Active Surveillance of Low-Risk Papillary Microcarcinoma of the Thyroid in Indian Scenario: Are we Ready for it? A Narrative Review

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Abstract

Papillary microcarcinoma (PMC) is defined as papillary thyroid carcinoma (PTC) measuring ≤1 cm, irrespective of the presence or absence of the high-risk features. PMCs without any high-risk features referred to as the low-risk PMCs are generally indolent, and most of them remain latent without progression or with very slow progression. Active surveillance (AS) (observation without immediate surgery) could identify the small minority of PMCs that progress and rescue surgery for these PMCs should be effective resulting in no influence on the patients’ prognosis than performing immediate surgery which might result in more harm than good due to associated morbidity. Hence, with proper patient selection, organization, and patient counseling, AS has the potential to be a long-term management strategy for patients with PTC. The recent update of the American Thyroid Association guidelines (2015) incorporated AS as an option within the management protocol of PTC, making it a considerable rather than an experimental treatment option. The cost for immediate surgery is higher than the medical costs of AS for 10 years in most scenarios. Developing countries like India may have certain limitations such as lack of understanding, financial constraints, and lack of adequate radiology services, hence we propose additional recommendations along with standard surveillance strategy.

Keywords: Active surveillance, India, low-risk papillary microcarcinoma of the thyroid, surgery in PMCs, surveillance in PMCs

Introduction

Papillary microcarcinoma (PMC) is defined as papillary thyroid carcinoma (PTC) measuring ≤1 cm, irrespective of the presence or absence of the high-risk features, which are clinical node metastasis, distant metastasis, or significant extrathyroidal extension such as to the trachea and recurrent laryngeal nerve (RLN). PMCs without any high-risk features referred to as the low-risk PMCs are generally indolent, and most of them do not grow or grow very slowly. Latent small thyroid carcinoma has been documented in multiple autopsy studies on subjects who died of nonthyroidal diseases, with up to 0.5%–5.2% of reported latent PMCs measuring 3–10 mm (which correlates to the size detectable by ultrasound [US] examinations). Various studies conducted worldwide concluded that the expeditious increase in the thyroid carcinoma incidence in the past few decades is attributed to the increasing diagnosis (mainly due to improving diagnostic modalities for neck imaging) of the clinically occult and indolent cases, most of which, up to 90%, consisted of small papillary thyroid cancers. However, the incidence of clinically apparent cases and thyroid carcinoma mortality remains stable over time, thus suggesting a majority contribution of subclinical and indolent cases in increasing the incidence and hence a need for a conservative management strategy. Here, we are discussing two cases to share our experience with active surveillance (AS) for PMC at a tertiary cancer care center in India.

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Case 1
A 51-year-old woman was diagnosed with right breast cancer (infiltrating ductal carcinoma, estrogen receptor/progesterone receptor [ER, PR], and c-erbB2 positive) in September 2015 for which she underwent right breast conservative surgery followed by adjuvant chemotherapy and hormonal therapy along with locoregional radiotherapy. During pretreatment workup, positron emission tomography–computed tomography done outside our institution reported multinodular goiter with increased uptake in the left thyroid lobe. While on active treatment, in December 2015, on further evaluation, the patient had clinically occult thyroid nodules in both the lobes on US. A 9.2 mm × 9.4 mm sized solid, hypoechoic, taller than wider nodule with irregular margins showing minimal vascularity and incomplete peripheral calcification was seen in the left lobe – Thyroid Imaging Reporting and Data System (TIRADS) 5 and Thyroid Multimodal-Imaging Comprehensive Risk Stratification Scoring (TMC-RSS score 8) [Figure 1]. Another benign-appearing well-defined, wider than taller, 8 mm × 6 mm sized cyst with isoechoic solid component and no internal echogenic foci were seen in the right thyroid lobe (TIRADS 2 and TMC-RSS score 1). No suspicious neck nodes were seen. US-guided fine-needle aspiration cytology (FNAC) reported the left thyroid nodule as suspicious for PTC (Bethesda category V) and the right thyroid nodule as nodular colloid goiter (Bethesda category II). The multidisciplinary tumor board concluded that breast cancer takes precedence over thyroid carcinoma and thyroid surgery can be contemplated after breast cancer treatment is over. After the breast cancer treatment, the option of AS was discussed with the patient and agreed upon, based on the stability of the nodule demonstrated by the ultrasonography (USG) while on treatment. The patient was counseled, and an AS strategy was implemented. The patient was followed up with 6 monthly neck US, which showed stability of the size and features of the thyroid microcarcinoma. No suspicious neck nodes or new suspicious thyroid nodule was detected. As the coronavirus disease 2019 pandemic hit India in 2020, the follow-up was delayed by 1 year. The last follow-up US, done on August 27, 2021, revealed stability of the left thyroid nodule, measuring 8 mm × 9 mm, and no suspicious cervical adenopathy. The patient has completed 6 years of follow-up and continues to stay on AS.

