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REVIEW ARTICLE

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Papillary thyroid microcarcinoma: Is active surveillance always enough?

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Abstract

The incidence of papillary thyroid carcinoma (PTC) has increased over recent decades. This apparent epidemic has been attributed to the overdiagnosis of small PTC ≤10 mm in diameter (papillary thyroid microcarcinoma [PTMC]) incidentally detected on imaging for unrelated presentations. Although most PTMCs follow an indolent disease course, there is a small but significant proportion of cases that display more biologically aggressive features such as early metastasis and lymph node involvement. Management of PTMC diagnosed preoperatively should be distinguished from managing those PTMCs incidentally discovered after thyroidectomy. Here, we will focus on the challenge of managing the preoperative patient. Current guidelines recommend against routine biopsy of nodules ≤10 mm, even if they display highly suspicious features on ultrasound; however, it is not known how to identify those PTMCs at higher risk of disease progression. In view of their good prognosis even without surgical resection, active surveillance has emerged as an alternative to operative management for low-risk PTMC without lymph node involvement or distant metastasis. This review aims to summarise active surveillance data for PTMC and identify clinical features that may differentiate the indolent majority from those PTMCs that exhibit early disease progression and metastasis.

KEYWORDS
active surveillance, microcarcinoma, papillary carcinoma, thyroid cancer, thyroid nodule

1 | INTRODUCTION

The incidence of thyroid cancer has increased over the past few decades.[1] In Australia, the incidence has quadrupled from 2.7 cases per 100,000 in 1982 to 12 cases per 100,000 in 2015.[2] These statistics have been mirrored in many countries around the world including the United States,[3] South Korea,[4] Europe, and England,[1] and are largely attributed to the increased diagnosis of small papillary thyroid carcinoma (PTC) ≤10 mm in diameter (papillary thyroid microcarcinoma [PTMC]).[3] Despite the epidemic of PTC, mortality is largely stable,[2,3] except in larger (>4 cm) or more poorly differentiated cancers.[5] Low associated mortality and high rates of occult PTMC found both on autopsy studies[6] and in thyroidectomy specimens resected for benign thyroid conditions[7] suggest that the increased incidence of thyroid cancer is due to increased detection of asymptomatic PTMC. Given the indolent nature of PTC, it is anticipated that the majority of these PTMCs would either not progress or progress so slowly as to never cause clinically significant disease during a patient's lifetime. Overdiagnosis of PTMC is attributed to incidental detection of thyroid nodules on investigations completed for unrelated presentations, and the availability of high-resolution ultrasonography and ultrasound (US)-guided fine-needle aspiration

biopsy (FNAB) which has enabled the diagnosis of nodules from 3 mm in diameter.[1,8,9] Modelling has estimated that up to 73% of thyroid cancers in Australia in 2012 were overdiagnosed compared with 1982 when incidental detection of thyroid nodules was uncommon.[10] Overdiagnosis is emotionally and economically costly and is associated with iatrogenic harms by unnecessarily exposing patients to risks of active management. Solutions to mitigate the downstream effects of overdiagnosis present a challenge for clinicians and healthcare systems alike.

Where there is no evidence of extrathyroidal extension or distant metastasis, the American Thyroid Association (ATA) guidelines recommend against biopsy of thyroid nodules ≤10 mm in diameter, even when they display highly suspicious features on US.[12] Sonographic features of PTC that may be associated with malignancy include nodule hypoechogenicity, irregular margins, presence of microcalcifications and taller than wide shape measured in transverse view. Although the predictive value of any single feature varies widely, the presence of multiple suspicious features increases the likelihood of malignancy.[13,14] Grading systems such as thyroid imaging reporting and data systems (TIRADS) use sonographic features to stratify the risk of malignancy and guide decisions regarding the biopsy of nodules (Figure 1).[15] However, the diagnostic accuracy of US characteristics may vary depending on nodule size and observations of reduced diagnostic accuracy of suspicious features on US for nodules ≤10 mm, compared with those >10 mm, have been reported.[13] In contrast to the ATA guidelines, the Japan Association of Endocrine Surgery (JAES) consensus statement[16] recommends early fine needle aspiration cytology to facilitate staging and guide management. Although early staging may be useful, it is our opinion that the efficacy of rescue surgery in the event of disease progression and the comparable outcomes of patients requiring rescue surgery versus those who undergo immediate surgery justify avoiding or delaying biopsy in patients with PTMC.

