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Individualized Management of Papillary Thyroid Microcarcinoma: Clinicopathological Risk Factors, Multifocality and Active Surveillance

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Abstract **Objectives:** Papillary Thyroid Microcarcinoma (PTMC), defined as papillary thyroid carcinoma ≤1 cm, accounts for an increasing share of thyroid cancer diagnoses worldwide. Although generally indolent, a subset exhibits aggressive clinicopathological features, including multifocality, extrathyroidal extension and lymph node metastasis, which complicate risk stratification and treatment. To summarize the current evidence regarding the prognostic significance of multifocality in PTMC, its underlying pathogenetic mechanisms and the evolving role of Active Surveillance (AS) versus surgical management. **Methods:** This narrative review integrates epidemiological, molecular, guideline and outcome data to outline a risk-adapted approach. Evidence was identified through a non-systematic literature search and no formal systematic-review or quantitative synthesis methodology was applied; findings should therefore be interpreted in this context. Institutional review board approval and informed consent were not required for this review of previously published literature. **Results:** Multifocality occurs in 20-36% of papillary thyroid carcinomas and may arise from independent multicentric tumorigenesis or intrathyroidal clonal spread. Observational evidence has associated multifocality with an increased risk of recurrence in some, though not all, studies, particularly when combined with tumor size ≥6 mm, nodal involvement, or aggressive histologic variants; its independent effect on disease-specific mortality is less certain. Although AS is endorsed for selected low-risk PTMC, eligibility criteria vary internationally, especially for multifocal disease. The extent of surgery remains individualized. **Conclusion:** PTMC management should follow a risk-adapted strategy that integrates tumor focality, pathological features and patient factors to avoid overtreatment and undertreatment.

Key Words Papillary Thyroid Microcarcinoma, Multifocality, Active Surveillance, Risk Stratification, Thyroidectomy, Recurrence, Molecular Pathogenesis

INTRODUCTION

Incidence

Thyroid cancer is the fifth most frequently diagnosed malignancy among women worldwide, accounting for 4.9% of all newly diagnosed female cancers according to GLOBOCAN 2020 data [1]. The sustained increase in incidence over recent decades has been driven primarily by enhanced diagnostic detection of Papillary Thyroid Carcinoma (PTC), most notably its microcarcinoma variant (PTMC).

PTMC, a subtype of PTC with a maximum diameter of ≤1 cm, accounts for a growing share of thyroid cancer diagnoses, representing up to 43% of all thyroid malignancies and nearly half of newly identified PTC cases [2,3]. Notably, rising PTMC rates have been documented even in populations without active screening programs, indicating contributing etiological factors beyond surveillance bias alone [4].

Multifocality is commonly observed in PTC, reported in 20-36% of patients, with bilateral involvement noted in 50-70% of multifocal cases [5]. This high prevalence underscores the multicentric nature of this disease and its potential implications for surgical management.

A large institutional series further demonstrates the growing burden of PTMC. In one study, papillary microcarcinomas accounted for 49.9% of all thyroidectomies performed [6]. Autopsy studies have revealed an even wider prevalence of occult small PTCs, ranging from 1.0% to 35.6%, depending on the pathological examination techniques [7].

Notably, lymph node metastases have been detected in 3.1-18.2% of cases, indicating that even microcarcinomas may possess metastatic potential [7].

The reported prevalence of multicentric diseases varies widely across studies, ranging from 18-87%, which is largely attributable to differences in pathological examination techniques and sectioning protocols [8,9].

Together, these data highlight the increasing incidence of PTMC and the frequent occurrence of multifocal and bilateral disease, reinforcing the need for accurate risk stratification and individualized surgical decision-making.

Against this background, the specific objective of this narrative review is to critically appraise the prognostic significance of multifocality in PTMC, to examine its proposed pathogenetic mechanisms and to synthesize current international evidence on the relative roles of active surveillance and surgery. Unlike previous reviews that have addressed these topics separately, the present review integrates epidemiological, molecular, pathological and guideline-based evidence within a single risk-adapted framework and explicitly contrasts the differing eligibility criteria of major international guidelines for multifocal disease. Its intended contribution is therefore a consolidated, clinically oriented decision framework rather than the introduction of new primary data.

