴⁴.

Recommendations:

(19) ¹³¹I radioablation is not recommended as a routine procedure after PTMC surgery. Recommendation rating: E.

(20) Radioactive iodine (RAI) treatment should be applied individually in accordance with the patient's specific condition. Recommendation rating: B.

(21) The dosage and the principles of RAI in PTMC are basically the same as those for PTC patients. Recommendation rating: A.

Post-operative TSH suppression therapy and follow-up for PTMC

TSH suppression therapy of PTMC

Overall, the principles, medication, targets, and adverse reactions of postoperative TSH suppression therapy for PTMC are similar to those for nonmicro PTC TSH suppression therapy in the 2012 Chinese edition of "Thyroid Nodules and Differentiated Thyroid Cancer Management Guidelines." As PTMC is not equivalent to low-risk DTC, post-operative management should also be based on recurrence risk stratification. According to recent findings, the approach to TSH suppression therapy has the following trends: 1) setting of the TSH suppression therapy target according to the individual patient's dual risk assessment (risk of tumor recurrence and risk of suppression therapy adverse effects); 2) compared with mild TSH suppression (0.1–0.5 mU/L), aggressive TSH suppression therapy target (<0.1 mU/L) provides no further benefits for low-risk PTMC patients; 3) the TSH suppression target value may be set at 0.5–2.0 mU/L for post-surgical, low-risk PTMC patients with undetectable Tg levels, negative anti-thyroglobulin antibodies

(TgAb), and no evidence of recurrent or metastatic disease on imaging; 4) the TSH suppression therapy target is dynamic and should be adjusted based on the continuing evaluation of patient response to treatment⁴⁵.

Recommendation:

(22) PTMC still requires TSH suppression therapy after surgery, and individualized treatment should be implemented based on the risk of tumor recurrence and the risk of adverse effects of suppression therapy. Recommendation rating: B.

Follow-up of PTMC

PTMC patients should be followed-up for the long-term. Based on whether the patient underwent surgery or not, the goals and evaluation methods for the follow-up vary. For patients who have opted for close observation, the follow-up is aimed to detect tumor progression and determine the need for timely surgical treatment. High-resolution ultrasound is a common monitoring method in long-term follow-up. However, if follow-up is inconclusive, the initial observation period can be extended for 3 to 6 months and adjusted thereafter based on the disease. If there are no signs of progression, the interval between follow-up appointments may be extended (for example, every 6–12 months after the initial 2–3 years). For post-operative PTMC patients, the goals of long-term follow-up are: 1) early detection of tumor recurrence and metastasis, active surveillance of disease progression and treatment response, and adjustment of the treatment plan; 2) monitoring of the response to and the adverse reactions of TSH suppression therapy, with active observation of other concomitant diseases, such as heart disease and other malignancies⁴⁷⁻⁵².

Recommendation:

(23) Long-term follow-up is needed for PTMC patients regardless of surgical or nonsurgical treatment. Recommendation rating: A.

Prospects

More molecular markers for the diagnosis, prognosis, and therapy of PTMC should be discovered

As basic medical research continues to advance, more molecular markers are used in the diagnosis, prognosis, and therapy of thyroid cancer. American researchers formed the Cancer Genome Atlas Research Network and have targeted PTC for genetic analysis. The detection of mutations in

BRAF, TERT, TP53, and other genes can help to further stratify risk of PTC. We hope to discover more molecular markers that can translate into PTMC management to further improve PTMC risk stratification, prognosis, therapy, and other areas.

More prospective multi-center clinical studies on PTMC patients

Foreign nonsurgical observational studies on PTMC patients have provided important data for PTMC treatment decisions. Nevertheless, many questions remain, such as the nonrandomized selection of patients, the observed parameters of PTMC, the justification of follow-up strategies, and TSH suppression targets. We look forward to the emergence of more valuable prospective clinical studies. Large multi-center national clinical trials might provide more accurate and stronger evidence for the biological characterization of PTMC.

Evaluation of PTMC ablation treatment

Given that ablation (radiofrequency or microwave) is localized, it cannot guarantee complete PTMC ablation and does not meet the minimum extent of treatment in the lateral lobe. Therefore, PTMC has high risk for recurrence after ablation treatment. Even if the PTMC clinical stage is cN0, occult cervical lymph node metastasis, which cannot be resolved via ablation, may still be present in some patients. In addition, post-ablation lesions are more difficult to surgically excise. Therefore, ablation is not recommended as a routine treatment for PTMC. The efficacy of ablation treatment for PTMC in strictly intrathyroidal cases with fully patient consent under the operation of qualified professionals still awaits more scientific observations⁴⁶⁻⁴⁸.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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