Int J Clin Exp Med 2016;9(9):17165-17174
www.ijcem.com /ISSN:1940-5901/IJCEM0032732

Original Article

Risk factors for central lymph node metastasis in patients with papillary thyroid microcarcinoma: a meta-analysis

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Received May 24, 2016; Accepted August 3, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Objectives: To perform a meta-analysis to demonstrate the predictive factors for central lymph node metastasis (CLNM) in papillary thyroid microcarcinoma (PTMC) patients. Methods: Published articles about PTMC were searched in PubMed, EMBASE, and MEDLINE until March 2016 to detect the risk factors of CLNM. RevMan 5.0 software was used for the meta-analysis. Results: Fourteen articles met the inclusion criteria and were included in our meta-analysis. CLNM occurred more frequently in PTMC patients aged ≥45 years (OR=1.33, 95% CI: 1.06-1.67, P=0.01), with extrathyroidal invasion (OR=2.20, 95% CI: 1.67-2.90, P<0.00001), and with vascular invasion (OR=15.85, 95% CI: 0.85-295.85, P<0.00001). CLNM was less prevalent in patients with unifocal tumors compared to in the multifocal group (OR=0.55, 95% CI: 0.46-0.65, P<0.00001). However, there was no difference in the CLNM status according to sex, tumor size ≤0.5 cm, unilaterality, or the presence of combined Hashimoto's disease. Conclusions: PTMC patients should be considered at high risk for CLNM when aged ≥45 years and when presenting with extrathyroidal invasion, vascular invasion, and multifocal tumors. These findings may assist in the decision-making regarding further treatment in PTMC patients.

Keywords: Papillary thyroid microcarcinoma, central lymph node metastasis, meta-analysis, risk factors, extrathyroidal invasion, vascular invasion, multifocal tumors

Introduction

Thyroid cancer is the most common malignant tumor of the endocrine system, and its global incidence has rapidly increased in recent decades [1]. The most frequent type of thyroid malignancy is papillary thyroid cancer, which is derived from the follicular epithelium [2]. Of these tumors, papillary thyroid microcarcinoma (PTMC) represents a large proportion [3, 4].

For PTMC, lymph node metastasis, especially central lymph node metastasis (CLNM), is considered to be the most important risk factor associated with recurrence. However, the efficacy of prophylactic central lymph node dissection (PCLND) for PTMC remains unclear. Hence, it is necessary for surgeons to evaluate the clinicopathological characteristics associated with a high risk of CLNM before surgery of PTMC patients.

Recently, some studies have demonstrated the risk factors for CLNM in PTMC. However, the conclusions remain controversial and require more investigation due to the different ethnicities of the study patients and geographical regions of the studies [3, 5]. Therefore, we performed a systematic review and meta-analysis to elucidate the associations of CLNM with clinicopathological characteristics in PTMC patients.

Material and methods

We performed an extensive search for studies that examined the association of CLNM with clinicopathological factors in PTMC. The investigations that were included in our study are described below. The patients' age and sex, and the presence of extrathyroidal invasion, larger tumor size, unifocality, and vascular invasion were chosen as the outcome measures.

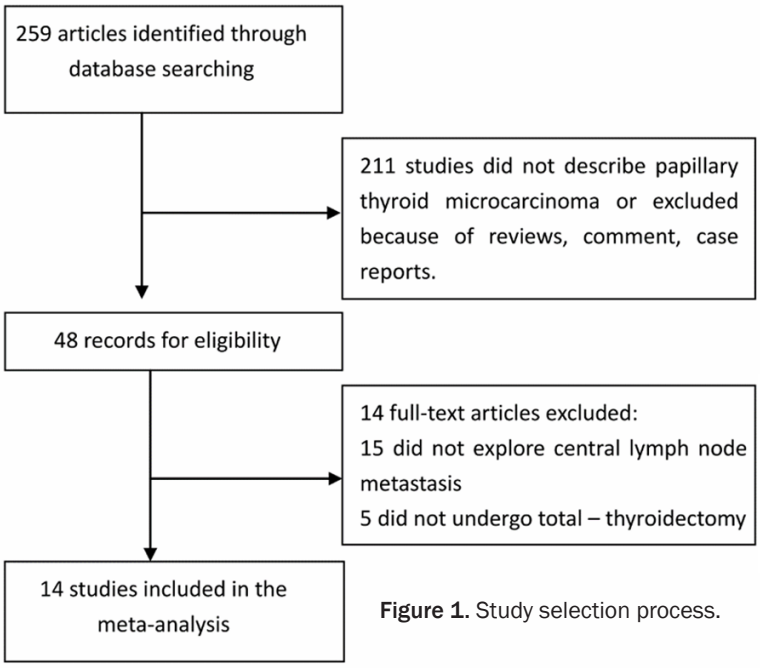

Figure 1. Study selection process.