METHODS

This narrative review integrates epidemiological data, molecular studies, international guideline recommendations and outcome analyses to outline a risk-adapted management approach. To improve transparency, the literature search and study-selection process are described below, although this remains a narrative rather than a systematic review. The PubMed/MEDLINE, Embase and Scopus databases were searched for English-language articles published between January 2000 and December 2025, supplemented by hand-searching of the reference lists of key articles and current clinical practice guidelines. Search terms combined the following keywords using Boolean operators: “papillary thyroid microcarcinoma,” “papillary thyroid carcinoma,” “multifocality,” “multicentricity,” “active surveillance,” “thyroidectomy,” “lobectomy,” “recurrence,” “risk stratification,” and “clonality.” Original research articles, registry-based and cohort studies, meta-analyses, systematic reviews and society guidelines addressing the pathogenesis, prognosis, or management of PTMC and multifocal PTC were eligible for inclusion. Case reports, conference abstracts, non-peer-reviewed sources and articles not available in English were excluded. Titles and abstracts were screened for relevance and full texts of potentially relevant articles were reviewed; final inclusion was based on relevance to the review objectives and the quality of the supporting evidence, determined by author consensus rather than by formal critical-appraisal instruments. Because study selection was not systematic, the possibility of selection and publication bias is acknowledged in the Limitations section. Reporting was guided by the Scale for the Assessment of Narrative Review Articles (SANRA) to enhance methodological transparency. Institutional review board approval and informed consent were not required for this review of previously published literature.

RESULTS

Pathogenetic Theories of Multifocal Papillary Thyroid Carcinoma

The pathogenesis of synchronous PTC tumor foci remains controversial. Two mechanisms have been proposed: independent multicentric tumorigenesis and intrathyroidal metastatic spread from a single primary clone.

Shattuck *et al.* [10] applied X-chromosome inactivation analysis via the HUMARA assay to assess clonal relationships among separate tumor foci and demonstrated discordant patterns consistent with independent clonal origins rather than clonal dissemination.

In contrast, McCarthy *et al.* [11] reported a high concordance of allelic loss and X-chromosome inactivation patterns across different tumor foci, suggesting a common clonal origin and supporting intrathyroidal dissemination. In this model, additional foci may represent intrathyroidal micrometastases rather than newly arising tumors.

A comprehensive review of molecular evidence indicates that both mechanisms are likely to coexist. Multifocal PTC may arise either from independent tumorigenic events or from intraglandular spread, depending on the molecular characteristics of the individual cases [12].

More recent studies employing higher-resolution genomic techniques, including next-generation sequencing and genome-wide genetic profiling, have helped to clarify the clonal relationships between separate tumor foci. Mutation-based analyses indicate that the BRAF V600E mutation, the most common molecular alteration in PTC, may be present in some foci but absent in others within the same gland, a discordance that is most consistent with independent clonal origin [3,5]. Conversely, when concordant mutational and allelic-loss profiles are shared across foci, an intraglandular metastatic relationship is favored [5,11]. Taken together, contemporary molecular and sequencing data reinforce the view that multifocal PTC is genetically heterogeneous and that both independent tumorigenesis and intrathyroidal spread can occur, sometimes within the same patient [12]. These observations suggest that broader genomic characterization, where feasible, could help refine surgical decision-making, although such testing is not yet part of routine clinical practice.

These findings underscore the biological heterogeneity of multifocal PTC and have important implications for surgical decision-making and risk stratification.

Prognostic Impact of Multifocality

Multifocality is increasingly recognized as a clinically relevant feature of papillary thyroid carcinoma, with a direct impact on both oncological outcomes and therapeutic planning. Accumulating evidence has demonstrated that the presence of multiple tumor foci is a distinct predictor of recurrence following total thyroidectomy, with its prognostic significance particularly pronounced in tumors >1 cm in diameter [13].

However, the prognostic value of multifocality remains debatable. Geron *et al.* [14] argued that multifocality in PTC does not function as a standalone adverse determinant but rather reflects the overall extensiveness of the disease. In contrast, a meta-analysis by Joseph et al. demonstrated that multifocality was robustly linked to elevated recurrence rates and disease progression, supporting its classification as an independent adverse prognostic variable [15].

When interpreting this evidence, it is important to distinguish between the two principal oncological endpoints. Most studies linking multifocality to worse outcomes use structural or biochemical recurrence as the endpoint, whereas disease-specific mortality in PTMC is uniformly low and has rarely been shown to be independently increased by multifocality alone. The available data therefore associate multifocality more consistently with a modest increase in recurrence risk than with any measurable rise in cancer-related death. This distinction is clinically relevant: concern framed around recurrence risk justifies intensified surveillance or completion surgery, whereas concern framed around mortality would justify more aggressive intervention and the current evidence supports the former rather than the latter for most patients with low-risk multifocal PTMC.

