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REVIEW

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Clinical outcomes of multifocal papillary thyroid cancer: A systematic review and meta-analysis

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Abstract

Objective: Papillary thyroid cancer (PTC) is the most common endocrine malignancy with a steadily increasing incidence. Researches have reported that tumor multifocality occurs in an extensive number of cases. Nevertheless, the clinical characteristics and prognostic value remained controversial. This study was performed to investigate the relationship between multifocal PTC and adverse clinicopathologic features and the prognosis.

Methods: A systematic review and meta-analysis were conducted based on three electronic databases up to December 31, 2021. Parameters of interest included five clinical features (extrathyroidal extension, lymphovascular invasion, central lymph node metastasis, lateral lymph node metastasis, distant metastasis) and were pooled into risk ratios (RRs). Time-to-event data (recurrence-free survival and all-cause mortality) were evaluated using hazard ratios (HRs). Publication bias was examined using funnel plots and Egger's test.

Results: A total of 23 articles were included according to the inclusion criteria; all of the studies were retrospective cohorts. In comparison with unifocality, multifocality showed an increased risk of extrathyroidal extension (RR 1.38, 95% CI 1.25–1.53), lymphovascular invasion (RR 1.27, 95% CI 1.04–1.55), central lymph node metastasis (RR 1.21, 95% CI 1.12–1.30), lateral lymph node metastasis (RR 1.86, 95% CI 1.62–2.14), and distant metastasis (RR 1.35, 95% CI 1.03–1.76). Multifocal patients were predisposed to postoperative recurrence (HR 1.76, 95% CI 1.50–2.07). The rate of all-cause mortality did not reach a statistical difference.

Level of Evidence: 2.

Conclusion: Multifocal PTC is more aggressive in contrast to unifocal PTC and is accompanied by an increased risk of recurrence. They were usually diagnosed in higher grades and stages. To achieve the maximal benefit, we recommend personalized therapy and close follow-up for multifocal PTC patients. Further prospective studies will clarify the best-fitted treatment plans.

KEYWORDS
clinical performance, multifocality, papillary thyroid cancer, risk factor

1 | INTRODUCTION

Papillary thyroid cancer (PTC) accounts for 80%–90% of thyroid neoplasms and the incidence continues to increase.[1] Although patients with PTC have a much better outcome than individuals with other pathological subtypes of thyroid cancer,[2] personalized regimens for low-to-medium risk patients remain to be determined. In clinical practice, controversies regarding the treatment of low-to-medium risk PTC include but are not limited to: dynamic surveillance, surgery extent, and postoperative radioactive iodine (RAI).[3,4]

The American Thyroid Association (ATA) declared several clinicopathological characteristics as the stratification criterion for recurrence in differentiated thyroid cancer to help with clinical strategies. To date, the 8th American Joint Committee on Cancer/Union for International Cancer Control (AJCC) TNM staging system still considers sex, age, tumor size and lymph node metastasis as independent factors for determining tumor prognosis.[5] Risk for recurrence increases with the presence of tissue invasion, local/distal metastasis as well as microscopic/gross infiltration. Response to initial surgery and RAI therapy are also closely related with clinicopathological features.[6] In present clinical practice, advanced age (over 55 years), minor extrathyroidal extension (mETE) and central/mediastinal (VI&VII compartment: pretracheal/paratracheal/prelaryngeal and mediastinal region) lymph node metastasis are well-established indicators for PTC persistent/recurrence.[7]

Tumor multifocality, whether unilateral or bilateral, is not rare in thyroid cancer. However, the clinical evolution and the prognostic significance of multifocal PTCs are debated.[8] The presence of multifocality is regarded as an unfavorable event that implies tumor deterioration. Related studies have reported the existence of tumor multifocality in small cell lung cancer (SCLC), medulloblastoma and prostate cancer, the curative effect and prognosis of them were inferior to those with unifocal disease.[9–12] Moreover, it is estimated that approximately 18%–87% of PTC patients were present with tumor multifocality.[13,14] McCarthy[15] stated that the separate tumor foci usually originated from the same clone. However, an alternative view has suggested that multifocal PTCs developed from discrete clones with irrelevant genetic backgrounds.[16,17] In addition, scattered tumor lesions usually exist as microcarcinomas of less than 1 cm. The mean tumor size of multifocal PTCs is smaller than that of a solitary tumor,[18] and thus the risk of multifocal PTCs might be misinterpreted.