Relevant unpublished data that were presented at international meetings such as the American Thyroid Association meeting were also included. We contacted the authors for additional tabular data when necessary [6]. Abstracts, single case reports, and reviews were excluded. Studies lacking clinicopathologic data were also excluded. Duplication of data was carefully avoided by examining the names of all authors and medical centers that were involved in each publication.

A literature search was performed using the PubMed, MEDLINE, and EMBASE databases until December 2015 and aided by manual searching and reference backtracking using the following Medical Subject Headings and keywords: "papillary thyroid microcarcinoma, subcentimeter cancer, occult thyroid cancer", "central or level VI lymph node dissection or metastasis", or "risk factors".

Individual study-specific odds ratios (ORs) and confidence intervals (CIs) were calculated, as were the Mantel-Haenszel pooled ORs for the combined studies. All procedures conformed to the guidelines for meta-analyses of observational studies in epidemiology.

Statistical analysis

We used RevMan (version 5) to calculate the summary ORs with 95% CIs, using a random-effects model when the *P* value (chi-square test of homogeneity) was <0.1, and a fixed-effects model when the *P* value (chi-square test of homogeneity) was ≥0.1. We assessed the heterogeneity of the studies using the chi-square test of heterogeneity and the I^2 measure of inconsistency. Significant heterogeneity was defined as a chi-square test *P* value of <0.10 or as an I^2 measure >50%. The extent to which the combined meta-risk or heterogeneity was affected by individual studies was assessed further by sequentially excluding each study from the meta-analysis. We investigated potential sources of the identified heterogeneity among the studies using a stratification process according to the country in which the research was conducted. The potential for publication bias was assessed using a funnel plot analysis.

Results

Results of the search and study characteristics

Figure 1 shows the study selection process. A total of 259 abstracts and titles were obtained through electronic searches. Of these abstracts and papers, 48 full-text papers were deemed to be relevant and were examined in detail. Following this detailed review, 14 studies met our inclusion/exclusion criteria [3, 5, 7-18], and these studies contributed 3692 patients with PTMC to the meta-analysis.

The main features of the 14 eligible studies are summarized in **Table 1**. All cases underwent total thyroidectomy plus PCLND. Among these studies, seven studies from Keron, one study from France, five studies from China and one study from Japan. The funnel plots for each outcome did not suggest the presence of publication bias (data not shown).

Meta-analysis of the effects of various clinicopathological risk factors on CLNM in PTMC patients

Age and CLNM: Ten studies presented clinical data, including age and central lymph node metastasis. A random-effects model was ado-

Table 1. Summary of the 14 included studies that compared the incidence of central lymph node metastasis according to clinicopathological factors of PTMC

No	Authors	Year	Country	Research design	Case number	Surgical approach
1	Lim 2009	2009	Korea	Retrospective clinical study	86	TT or NTT+PCLND
2	S vergez 2010	2010	France	Retrospective clinical study	82	TT or NTT+PCLND
3	Zhao 2012	2012	China	Retrospective clinical study	212	TT or NTT+PCLND
4	Kim 2013	2013	Korea	Retrospective clinical study	483	TT or NTT+PCLND
5	So 2010	2010	Korea	Retrospective clinical study	551	TT or NTT+PCLND
6	Wada 2003	2003	Japan	Retrospective clinical study	259	TT or NTT+PCLND
7	Lee 2008	2008	Korea	Retrospective clinical study	52	TT or NTT+PCLND
8	Shao 2009	2009	China	Retrospective clinical study	117	TT or NTT+PCLND
9	Wang 2008	2008	China	Retrospective clinical study	86	TT or NTT+PCLND
10	Kim 2012	2012	Korea	Retrospective clinical study	160	TT or NTT+PCLND
11	Chang 2015	2015	Korea	Retrospective clinical study	613	TT or NTT+PCLND
12	Park 2015	2015	Korea	Retrospective clinical study	193	TT or NTT+PCLND
13	Xu 2014	2014	China	Retrospective clinical study	507	TT or NTT+PCLND
14	Yang 2014	2014	China	Retrospective clinical study	291	TT or NTT+PCLND

PTMC: papillary thyroid microcarcinoma; TT: total thyroidectomy; PCLND: prophylactic central lymph node dissection.