Case 2
A 58-year-old woman was diagnosed with multicentric carcinoma left breast (infiltrating ductal carcinoma, ER and PR positive, and c-erbB2 negative) in December 2015. The patient was detected to have thyroid swelling while on workup. On examination, a 2 cm × 2 cm sized diffuse swelling, moving with deglutition, was noted in the midline neck. Thyroid function tests were normal with thyroid-stimulating hormone (TSH) of 4.7 mIU/mL. On neck US, multiple benign-appearing nodules were seen in both the lobes of the thyroid and isthmus while an irregular, solid, markedly hypoechoic, taller than wider, suspicious 7.5 mm × 8.3 mm sized nodule was seen in the left lobe. It showed irregular halo and internal microcalcifications and showed no vascularity. Extrathyroidal extension was absent. The nodule was hard on elastography (Asteria ES 4) [Figure 2]. This was labeled as TIRADS 5 and TMC-RSS score 9.

On FNAC, this subcentimeter suspicious nodule was found consistent with PTC (Bethesda category VI) while the other nodules were benign (Bethesda category II). An indeterminate node at left level IV was seen on USG which was reactive on FNAC.

The patient underwent modified radical mastectomy followed by adjuvant chemotherapy and hormonal therapy along with locoregional radiotherapy. Based on the decisions in the multidisciplinary tumor board, while on active treatment for breast cancer, the thyroid microcarcinoma was kept on surveillance with 3 monthly neck US and the patient was put on oral thyroxine to aim at lowering of TSH to 0.5–2 mIU/mL. The US findings were stable until January 2018 when a 20% increase in the size of the nodule (now measuring 10.1 mm × 8.5 mm) and the appearance of two left level IV and three right level VI suspicious nodes were noted [Figure 2]. After about 3 years of AS, in view of progression, the patient underwent total thyroidectomy with bilateral central compartment and left level II–IV clearance in February 2018. The histopathology was reported...
as differentiated PTC, classical type, with reactive regional lymph nodes. The tumor was multifocal and extrathyroidal extension was present.

**DISCUSSION**

**Active surveillance over surgery**

Takebe et al. conducted a screening study for thyroid cancer on women who visited for breast cancer screening, using an US examination and US-guided fine-needle aspiration; it showed an incidence of 3.5% of thyroid carcinoma in otherwise healthy Japanese women aged ≥30 years and that 85% of these thyroid carcinomas measured ≤15 mm. This detected incidence was more than 1000 times the prevalence of clinical thyroid carcinoma in the Japanese women reported at that time.[5] Based on this study, it can be suggested that small thyroid carcinomas are frequently present in healthy adult population which may go unnoticed not manifesting in the lifetime of the individual and are therefore harmless.

Based on the above observations, Ito et al. hypothesized that most low-risk PMCs remain latent without progression or with very slow progression.[1,2] Based on this hypothesis, an observational clinical trial for low-risk PMC was proposed in 1993 and subsequently implemented at Kuma Hospital in Kobe, Japan.[6] Ito et al. continued this practice in Kobe,[1,2,6] as did Sugitani et al. in 1995 at the Cancer Institute Hospital in Tokyo, Japan,[7] making these two hospitals have the largest and longest experience in offering AS to patients with PMC.

In the trial at Kuma Hospital, 1235 patients were put on AS instead of surgery. After 10 years of observation, only 8% and 3.8% of cases showed size enlargement and new nodal metastasis, respectively.[8,9] The study also showed that the PMC of young patients is more likely to progress than those of the old patients. In another study by the same authors, 50 females with 51 pregnancies were on AS, of which only 8% of the patients showed PMC progression and none develop new node metastasis, with rescue surgery post delivery being successful. In Japan, surveillance was more cost-efficient than immediate surgery.[10] There was no recurrence or death after rescue surgery due to disease progression.

The Cancer Institute Hospital (Tokyo, Japan) started a similar observation trial for low-risk PMC in 1995. In the trial at Cancer Institute Hospital, out of 230 patients (300 lesions), 7% and 1% showed size enlargement and new nodal metastasis, respectively.[7] Ito et al. hypothesized that very few PMCs will undergo disease progression and hence AS could be offered to these patients which would identify the PMCs with progression. These patients can then be offered surgery without adversely affecting the prognosis. They believed that offering surgery to all would lead to harm due to associated morbidity.[1]
A Korean group also published a retrospective report about its experience with AS of 192 papillary thyroid microcarcinoma (PTMC) patients. Similar results of relatively low rates of tumor growth were noted with 24 patients, undergoing delayed thyroid surgery. No recurrence was noted following surgery.