Several studies have shown that central lymph node metastasis (CLNM) was correlated with tumor multifocality in comparison with unifocality.[18–20] A retrospective analysis[21] of 150 pediatric thyroid cancer patients revealed a higher recurrence rate than adult patients with multifocal tumors. However, inconsistencies[14,22] in the reported clinical outcomes of multifocal PTCs led to confusion and dilemmas, which tended to depend on one's empirical understanding. In addition, the lack of existing consensus about the prognostic value for multifocal PTCs has impeded decision-making. Currently, only two institutions[23] emphasize multifocality as a risk of disease-specific mortality. It is crucial to understand other indicators of disease screening.

In this study, we conducted a comprehensive systematic review and meta-analysis to identify the association between multifocality and adverse clinicopathologic outcomes in PTCs.

2 | METHODS

This report was implemented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement).[24,25] MEDLINE, Embase and Web of Science databases were retrieved up to December 31, 2021. The search was restricted to original studies concerning multifocality for PTC patients. Search terms are shown in Table 1. The study was performed with the following PICOS strategy

a. Population: patients presenting with PTC for the first time.
b. Intervention: pathologically proved multifocal lesions.
c. Comparison: a single unilateral tumor.
d. Outcome: adverse clinicopathological performance, postoperative recurrence, and all-cause mortality.
e. Study design: retrospective cohorts.

2.1 | Literature selection and quality assessment

Inclusion criteria were as follows: (a) patients undergone thyroid surgery for the first time, (b) the pathologic findings were confirmed as multifocal/unifocal PTC, and (c) studies reported both multifocality and unifocality. Level of confidence was determined according to the Oxford Centre for Evidence-Based Medicine, Levels of Evidence (OCEBM Levels of Evidence 2009).[26]

TABLE 1 Search strategy.

MEDLINE	thyroid cancer, papillary [Mesh] AND ("multifocal"[Title/Abstract] OR "multifocality"[Title/Abstract])
Web of Science	TI = (papillary thyroid cancer) OR TI = (papillary thyroid carcinoma) OR TI = (papillary thyroid neoplasm)) AND (TS = multifocal OR TS = multifocality
Embase	multifocality: ab, ti OR multifocal: ab, ti) AND ("papillary thyroid cancer": ti OR "papillary thyroid carcinoma": ti OR "papillary thyroid neoplasm": ti

Exclusion criteria were as follows: (a) non-English articles; (b) insufficient data; (c) overlapping reports in multiple publications; (d) case report, editorials, letters or meeting abstracts; (e) patients with non-neoplastic thyroid disease were included; and (f) restricted pathological subtypes or genetic background.

The Newcastle–Ottawa Scale (NOS) was used by two investigators (LK Cui and CF Zhu) according to the Cochrane collaboration.[27] Stars were awarded based on patient selection (four items), comparability (one item) and the evaluation of outcomes (three items). In cases of disagreement, another investigator (QY Li) provided assessment.

2.2 | Data extraction and statistical analysis

Two investigators (LK Cui and DD Feng) independently extracted the original data as referred to the predetermined criteria. Extracted data include study design, patient demographics, clinicopathological features and follow-up data. Disagreement was addressed through a review of the full-text article and input from a third investigator (CF Zhu). Any disagreement was discussed in our group. Meta-analysis was conducted using Stata 14.0 (Stata Corporation, College Station, TX), RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) and Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ). Relative risk (RR), hazard ratio (HR) and the corresponding 95% confidence interval (CI) were calculated. To avoid confounding factors, only multivariant adjusted time-to-effect data were collected.

We quantified the heterogeneity across studies with the I^2 statistic.[28] An $I^2 \geq 50\%$ indicates that there was medium to high heterogeneity among eligible studies. A random-effects model was used for heterogeneous trials. Sources of the inconsistency among studies were identified by: (a) subgroup analysis based on countries and (b) sensitivity analysis by eliminating each of the included studies. Publication bias was presented with funnel plot and Egger's test in each analysis which included over nine articles. Egger's linear regression method was used to detect asymmetry, and a p value less than .05 was considered the existence of publication bias. The trim and fill method[29,30] was further applied to confirm the stability of our estimates.

3 | RESULTS

3.1 | Study selection and quality assessment

We identified 1194 records after the initial retrieval. After evaluating the remaining articles according to the selection criteria, 23 studies published from 2006 to 2021 were identified for subsequent analysis (Figure 1).