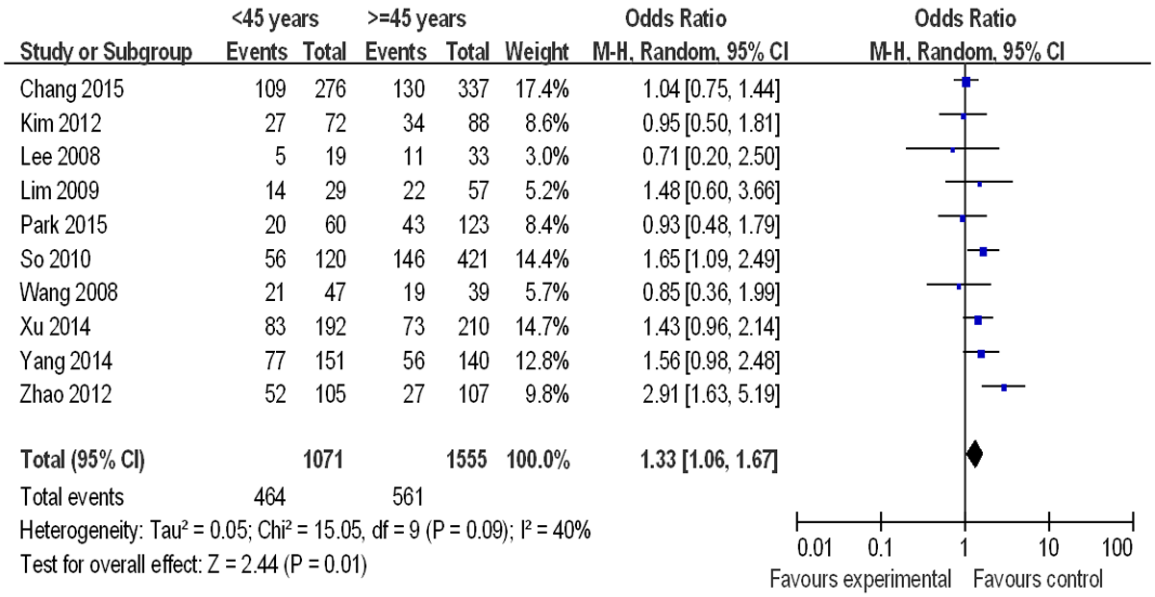

Figure 2. Odds ratios (ORs) with 95% confidence intervals (CIs) for the association between age and central lymph node metastasis. M-H, Mantel-Haenszel.

pted because the heterogeneity of the data was significant (P=0.09), and the I^2 estimate of the variance between the studies was 40%. CLNM was present in 464 (43.3%) of 1071 patients <45 years and in 561 (36.1%) of 1555 patients ≥45 years. Thus, according to our analysis, CLNM occurred more frequently in patients aged <45 compared to ≥45 years (OR=1.33, 95% CI: 1.06-1.67, P=0.01; **Figure 2**).

Sex and CLNM: Twelve studies presented clinical data including sex and central lymph node metastasis. A random-effects model was adopted because the heterogeneity of the data was significant (P<0.00001), and the I^2 estimate of the variance between the studies was I^2=81%. CLNM was present in 248 (45.4%) of 546 male patients and in 957 (36.0%) of 2655 female patients. According to our analysis, central lymph node metastasis occurred more fre-