Despite recommendations against biopsy of low-risk thyroid nodules ≤10 mm, it is not uncommon to see newly diagnosed PTC in patients with an 8 mm lesion with microcalcifications on US that has been biopsied before specialist review. Diagnosis and investigation of cancers that may never become clinically apparent fosters unnecessary anxiety and exposes patients to risks and harms in the course of treatment that could be otherwise avoided.[17] The challenge of managing PTMC preoperatively is characterised by high patient anxiety and a likelihood that aggressive management could attenuate treatment benefits. Active surveillance has been proposed as an alternative to active management for low-risk PTMC and is defined as regular monitoring (usually by ultrasonography) for disease progression. Safely deferring intervention relies on the ability to accurately define low-risk PTMC and select appropriate patients as outlined by Tuttle et al.,[18] who defined low preoperative risk as an absence of nodal or distant metastasis, extra-thyroidal extension, or evidence of recurrent laryngeal nerve (RLN) or tracheal invasion. The location of the PTMC is also crucial if growth will impact local structures such as the RLN. Tuttle et al.[18] usefully categorised patients as either ideal, appropriate or inappropriate for active surveillance and offers a practical guide to help clinicians group patients effectively. In the event of disease progression during active surveillance or change of patient preference, active management is pursued. Similarly, the JAES consensus statement[16] provides guidance for clinicians on the appropriateness of active surveillance for different patient groups based on available evidence. In a recent prospective study, Sawka et al.[19] showed that 71% of patients preferred active surveillance over surgical intervention for low-risk PTCs <2 cm. There is, however, a small subset of patients in whom PTMC marks the beginning of an aggressive malignancy. This mini-review aims to summarise active surveillance data for PTMC to date, to highlight the small group of patients with early aggressive malignancy, and address the challenge of identifying and managing each of these cohorts.

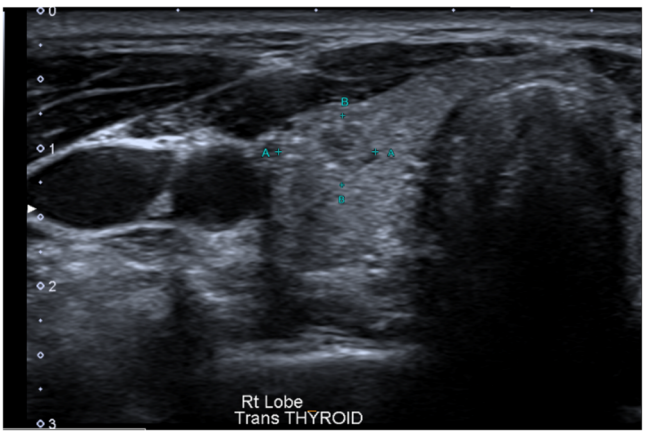

FIGURE 1 Ultrasound demonstrates a 7 mm nodule in the right thyroid lobe which is solid, isoechoic to background parenchyma, wider than tall, with ill-defined margins and punctate echogenic foci (TIRADS 4)

1.1 | Prognosis

The favourable prognosis of PTMC is well-documented and reassuring. Indeed, for all PTC, disease-specific mortality is low such that there is no difference in mortality between young patients with larger tumours and their PTMC counterparts.[12] In a prospective study of 1077 patients with PTMC, the mortality rate among patients without metastatic disease at diagnosis was 6% over a 16-year period.[20] Similarly, in a cohort observed over 50 years only 3 patients died as a result of thyroid cancer (0.3%), compared with 29% who died of other causes.[9] When examining PTMC progression over 10 years in a different cohort undergoing active surveillance, only 3% of PTMC displayed rapid growth using a model of tumour doubling time derived from serial ultrasonographic examinations.[21] In contrast, 57% remained stable and 17% reduced in size. In another study of 230 patients with asymptomatic PTMC, 90% of PTMC remained stable and 3% decreased in size over the 17-year observation period.[22] Although three patients (1%) developed new lymph node metastasis, none developed distant metastasis or died as a result of the disease.