The significance of multifocality extends to microcarcinoma subgroups. In a comparative registry-based study, Malandrino *et al.* [16] reported that concurrent multifocality was commonly found alongside advanced tumor size, nodal spread and capsular or soft tissue invasion, affirming its status as a key variable in comprehensive risk stratification. The authors recommended that postoperative radioiodine therapy be considered for multifocal PTMC cases in which the dominant lesion measures ≥6 mm, particularly in patients aged <45 years or in male patients, regardless of whether lymph node status is available. Notably, >35% of PTMCs in both registries presented with two or more concomitant risk factors, supporting a management approach analogous to that applied to larger carcinomas [16].

Tumor size represents a well-established continuous risk determinant in PTMC; smaller tumors generally confer a better prognosis, yet small size alone does not guarantee low-risk disease. A significant proportion of PTMCs ≤6 mm were found to harbor multiple adverse features, underscoring the inadequacy of size-based risk assessment in isolation [16]. Gür et al. corroborated these findings by identifying tumor size >5 mm and multifocality as significant factors associated with the aggressive behavior of micropapillary tumors [17].

Current guidelines from the American Thyroid Association (ATA) specify that multifocality in tumors <1 cm in size does not independently constitute an indication for radioactive iodine therapy [18]. Nevertheless, the cumulative burden of coexisting risk factors, including multifocality, male sex and tumor size >5 mm, should inform individualized treatment decisions [17,4].

Histological subtype further modulates the prognostic impact of multifocality. A systematic review and network meta-analysis by Zhao *et al.* [19] concluded that aggressive variants, including tall-cell, diffuse sclerosing and columnar cell variants, warrant more intensive treatment strategies, whereas the follicular variant of PTC and PTMC subtypes generally have a more favorable prognosis and are at risk of overtreatment. These findings reinforce the necessity of integrating histopathological subtypes, tumor focality and associated risk factors into a comprehensive individualized risk-stratification framework for PTC management.

DISCUSSION

Management of Papillary Thyroid Microcarcinoma

The optimal management of PTMC continues to generate considerable debate, with current strategies spanning a spectrum from watchful observation to total thyroidectomy guided by individualized risk assessment. The 2015 ATA guidelines recognized Active Surveillance (AS) as an acceptable therapeutic pathway in carefully selected low-risk patients, principally those harboring incidental intrathyroidal microcarcinomas with no sonographic or clinical indicators of nodal involvement, distant disease, or histologically aggressive behavior [18]. The foundation for this approach was established by pioneering Japanese institutions, whose longitudinal cohort data confirmed that the majority of PTMCs under close monitoring exhibited a stable, non-progressive course, with disease progression occurring in only a minority of cases [20,21].

Despite the established safety of AS, its adoption outside Japan remains limited, partly due to reports of clinically significant regional or distant metastases in a subset of PTMC patients [21]. The ATA further stratifies intrathyroidal papillary microcarcinomas (T1a, N0, M0) as low-risk tumors, even in the presence of the BRAFV600E mutation, unless accompanied by additional adverse features, such as extrathyroidal or vascular invasion, aggressive histological variants, or lymph node metastases. Patients with multifocal PTMC combined with extrathyroidal invasion and BRAFV600E positivity are reclassified as intermediate risk, although routine BRAF testing for risk stratification in PTMC without other worrisome features has limited clinical utility [18].

The eligibility criteria for AS vary across international guidelines. The European Society for Medical Oncology (ESMO) restricts AS to unifocal PTMC and recommends initial surgical treatment for multifocal or bilateral lesions. In contrast, the Japanese Association of Endocrine and Thyroid Surgery (JAES) and the Brazilian Society of Endocrinology and Metabolism (SBEM) have included patients with multifocal lesions as potential AS candidates, citing prospective data that demonstrate that multiplicity is not an independent predictor of disease progression [22]. Age is a consistent determinant across guidelines; AS is generally favored in older patients, whereas patients under 18–20 years of age are considered poor candidates. The Korean Thyroid Association (KTA) and SBEM (2022) define the optimal AS population as patients aged ≥60 years, with conditional suitability for those aged 18–59 [22]. The ATA also identifies AS as appropriate for patients at elevated perioperative risk owing to the substantial comorbid burden or limited life expectancy [18] (Table 1).