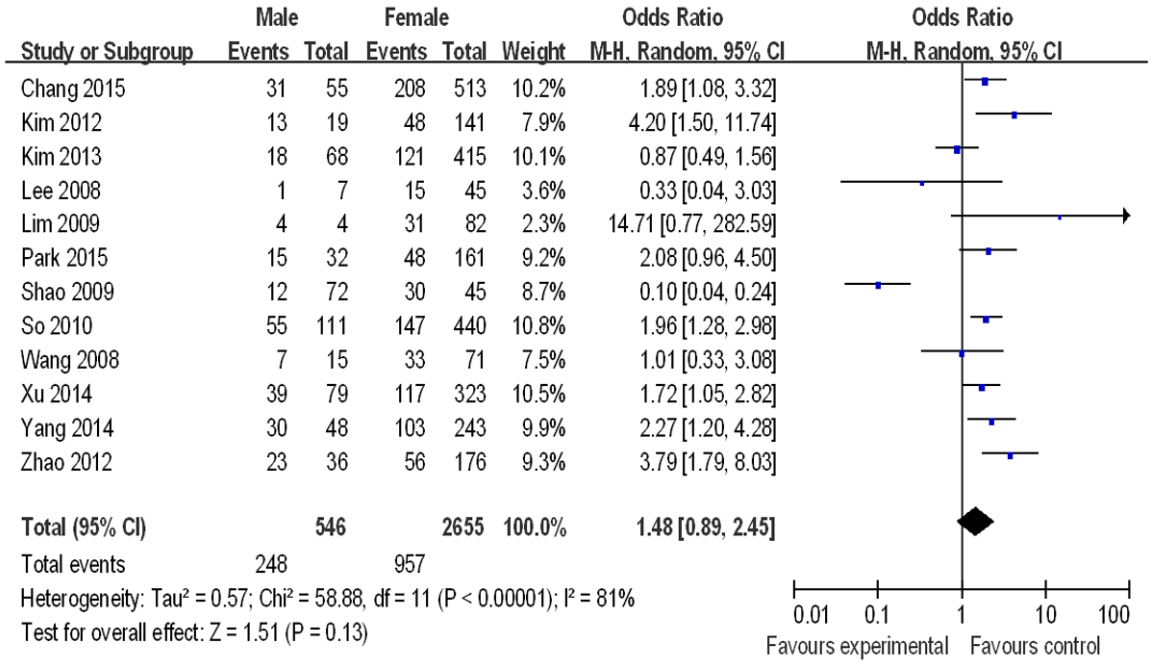

Figure 3. The odds ratios (ORs) with 95% confidence intervals (CIs) for the association between gender and central lymph node metastasis. M-H, Mantel-Haenszel.