Historically, patients diagnosed with PTMC were often recommended to undergo immediate surgery (thyroidectomy or subtotal thyroidectomy). Although surgery ensures low rates of disease recurrence, the associated risks can outweigh the benefits when the disease is typically indolent and associated with a low likelihood of progression.[9] Complications of thyroidectomy include transient vocal cord paralysis, postoperative infection, and more serious hypoparathyroidism and complications from anaesthesia. Post-thyroidectomy complications in low-risk PTMC have been reported as 0.2% for vocal cord paralysis and 1.5% for permanent hypoparathyroidism.[23] Together, the low probability of PTMC progression and the risk of surgical complications have led to the promotion of active surveillance for appropriately selected patients.

1.2 | Active surveillance

The active surveillance model for the management of PTMC has mostly been investigated in Japan.[24-27] Using 6-monthly ultrasonography, 162 patients with PTMC were observed over an average of 46.5 ± 21.5 months to find that more than 70% of tumours either remained the same or decreased in size.[24] In a subsequent study of 1235 patients with low-risk PTMC, tumour enlargement ≥3 mm and new lymph node metastasis occurred in 8.0% and 3.8% of patients, respectively, over the 10-year observation period.[27] Reassuringly, among patients who progress to clinically significant disease, delayed (rescue) surgery does not affect overall disease-specific survival.[22] Moreover, patients with low-risk PTMC who are managed by active surveillance with twice-yearly neck US have comparably good oncological outcomes compared with those who undergo immediate surgical management.[23]

Notwithstanding, there are a small but significant number of aggressive PTMCs that may exhibit early metastasis and lymph node involvement.[24] Identifying these patients before surgery unless obvious lymph node disease is identified on USS is a clinical challenge (Table 1). For PTMC without obvious nodal involvement, preoperative prognostication is controversial. Genetic signatures are largely similar in N1b and N0 disease and therefore the driver for these aggressive presentations is still unknown.[28]

TABLE 1 Preoperative clinical features and assessing suitability for active surveillance in PTMC

	Quality of evidence[a]
Features supporting active surveillance	
Age ≥ 60 years	Low quality
Poor vascular supply on Doppler US	
Tumour attached to trachea at an acute angle	
Tumour separated from trachea/RLN by rim of normal thyroid tissue	
Well-defined border edge	
Multifocality	
Features associated with increased risk of PTMC progression	
Age < 40 years	Moderate quality
Rich vascular supply on Doppler US	Low quality
Tumour attached to trachea at an obtuse angle	
Features of indeterminate suitability for active surveillance	
Microcalcifications	Low quality
Family history of thyroid cancer irregular border	
Pregnancy	
Elevated serum TSH concentration	
Male gender	

Abbreviations: PTMC, papillary thyroid microcarcinoma; RLN, recurrent laryngeal nerve; TSH, thyroid-stimulating hormone; US, ultrasound.
[a]GRADE system for evaluating the quality of evidence.[11]

1.3 | Preoperative features related to PTMC progression

In contrast to PTC where older age is a risk factor for aggressive disease and death,[29] younger age at diagnosis (particularly <40 years) is associated with an increased risk of PTMC progression.[27,30] In a cross-sectional study of 1211 patients with low-risk PTMC who opted for active surveillance, there was an inverse association between age and both tumour enlargement ≥3 mm and the appearance of new nodal metastasis.[30] These findings are similar to those of another group who reported that younger age (<40 years) is an independent risk factor for disease progression: primary tumour enlargement, new nodal involvement and progression to clinical disease were significantly more common in young patients (<40 years) than in middle-aged (40–59 years) and older patients (≥60 years).[27] Similar findings have been reported by other authors[22,30-32] and may be due to the relative loss of tumour growth activity in middle and older age groups.[27] Although some authors have suggested that older patients may be better suited to active surveillance, the favourable prognosis of PTMC overall and the efficacy of rescue surgery in the event of disease progression suggest that active surveillance is also reasonable for carefully selected patients less than 40 years without lymph node metastasis. Although the JAES consensus statement suggests that age less than 20 years is an indication for immediate surgery,[16] there is no current evidence supporting this approach.

There is limited and conflicting data regarding the prognostic value of other demographic factors in the setting of low-risk PTMC. Whereas some authors have found male gender to be a poor prognostic feature of PTMC,[26] other studies have found no statistically significant association.[22,25,33,34] However, these studies have been limited by the inclusion of relatively few male participants.