Table 1: Comparison of Active Surveillance (AS) Criteria in International Guidelines

Parameter	ATA (2015)	ESMO (2019)	KTA (2023)
Tumor size	≤1 cm (T1a)	≤1 cm	≤1 cm
Multifocality	Acceptable if intrathyroidal and low-risk	Surgery preferred in multifocal/bilateral disease	Acceptable if no other high-risk features
Extrathyroidal extension	Contraindication	Contraindication	Contraindication
Lymph node metastasis	Contraindication	Contraindication	Contraindication
Age	Favored in older patients	Not specifically age-stratified	Preferred ≥60 years; conditional 18-59
Molecular markers	BRAF alone not indication for surgery	Not emphasized	Not routinely required

ATA: American Thyroid Association, ESMO: European Society for Medical Oncology, KTA: Korean Thyroid Association

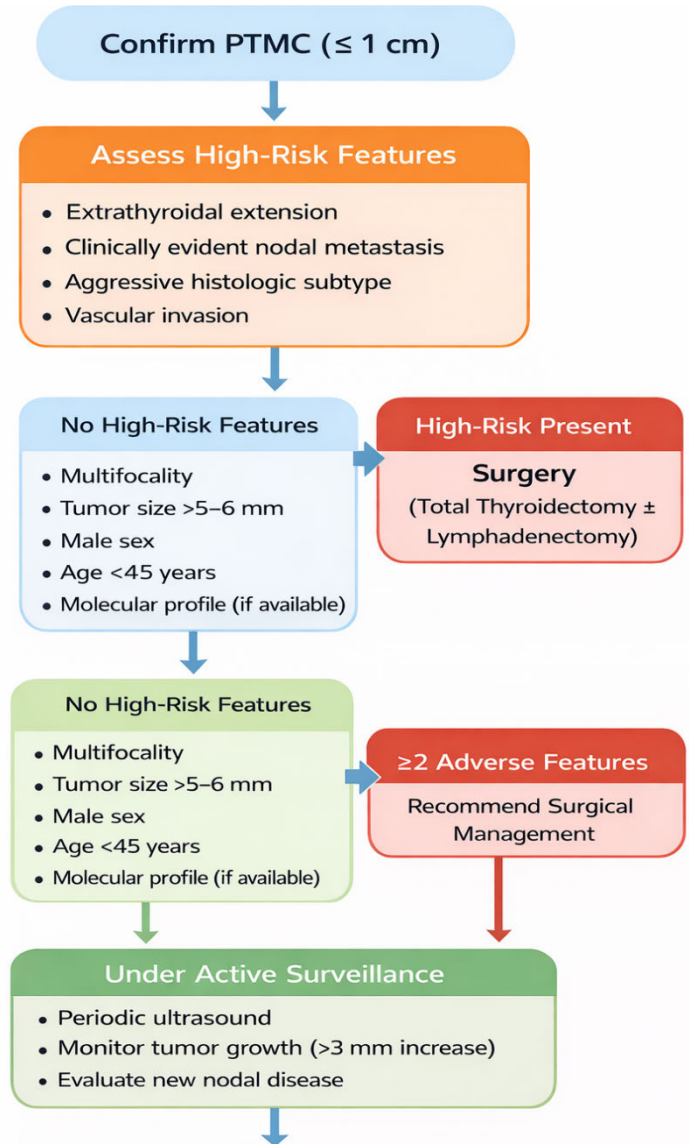

Figure 1: Risk-Adapted Algorithm for PTMC Competing pathogenetic mechanisms of multifocal TTMC (Proposed risk-adapted decision algorithm for confirmed PTMC (≤1 cm). After cytological confirmation, patients are first assessed for high-risk features (extrathyroidal extension, clinically evident nodal metastasis, aggressive histological subtype, or vascular invasion); their presence favors surgery (total thyroidectomy ± lymphadenectomy). In the absence of high-risk features, additional adverse factors (multifocality, tumor size >5-6 mm, male sex, age <45 years, and adverse molecular profile where available) are weighed: the coexistence of two or more adverse features favors surgical management, whereas their absence supports active surveillance with periodic ultrasound, monitoring for tumor growth (commonly defined as a ≥3 mm increase in diameter) and new nodal disease. Indicative strength of evidence for each pathway: the safety of active surveillance in low-risk disease is supported by prospective cohort studies (moderate certainty); the recommendation for surgery in the presence of overt high-risk features is supported by guideline consensus and cohort data (moderate certainty); and the use of combined adverse features to escalate management is based largely on retrospective and registry data (low-to-moderate certainty). This figure is intended as an educational decision aid and does not replace individualized, guideline-based clinical judgement)