All of the 23 studies were hospital-based studies. Two articles[18,31] only reported papillary thyroid microcarcinomas (in which the maximal diameters were less than 1 cm) and the rest reported PTC patients.[14,22,32–49] The eligible studies were retrospective cohorts. Cao et al.[50] conducted a case–control study, so we did not include this article for further evaluation. Baseline

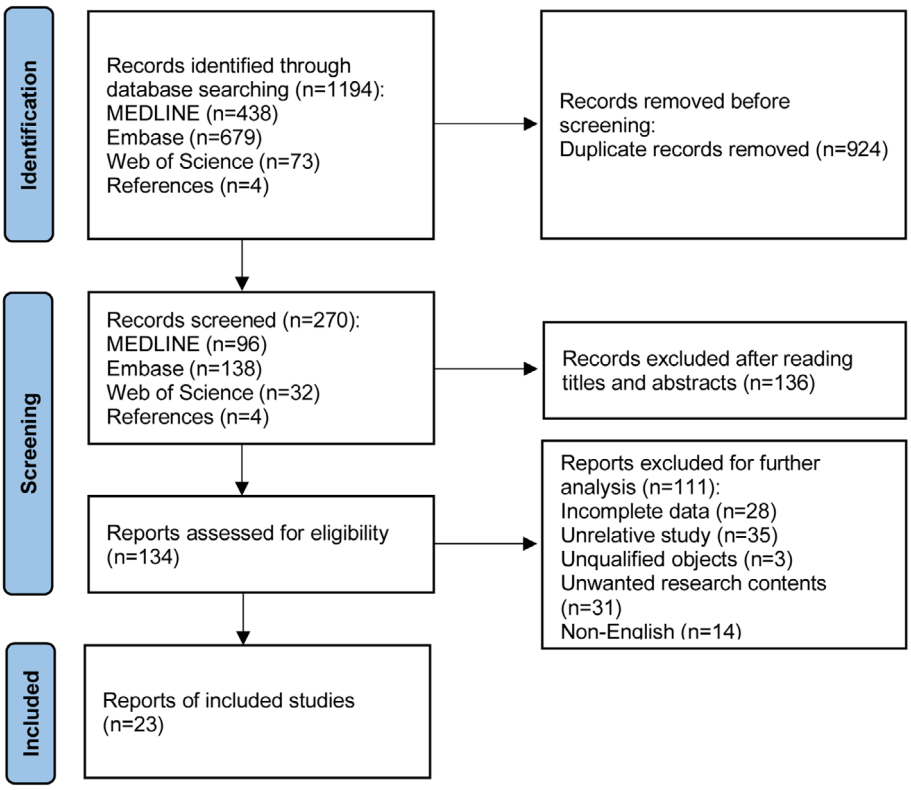


FIGURE 1 Overview of studies search and selection.

TABLE 2 Baseline characteristics of included studies.

Author	Year	Country	Study design	Cases	Pathology[a]	Age (average ± SD)	Gender (M/F)	Follow up (year, average ± SD)	Multifocality (M/U[b])	Size (mm)
Kim JM[38]	2006	Korea	Retrospective cohort	662	PTC	44.8	77/585	5.7 (0.25–9)	266/396	–
Grogan[34]	2013	America	Retrospective cohort	269	PTC	35.9 ± 15.5	89/180	7.6 ± 8.1 (11–27)	121/148	–
Kim KJ[30]	2015	Korea	Retrospective cohort	1661	PTMC	45.5 ± 11.5 (13–83)	392/1917	5.6 ± 0.9 (0.1–7.3)	549/1112	–
Kim HJ[50]	2015	Korea	Retrospective cohort	2095	PTC	46 ± 13	275/1820	7 (0.1–7.3)	672/1423	16 ± 12
Qu[42]	2016	China	Retrospective cohort	496	PTC	43.8 ± 17.3 (7–85)	160/336	10.4 ± 5.7 (0.8–28.6)	209/287	–
Tam[45]	2016	Turkey	Retrospective cohort	912	PTC	49.2 ± 12.5	193/723	3.1 (0.5–8.3)	308/604	–
Wang W[46]	2016	China	Retrospective cohort	2211	PTC	44.3 ± 11.8/44.4 ± 12.3[d]	507/1704	6 (0.5–15)	636/1575	–
Kim SK[39]	2016	Korea	Retrospective cohort	5656	PTC	48.0 ± 10.4	1002/4654	5.1 (0.5–17.8)	1529/4427	6 ± 2
Wang F[21]	2017	Multinational[c]	Retrospective cohort	2624	PTC	46 (35–58)	385/2239	4.8 (2.2–8.9)	1000/1624	15 (10–25)
Hwangbo[35]	2017	Korea	Retrospective cohort	3282	PTC	47 ± 11	2897/385	5.8 (1.0–10.2)	1285/1985	1.1 (0.1–2.0)
Kim Y[40]	2017	Korea	Retrospective cohort	1928	PTC	53 (15–86)	355/1573	7.8 (2–11.1)	623/1305	–
Khan[37]	2018	Pakistan	Retrospective cohort	209	PTC	35.6 ± 13.8 (12–74)	63/146	4.1 (1–16.3)	87/122	–
Xu[47]	2018	China	Retrospective cohort	3607	PTC	47.5 ± 2	868/2739	5.7 (2.1–11.5)	675/2932	6 ± 30
Gui[17]	2018	China	Retrospective cohort	541	PTMC	47.2 ± 12.3	128/413	3.5 (2–5)	146/395	5.8 ± 2.4
Li[33]	2018	China	Retrospective cohort	570	PTC	45.3 ± 10.5/43.3 ± 11.5[d]	160/410	1.6 (1–2.2)	285/285	–
Ryu[44]	2018	Korea	Retrospective cohort	390	PTC	46 (17–80)	118/272	6.75 (0.5–13)	142/248	1.61 ± 0.97
Nam[41]	2018	Korea	Retrospective cohort	2384	PTC	52 (12–86)	495/1889	7.8 (2–10.9)	142/248	–
Geron[13]	2019	Israel	Retrospective cohort	1039	PTC	48.4 ± 15.3	222/817	10.1 (4.7–16.3)	534/505	15 (10–25)
Feng[33]	2019	China	Retrospective cohort	442	PTC	45.4 ± 12.3	109/333	3.6 (0.9–8.25)	119/323	12.3 ± 9.3
Choi[31]	2019	Korea	Retrospective cohort	2390	PTC	52 (12–88)	516/1874	7.7 (2–11.9)	892/1498	1.3 (0.8–1.8)
Shin[51]	2020	Korea	Retrospective cohort	2902	PTC	51 (43–58)	619/2283	7.4 (5.3–10.3)	1580/1322	11 (7–14)
Jiang[36]	2020	China	Retrospective cohort	4107	PTC	45.21 (12–82)	909/3198	3.75 (2–11.9)	1058/3826	9.2 (1–80)
Woo[48]	2021	Korea	Retrospective cohort	1249	PTC	47.4 ± 11.4	154/1095	5.5 ± 2.7	487/762	10 ± 7