One active surveillance study assessed familial PTC to find no differences in rates of disease progression, disease-free survival or mortality when compared with sporadic PTC.[27]

1.4 | Tumour location, size and multifocality

Primary tumour location is an important consideration when determining appropriate PTMC management. Surgical management is recommended for tumours that show actual or potential RLN or tracheal involvement on imaging.[16,35] Nevertheless, there is conflicting evidence about whether these features are indeed indicative of more biologically aggressive PTMC, and some have argued that only PTMCs attached to the trachea at an obtuse angle are at risk of tracheal invasion.[36] For assessing invasion of the RLN, the same authors suggest that the presence of a rim of normal thyroid parenchyma separating the tumour from the RLN correlates with low risk of invasion: among patients with PTMC ≥7 mm without a rim of normal thyroid tissue in the direction of the RLN, 9% showed invasion of the RLN requiring surgical dissection.[37] Neither tracheal nor RLN invasion was seen in tumours less than 7 mm.

There is no consensus on the prognostic significance of primary tumour size. In a study of 132 patients with low-risk PTMC, although tumours ≥7 mm tended to enlarge more frequently than smaller tumours over the 4-year observation period, the difference was not significant and there was no association between tumour size and development of lateral lymph node metastasis.[25] The same authors also suggested that tumours occupying two or more zones of the thyroid (where the thyroid was divided into bilateral upper, middle and lower zones and isthmus) and those located within the upper lobes are associated with an increased incidence of US-diagnosed lateral lymph node metastasis. In a more recent study, multivariate analysis found tumour diameter of ≥9 mm at diagnosis was an independent risk factor for progression to clinical disease; however, it was not a predictor of tumour enlargement or lymph node metastasis alone.[27] As acknowledged by the authors, this finding may be due to their definition of clinical disease as tumours reaching 12 mm or more in diameter, as larger tumours would be expected to more readily reach this cut-off. Other active surveillance trials have found no relationship between tumour size at diagnosis and progression of disease.[24,31,34]

Border irregularity on ultrasonographic examination may be an indicator of aggressive disease. In a study of 155 cases, PTMC with a poorly defined tumour edge was associated with increased rates of lateral lymph node metastasis and poorer disease-free survival compared with tumours with a well-defined edge.[38] However, others have found no difference.[22] The significance of tumour calcification patterns has produced similarly disparate results: whereas one group found that tumours with strong calcification patterns (macroscopic or rim) were less likely to progress to clinical disease,[39] others found no association.[22] Two studies have found a significant association between tumour vascularity and growth. In a prospective study of 384 patients undergoing active surveillance for low-risk PTMC, rich vascular supply on Doppler US was associated with growth in tumour diameter by ≥3 mm.[39] However, most (61%) tumours with rich vascular supply at the first examination reduced in size over the study period. Another author found that 30% of tumours with rich vascularity on US increased in diameter by ≥3mm, compared with 4% of those with poor vascular supply ($p < .0001$).[22] Multifocality was not associated with disease progression in any of the active surveillance trials reviewed.[22,26,27,40]

1.5 | Serum TSH concentration

Serum TSH concentration is an important prognostic factor in PTC; however, there is limited evidence that elevated TSH is predictive of PTMC progression. In a retrospective study of 126 patients from a single centre in South Korea, elevated TSH during active surveillance was associated with PTMC progression (≥50% increase in tumour volume).[41] However, this cohort included patients who declined surgery despite physician recommendations and those in whom high anaesthetic risk precluded surgical resection. In the active surveillance trials reviewed here, there was no significant association between serum TSH concentration and PTMC progression.[22,40,42]

1.6 | Pregnancy

According to the 2015 ATA Guidelines, the approach to PTC diagnosis during pregnancy is comparable to that for nonpregnant women. Owing to the indolent nature of the disease, treatment of PTC diagnosed during pregnancy is usually delayed until the postpartum period to minimise the risk posed to the mother and foetus.[43] There is limited data regarding the management of PTMC during pregnancy. In a retrospective study of 51 pregnant women with low-risk PTMC, 4 participants (8%) displayed tumour enlargement and none developed new lymph node metastasis.[44] Further studies with larger cohorts are required to establish whether the pregnancy is a true risk factor for disease progression.