In a study conducted at the Memorial Sloan Kettering Cancer Center in New York, a risk-stratified approach to decision-making in probable or proven PMC was proposed by Brito et al., in which PMC was classified into three categories: ideal, appropriate, and inappropriate as candidates for AS based on tumor/neck US, patients, and medical team characteristics.

A review article published by Haser et al. critically analyzed the available data and concluded that with proper patient selection, organization, and patient support, AS has the potential to be a long-term management strategy for select patients in this setting and that the patients’ quality of life, cultural differences, and the patients’ clinical status should be taken into consideration.

Following the data suggesting the effectiveness of AS of low-risk PMC, the recent update of the American Thyroid Association (ATA) guidelines (2015) incorporated AS as an option within the management protocol of these tumors, making it considerable rather than an experimental treatment option, for appropriately selected patients with low-risk thyroid cancers to prevent over treatment for PMCs.

Attempts have been made to identify the markers for aggressive disease in these cases. Markers such as epidermal growth factor receptor expression, COX-2, V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF), telomerase reverse transcriptase (TERT) and their association with aggressive features such as lymph node metastasis, multifocality, and extrathyroidal extension have been studied on the PTMC specimen after surgical excision. However, the role of these markers in disease progression in patients on AS is unclear and still needs to be researched. In the small study, a cohort of 26 patients who underwent surgery after AS for various reasons from Kuma hospital, authors analyzed the presence of BRAF and TERT mutation. These patients were categorized into nonprogressive, increase in size, and with lymph node metastasis. TERT mutation was absent in all the cases, and BRAF mutation was present in 64%, 70%, and 80% of cases, respectively. Another study from the same hospital in patients who underwent surgery after following AS showed that Ki-67 expression of >5% and >10% was present in 50% and 22.2%, respectively, in cases with disease enlargement. This expression was significantly higher than cases with nonenlargement of disease. Although the concept to risk stratify these patients based on molecular markers is attractive, there is a need to identify the markers that can be detected on cytology and validation of these markers before the concept becomes a standardized practice.

**Workup and management**

Patient Selection: Patients with very low-risk tumors, i.e., with the absence of high-risk features as proposed by Ito et al.; the high-risk features are as follows [Figure 3]:

- Tumors located adjacent to the trachea
- Tumors located on the dorsal surface of the thyroid lobe, possibly invading the RLN
- Fine-needle aspiration biopsy findings suggesting high-grade malignancy
- Presence of regional node metastasis or presence of distant metastasis (extremely rare).

In addition, the ATA 2015 guideline update includes the following criteria as candidates for AS apart from the low-risk PMC:

- Patients with multiple comorbid conditions and high surgical risk, OR
- Patients with short life expectancy (significant cardiopulmonary disease, other malignancies, and advanced age), OR
- Patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery.

Based on the 2015 guideline update, Brito et al. proposed a scheme for stratification of low-risk PTMC patients into ideal, appropriate, and inappropriate candidates for AS based on the fulfillment of the criteria summarized in Figure 4.

**Active surveillance strategy**

Patients’ eligibility to the AS must be accurately evaluated using mainly the imaging studies such as US and in selected patients, using a CT scan, to determine the location of the lesion and whether nodal metastases are present. The diagnosis of the lesion is established with the US-guided FNAC. This helps to rule high-grade malignancy in which case upfront surgery should be offered. Establishing the diagnosis is important so that the patient complies with the regular follow-up. This also helps in preventing the patients to consult another hospital and undergo unnecessary surgical treatment by nonexperts after being diagnosed as cancer later. If found eligible for AS, the patient is offered management options, i.e., AS and immediate surgery. Patients are counseled about the pros and cons of both the approaches. If patients agree and meticulous follow-up ensured then they may be kept under AS. Patients are followed up by serial US scans at every 6–12 months to look for the red flag signs advocating for a rescue surgery.

**The red flag signs**

A rescue surgery is recommended when one or more of the following observations are noted anytime during follow-up:

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1. Increase in tumor size and neck lymph node metastases
2. Red flag signs: Pain, tenderness, and swallowing difficulties
3. Change in voice and hoarseness
4. New symptoms such as cough, dyspnea, or weight loss
5. New signs of systemic symptoms such as fatigue, fever, or chills

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1. Mahajan, et al.: Active Surveillance of Low-risk papillary thyroid micro carcinoma in Indian scenario
2. Brito et al.: Scheme for stratification of low-risk PTMC patients into ideal, appropriate, and inappropriate candidates for AS based on the fulfillment of the criteria summarized in Figure 4.
Enlargement in size by ≥3 mm, or
- 20% increase in the dimensions or >50% increase in the volume, or
- Appearance of node metastasis, or
- Discovery of new foci.