[a]PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma.
[b]M/U, multifocal/unifocal.
[c]America, China, Italy, Poland, Australia, Spain.
[d]The data were presented separately.

TABLE 3 Quality assessment.

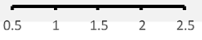
Studies	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort[a]	Selection of the non-exposed cohort[b]	Ascertainment of exposure	Outcome of interest was not present at start of study[c]	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up duration	Adequacy of follow up of cohorts	
Kim JM[39]	–	–	★	★	★	–	★	★	5
Grogan[35]	–	–	★	★	–	★	★	★	5
Kim KJ[31]	–	–	★	★	★★	★	★	–	6
Kim HJ[51]	–	–	★	★	★	–	–	★	4
Qu[43]	–	–	★	★	★	★	★	★	6
Tam[46]	–	–	★	★	★	★	–	★	5
Wang W[47]	–	–	★	★	★	–	–	★	4
Kim SK[40]	–	–	★	★	★	★	★	–	5
Wang F[22]	–	–	★	★	★★	★	★	–	6
Hwangbo[36]	–	–	★	★	–	★	★	★	5
Kim Y[41]	–	–	★	★	–	★	★	★	5
Khan[38]	–	–	★	★	★	–	★	–	4
Xu[48]	–	–	★	★	★	★	–	★	5
Gui[18]	–	–	★	★	–	★	★	★	5
Li[34]	–	–	★	★	★★	★	–	★	6
Ryu[45]	–	–	★	★	★	★	★	★	6
Nam[42]	–	–	★	★	★	–	★	★	5
Geron[14]	–	–	★	★	★★	★	★	★	7
Feng[33]	–	–	★	★	★★	★	–	★	6
Choi[32]	–	–	★	★	★★	★	★	★	7
Shin[32]	–	–	★	★	★	★	★	★	6
Jiang[37]	–	–	★	★	★	★	★	★	6
Woo[49]	–	–	★	★	★★	–	★	★	6

[a]Patients were collected from certain medical institutions (subjects from Kim KJ and Gui were only consisted of PTMC).
[b]Multifocal and unifocal cases were extracted from a single medical center (except for Wang F, Hwangbo and Geron et al.).
[c]Outcome events include recurrence and death.

FIGURE 2 Summary of the results.