1.7 | Directions for future research

Preoperative risk stratification of patients with PTMC without lymph node metastasis on US remains a clinical challenge. Younger age (particularly <40 years) was consistently associated with increased risk of disease progression in the studies reviewed here; however, further research evaluating clinicopathologic indicators of aggressive disease is needed to enable early detection of the small subset of patients who are likely to do poorly. Future directions include evaluation with machine learning to determine sonographic risk in PTMC as well as prospective studies to investigate the role of molecular analyses of FNAB in PTMC with a focus on the prognostic value of molecular markers including microRNAs, *BRAF V600E* and *TERT* promoter mutations. Although *BRAF* and *TERTp* mutations are

associated with poor outcomes in the setting of PTC, evidence evaluating their prognostic significance in patients with PTMC is lacking. One study of 26 patients with PTMC found that the *BRAF V600E* mutation was not associated with tumour progression and *TERTp* mutations were not found in any PTMCs which had increased in size or progressed to lymph node metastases.[45] Clearly, there is more to be learnt regarding the role of molecular markers in PTMC risk stratification.

Health economics is also an important consideration and there are limited data directly comparing the cost-effectiveness of active surveillance versus immediate surgery. One study conducted in Japan reported a significantly lower cost associated with active surveillance (USD $1525), compared with immediate thyroidectomy (USD $9219) or hemithyroidectomy (USD $7225) over 10 years even when rescue surgery was performed during the follow-up period.[46] A recent Australian study found that active surveillance would become more costly than immediate surgery after 16.2 years using a model with biannual ultrasonography or 45.1 years if US monitoring was reduced to yearly.[47] Although there are obvious difficulties comparing costs across healthcare systems, the economic implications of overdiagnosis, different management options and long-term follow-up of PTMC require further consideration.

2 | CONCLUSION

While the majority of the recent increase in PTC incidence is attributed to overdiagnosis of PTMC, there remains a cohort of patients who require more nuanced risk stratification. Although most PTMCs behave in an indolent fashion, the small subset that behaves aggressively is not yet genomically or radiologically defined. While there is conflicting evidence regarding potential risk factors for disease progression, large groups in Japan and at Memorial Sloan Kettering Cancer Centre have demonstrated the safety and efficacy of active surveillance and have proposed risk stratification which can help to select appropriate patients. As the pendulum of treatment continues to swing towards conservative management, future research is required to clarify the natural history of all PTMCs and identify prognostic features among wider populations.

2.1 | Case example 1

An 80-year-old female is noted to have a thyroid nodule 7 mm in diameter during a carotid artery Doppler US for investigation of a suspected transient ischaemic attack. The patient is asymptomatic and there is no palpable mass or lymphadenopathy on examination. Her past medical history includes ischaemic heart disease and hypertension which is controlled with an ACE inhibitor. Thyroid US shows a solitary, isoechoic nodule within the right lobe of the thyroid; it has well-defined margins and poor vascular supply, with a rim of normal thyroid parenchyma separating the nodule from surrounding structures. There is no evidence of extrathyroidal extension or lymph node involvement on examination or US. Thyroid function tests are within normal ranges.

Approach: Active surveillance would be appropriate in this case. The nodule has a low risk of progression given its size (≤10 mm in diameter) and absence of suspicious features on US including evidence of lymph node involvement or extrathyroidal extension. Other factors favouring active surveillance in this case include the patient's age and comorbidities. FNAB is therefore not necessary in this instance.

2.2 | Case example 2

A 40-year-old female presents with a small, palpable neck lump. Thyroid US confirms a solid hypoechoic thyroid nodule 9 mm in diameter. The patient is clinically euthyroid and there is no evidence of extrathyroidal extension, lymph node involvement or distant metastasis on physical examination or US. There is no personal or family history of thyroid pathology and no significant past medical history. The nodule has an irregular, microlobulated margin with microcalcifications on US sonography without evidence of increased vascularity or close proximity to the RLN or trachea. Thyroid function tests are within normal ranges.

Approach: This patient has some suspicious features on US (irregular margin and microcalcifications) and her younger age may increase the risk of disease progression. However, there is no clinical or radiological evidence of lymphatic or metastatic spread. Given the low rates of disease progression for thyroid nodules ≤10 mm without evidence of extrathyroidal extension, lymph node involvement or distant metastasis, active surveillance could be offered in this case if it aligned with patient preference. FNAB could therefore be delayed and the patient should have a repeat thyroid US in 6 months.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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