It is noted that some of the characteristics, such as PMC with rich blood supply, lack of strong calcification, and younger age, are associated with increased risk of developing the red flag signs, hence these features may be considered in deciding interval of follow-up.\(^{[20]}\) The AS strategy with the red flag signs is summarized in Figure 5.

**Practical limitations in resource-constrained countries like India**

Need for frequent follow-up imaging under AS strategy may not be cordially met in developing countries like India where lack of understanding and financial constraints among a substantial part of the society and lack of radiology services in many parts of the country has been the cause of poor patient compliance. The medical cost of observation significantly differs from that of immediate surgery, varying from country to country, though it is unlikely for surgery to be significantly more cost-effective than observation in any country. In resource-constrained countries like India, advanced imaging modalities may not be easily accessible and may be unaffordable to patients of low socio-economic strata for frequent follow-ups, decreasing patient compliance for AS.

Furthermore, a CT scan may be necessary in addition to an US examination for an accurate evaluation in some cases, for example, to accurately evaluate the relationship

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**Figure 3:** High-risk features in papillary thyroid microcarcinoma: (a) 5-mm nodule in the isthmus of the thyroid with invasion of thyroid capsule (mean thickness of thyroid isthmus is 3–4 mm), (b) Nodule in the posteromedial aspect of the right lobe of the thyroid invading recurrent laryngeal nerve, (c) Nodule in the left lobe of the thyroid with metastatic ipsilateral cervical node and (d) Nodule along the medial aspect of the right lobe of the thyroid invading the trachea

**Figure 4:** Scheme for stratification of low-risk PTMC patients into ideal, appropriate, and inappropriate candidates for active surveillance based on fulfillment of the criteria mentioned, as proposed by Brito et al. PTMC: Papillary thyroid microcarcinoma
between PMC and trachea or the RLN, for tumors located at the dorsal side of the thyroid or for tumors with dense posterior acoustic shadow. An increase in imaging cost with the addition of CT may be a significant discouraging factor for observance of strict surveillance in developing countries.

Although surgery for low-risk PMC is not a difficult undertaking for experienced surgeons, any surgical intervention has its list of plausible complications. Risks of permanent RLN paralysis, permanent hypoparathyroidism, and dependence on L-thyroxine throughout the lifetime are some of the major risks associated with thyroid surgery which can be avoided by adopting an AS strategy in low-risk PTCs. A simple yet detailed explanation of what PMC is, the course of disease and treatment options available should be given to the patient. The rationale of selecting AS over surgery should be explained thoroughly to ensure optimum patient compliance.

**Recommendations**

Considering the abovementioned limitations in developing countries like India, we propose the following additional recommendations for patient selection for AS:

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**Figure 5: Schematic diagram showing the active surveillance strategy with the red flag signs**

Diagnosis of Papillary thyroid microcarcinoma by USG or FNAC i.e., nodule <10mm

- **High risk features:**
  - Tumor located adjacent to the trachea.
  - Tumor located on the dorsal surface of the thyroid lobe, possibly invading the recurrent laryngeal nerve.
  - Fine-needle aspiration biopsy findings suggesting high-grade malignancy.
  - Nodal or distant metastasis.

- **NO**
  - Patient compliant for active surveillance
  - **YES**
    - Every 6 to 12 monthly serial USG
      - Red Flag Signs:
        - Enlargement in size by ≥3 mm, or
        - 20% increase in the dimensions or >50% increase in the volume, or
        - Appearance of node metastasis, or
        - Discovery of new foci of PMCT
      - **YES**
        - Surgical Treatment
      - **NO**
        - Continue Active Surveillance

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With advanced diagnostic modalities, a revised approach to management is possible in developing countries like ours. We propose recommendations that can help improve patient compliance in resource-constrained countries like India. We propose recommendations that can help improve patient compliance in developing countries like ours.

Other treatment options
The available literature supports radiofrequency ablation to be an effective and safe option for low-risk PMC cases that are at high surgical risk or for patients who refuse to undergo surgical intervention.\textsuperscript{[21]}

Conclusions
PTC is the most common histological type of differentiated thyroid cancer. Multiple qualitative and quantitative US RSS systems for thyroid nodules have been proposed over time.\textsuperscript{[22,23]} With advanced diagnostic modalities, a significant proportion of these nodules fall in the definition of papillary microcarcinoma. Available literature supports AS as the optimal first line of management for patients with low-risk PMCs. Surgery for low-risk PMC is not difficult, but with surgery, there remains a possibility of complications including vocal cord paralysis and permanent hypoparathyroidism. The cost for immediate surgery is higher than the medical costs of AS for 10 years in most scenarios. The lack of understanding, financial constraints, and lack of adequate radiology services can lead to poor patient compliance for frequent imaging follow-ups in resource-constrained countries like India. We propose recommendations that can help improve patient compliance in developing countries like ours.

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Conflicts of interest
There are no conflicts of interest.

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