Clinical Features	Number of Studies	Risk Ratio (95% CI)	I^2 (%)
Extrathyroidla extension	13	1.38 (1.25-1.53)	88
Lymphovascular invasion	5	1.27 (1.04-1.55)	0
Central lymph node metastasis	10	1.21 (1.12-1.30)	77
Lateral lymph node metastasis	4	1.86 (1.62-2.14)	21
Distant metastass	5	1.35 (1.03-1.76)	10

Clinical Events	Number of Studies	Hazard Ratio (95% CI)	I^2 (%)
Recurrence-free survival	6	1.76 (1.50-2.07)	0
All-cause mortality	2	1.13 (0.81-1.56)	0



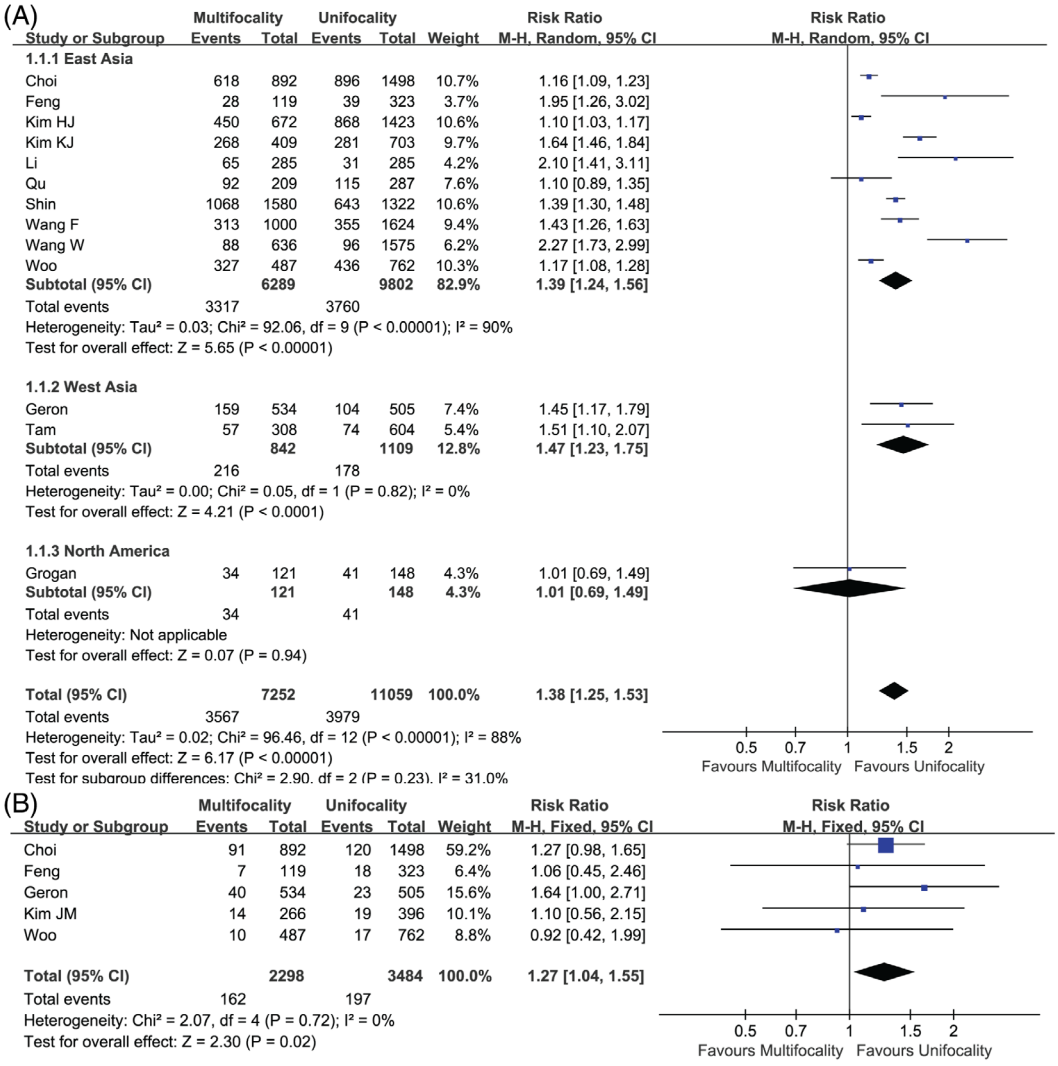


FIGURE 3 Forest plot of the studies. (A) Extrathyroidal extension and (B) lymphovascular invasion.

characteristics and NOS evaluation are shown in Tables 2 and 3. According to the included studies, all the subjects were from local medical centers, which may lead to great selection bias, and therefore we did not employ the first two scoring items ("representativeness of the exposed cohort," "selection of the non-exposed cohort"). Consequently, studies could be awarded a maximum of seven stars. A study with equal to or greater than five stars was considered as a high-quality study. Three

studies[38,47,51] were classified as "moderate quality" (four stars), and the rest ranged from five to seven stars.