Beyond oncological endpoints, the long-term outcomes and patient-reported experience of active surveillance warrant emphasis, as these increasingly influence guideline recommendations and shared decision-making. Long-term cohort data from established surveillance programs indicate that the great majority of low-risk PTMCs remain stable over a decade or more, that the minority showing growth or nodal progression can be salvaged with delayed surgery without compromising disease-specific survival and that immediate surgery and active surveillance yield comparable oncological outcomes in appropriately selected patients. Active surveillance also avoids surgery-related morbidity, including hypoparathyroidism, recurrent laryngeal nerve injury and lifelong levothyroxine dependence. At the same time, quality-of-life and patient-reported outcome studies show a more nuanced picture: some patients experience disease-related anxiety or reduced health-related quality of life while living with an untreated cancer, whereas others report greater satisfaction by avoiding surgery. These considerations underscore that eligibility for active surveillance should incorporate not only tumor and patient characteristics but also the individual's values, anxiety tolerance and ability to adhere to long-term follow-up (Figure 1).

With regard to surgical extent, total thyroidectomy has traditionally been recommended for preoperatively diagnosed multifocal PTMCs, as well as for incidentally detected multifocal disease following initial lobectomy, given the substantial likelihood of bilateral tumor involvement and the unfavorable prognostic implications of multifocal PTC [23]. This recommendation should, however, be applied with caution, as a growing body of evidence supports more conservative, thyroid-preserving management in carefully selected patients and contemporary guidelines increasingly favor lobectomy for low-risk unilateral disease. The optimal surgical extent for unilateral multifocal PTMCs remains unclear; however, lobectomy may be acceptable if followed by rigorous long-term surveillance [23]. Omi *et al.* [24] reported that pathological multifocality does not independently worsen the prognosis of PTC managed with non-total thyroidectomy when microscopic foci are confirmed, suggesting that immediate completion of thyroidectomy is not required in this context.

CONCLUSION

Long-term AS data further support the observation that multifocality does not significantly differ from unifocal disease in terms of the cumulative incidence of size increase, nodal spread, or overall clinical advancement. In multivariate analyses, younger age emerged as the sole independent predictor of AS progression, whereas multifocality did not reach statistical significance [24]. Nevertheless, patients with multifocal PTMC warrant more vigilant monitoring of lymph node involvement, because tumor multifocality may reflect the extent of intrathyroidal lymphatic infiltration [24]. The SEER cohort data indicate that when two or more adverse features are identified at diagnosis, escalation of surgical intervention should be strongly considered to minimize cancer-related mortality [16]. In such cases, total or near-total thyroidectomy with appropriate cervical lymphadenectomy is recommended and postoperative radioiodine ablation may be warranted when multiple adverse factors coexist [16].

Collectively, the available evidence supports a risk-adapted, individualized approach for PTMC management. Tumor size, focality, histological subtype, extrathyroidal extension, lymph node status, patient age and comorbidities should be integrated into treatment decision-making. While AS represents an oncologically sound strategy for carefully selected low-risk patients, the non-negligible proportion of PTMCs harboring multiple adverse features, estimated to be over 35% in registry-based cohorts, underscores the need for vigilant preoperative risk stratification to avoid undertreatment [16,18]. These recommendations should be interpreted with attention to the strength of the underlying evidence. Much of the data informing the prognostic role of multifocality and the thresholds used for risk stratification derive from retrospective cohorts and registry analyses, which provide associations of low-to-moderate certainty rather than high-level causal evidence, whereas the safety of active surveillance is supported by relatively robust prospective cohort data. Accordingly, the framework proposed here should be regarded as a pragmatic synthesis intended to guide shared decision-making rather than as a set of definitive, evidence-graded directives.

Limitations

Several limitations of this review should be acknowledged. First, as a narrative rather than a systematic review, the literature search was not exhaustive and study selection was guided by author judgement; consequently, the review is susceptible to selection bias and to publication bias, since studies reporting positive or statistically significant associations are more likely to be published and cited. Second, no formal critical-appraisal tool or quantitative synthesis was applied and the certainty of evidence supporting individual recommendations was not graded using a standardized system such as GRADE. Third, the included studies are heterogeneous in design, patient populations, pathological sectioning protocols, definitions of multifocality and length of follow-up, which limits the comparability of their findings and the generalizability of pooled estimates such as the reported prevalence ranges. Fourth, the international guidelines compared here differ in methodology, regional practice patterns and the evidence base available at the time of their publication, so their recommendations may not be directly transferable across all health-care settings. Finally, much of the prognostic evidence is derived from retrospective and registry data, which can be affected by residual confounding and incomplete capture of outcomes. These limitations should be borne in mind when applying the conclusions of this review to individual patients and they highlight the need for prospective, adequately powered studies and, where feasible, systematic reviews with formal evidence grading.

Conflicts of Interest

The authors declare no potential conflicts of interest. No financial support was received for this study.

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