3.2 | The association between multifocality and clinicopathological features

3.2.1 | ETE

Thirteen articles[14,22,31–33,35,43,46,47,49,51–53] reported the results for ETE. The meta-analysis suggested that multifocality is a risk factor of ETE (RR 1.38, 95% CI 1.25–1.53, $p < .001$) (Figures 2 and 3A). The statistical heterogeneity was significant ($I^2 = 88.2\%$, $p < .001$). Similarly, we further deduced a high heterogeneity in studies in China and Korea by subgroup analysis ($I^2 = 59.6\%$, $p = .12$). Still, sensitivity analysis did not reverse the aforementioned result (the pooled RRs ranged from 1.01 to 2.27, $p < .001$) (Figure S1).

3.2.2 | Lymphovascular invasion

Six studies[14,32,33,39,46,49] covered lymphovascular events, and the I^2 was 65.5%. The analysis indicated that the data from Tam et al.[46] was the source of the inconsistency; after excluding this study, the heterogeneity dropped to 0%. Finally, the pooled analysis implied that multifocality was a risk factor for lymphovascular invasion (RR 1.27, 95% CI 1.04–1.55, $p = .02$) (Figures 2 and 3B).

3.2.3 | CLNM

Ten articles[31–33,37,40,43,48,49,51,52] reported CLNM, and the pooled result suggested a strong relationship between multifocality and CLNM (RR 1.21, 95% CI 1.12–1.30, $p < .001$) (Figures 2 and 4A). The I^2 was 75% with a significant difference, especially among East Asia countries. The sensitivity analysis also

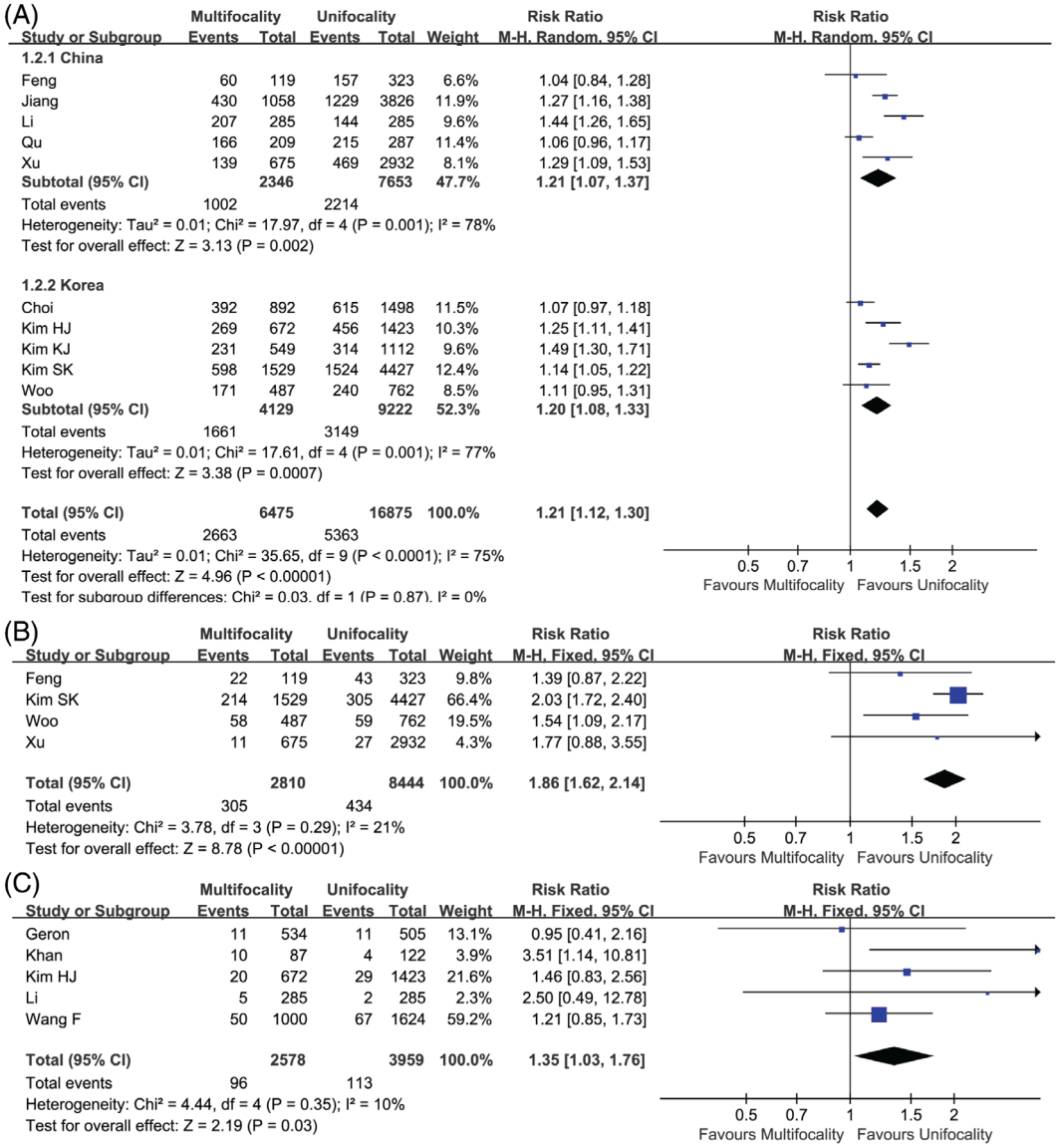


FIGURE 4 Forest plot of the studies. (A) Central lymph node metastasis, (B) lateral lymph node metastasis, and (C) distant metastasis.

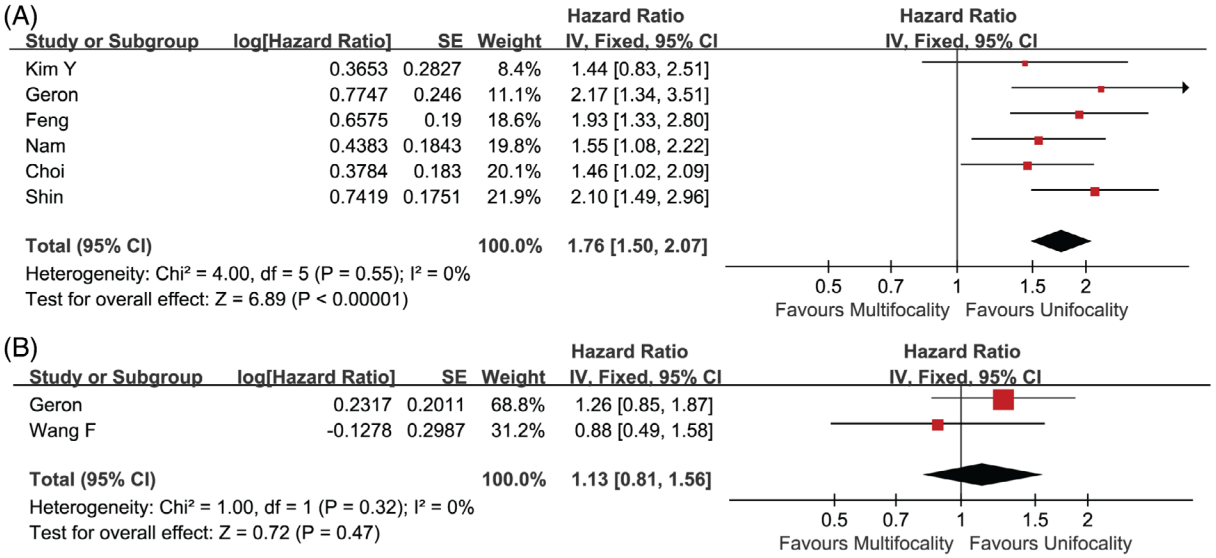


FIGURE 5 Forest plot of the studies. (A) Recurrence-free survival and (B) all-cause mortality.

verified its robustness (the RR ranged from 1.06 to 1.49, $p < .001$) (Figure S2).

3.2.4 | LLNM

We used a fixed effect model to evaluate the risk of multifocality for lateral lymph node metastasis (LLNM) among four studies.[33,40,48,49] The analysis showed that there was a significant association between tumor multifocality and LLNM (RR 1.86, 95% CI 1.62–2.14, $p < .001$) (Figures 2 and 4B).

3.2.5 | Distant metastasis

Five studies[14,22,34,38,51] indicated that multifocality was related to distant metastasis, and the propensity of metastasis was higher in multifocal PTCs (RR 1.35, 95% CI 1.03–1.76, $p = .03$) (Figures 2 and 4C).

3.2.6 | Recurrence-free survival

Six studies[14,32,33,41,42,53] provided multivariate adjusted data concerning the recurrence rate. Multifocal PTCs were easier to get involved in disease recurrence (HR 1.76, 95% CI 1.50–2.07, $p < .001$) (Figures 2 and 5A).

3.2.7 | All-cause mortality

We failed to detect any predisposition in mortality for multifocal PTCs ($p = .47$) (Figures 2 and 5B).[14,22] More follow-up data are required to investigate this association.

3.2.8 | Publication bias

Funnel plots and Egger's tests did not detect a significant publication bias when confronted with ETE and CLNM (p values were .09 and .45, respectively; Figures S3 and S4). After using the trim and fill method, the results were still robust.

4 | DISCUSSION

The natural evolution and specific clinical significance of multifocal PTCs remain inconsistent. This report was to summarize the clinicopathological performance of multifocal PTCs. To our knowledge, the results from 23 studies involving 41,616 patients revealed higher cumulative risks for multifocal PTCs, in developing into disease progression (Figure 2). Accordingly, multifocal PTCs are recommended to accept an intensive surveillance in case further intervention is required.

In a study by Choi[32] et al., multifocality is an independent risk factor for PTC recurrence. These patients usually present with advanced TNM staging. In contrast, Greca et al.[54] argued that disease persistence was rare after total thyroidectomy in patients with multifocal PTCs. According to the ATA,[3] before prophylactic cervical dissection, the risk factors for metastasis and recurrence (such as advanced/young age, lager tumor size, multiple sites, ETE, and LLNM) should be carefully considered. Notably, multifocal PTC has been classified in the moderate-to-high risk group. Moreover, except for multifocal PTCs larger than 1 cm, the latest ATA guideline[3] did not recommend aggressive approaches for multifocal papillary thyroid microcarcinomas, for instance, postoperative radioiodine ablation. In our research, multifocal patients accounted for 36% of the PTC population, which is consistent with the findings of Natalia et al.[55] Additionally, surgical approaches are heterogenous in different clinical centers for low-risk patients. It was

not until 2015 that the ATA guidelines[3] negated prophylactic lymph node dissection as a routine choice. And the rate of local recurrence varies across studies because of this discrepancy. We did not include any cross-sectional studies other than retrospective cohort studies to pursue intact time-effect data with a higher level of evidence.

We observed an issue with heterogeneity between research in China and Korea. Differences in the diagnostic criteria might be an explanation of this inconsistency. The proportion of thyroid microcarcinoma has gradually increased, which can be another source of the heterogeneity. Shin,[53] Choi,[32] and Li[34] excluded patients with radiation exposure, and Shin[53] and Choi[32] did not pool the results for T4 staging or poorly differentiated PTCs. Kim JM[39] and Jiang[37] each selected their surgical planning. The operations were performed by Kim JM et al. prior to 2009, after that the ATA published guidelines for differentiated thyroid cancer.[39] Jiang[37] et al. performed operations according to Guidelines for the Chinese Thyroid Association.[56,57] ATA and NCCN guidelines emphasized preoperative fine needle aspiration (FNA) while Chinese clinicians focus on the distinguishing of undetermined nodules, which rely on intraoperative frozen section examinations. Furthermore, most Chinese surgeons hold a more positive attitude toward prophylactic central lymph node dissection. Additionally, the 2016 Korea Thyroid Association (2016 KTA/KSThR)[58] advocated a tendentious recommendation for FNA for low risk nodules. From 2009 to 2013, inconsistencies have existed among the clinical centers in the Asian-Pacific region.[59] With the implementation of the 2015 ATA guidelines, surgical strategies for low-to-moderate PTCs will become standardized.

Joseph,[60] Kim[61] and Zhang[62] et al. performed meta-analyses in 2018 and 2021, which reported that multifocality is positively correlated with lymph node metastasis (both in central and lateral compartments), advanced TNM stage and recurrence. Here, we conducted a more comprehensive analysis concerning unfavorable clinicopathologic features and time-to-event outcomes result from multifocal PTC, of which should be classified as a higher risk category. Similarly, the presence of multifocality strongly indicates an increased risk of recurrence. As with the results, we intended to address the value of close surveillance to assist personalized therapy, especially for suspicious nodules and regional lymph nodes of multifocal PTCs. Nevertheless, the extent of surgery and the postoperative follow-up strategy require further investigation.

5 | LIMITATION

Nevertheless, 23 studies in our research were performed retrospectively, which may exhibit selection bias and withdraw bias to some extent. Cases with recurrence or deterioration were more easily recorded. Given the restriction of clinical screening methods, postoperative occult lymph nodes may not be detected. On the other hand, the time-to-event data were constrained by different length of follow-up. The representativity of patients was limited, for instance, geographical distribution and radiation exposure. Undoubtedly, many high-risk features were associated with tumor invasion and local/distant metastasis for PTC, including but not restricted to multifocality alone. Therefore, the results should be treated with caution.

6 | CONCLUSION

In summary, this study found that multifocal PTCs are predisposed to disease metastasis and recurrence. ETE and lymphovascular invasion are more likely to be concomitant with these patients. When possible, active surveillance should be considered. We look forward to subsequent prospective studies to guide personalized treatment and postoperative follow-up.

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CONFLICT OF INTEREST

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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SUPPORTING INFORMATION

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