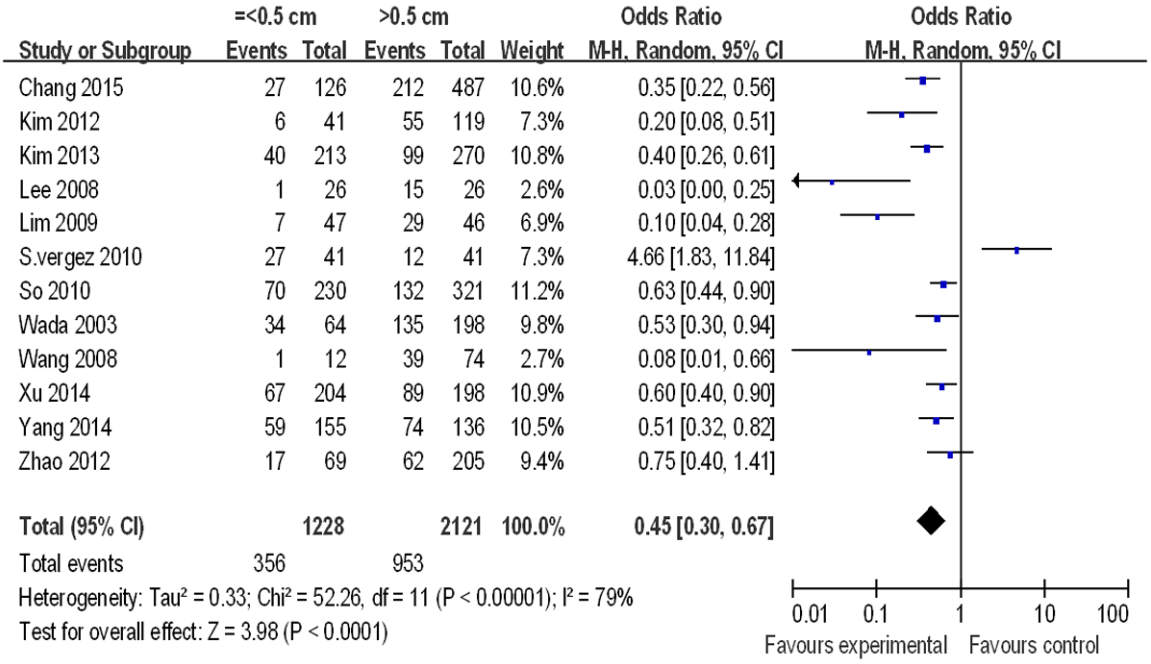

Figure 4. The odds ratios (ORs) with 95% confidence intervals (CIs) for the association between tumor size and central lymph node metastasis. M-H, Mantel-Haenszel.

quently in male patients compared to female patients but the difference was not significant (OR=1.48,95% CI: 0.89-2.45, P=0.13) (**Figure 3**).

Tumor size and CLNM: Twelve studies presented clinical data including tumor size and central lymph node metastasis. A random-effects model was adopted because the heterogeneity

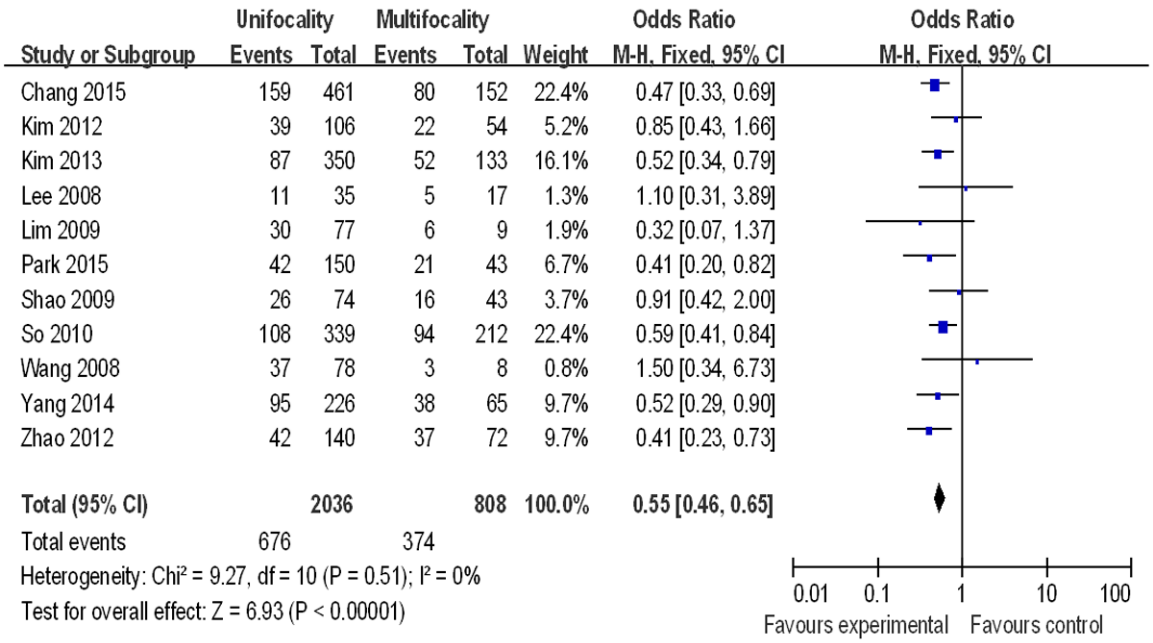

Figure 5. The odds ratios (ORs) with 95% confidence intervals (CIs) for the association between unifocality and central lymph node metastasis. M-H, Mantel-Haenszel.

of the data was significant (P<0.00001), and the I^2 estimate of the variance between the studies was I^2=79%. CLNM was present in 356 (29.0%) of 1228 patients with tumor size ≤0.5 cm and in 953 (44.9%) of 2121 patients >0.5 cm. According to our analysis, *CLNM* occurred less frequently in patients with tumor size ≤0.5 cm compared to patients >0.5 cm and the difference was significant (OR=0.45, 95% CI: 0.30-0.67, P<0.00001) (**Figure 4**).

Multifocality and CLNM: Eleven studies presented clinical data including Multifocality and central lymph node metastasis. A fix-effects model was adopted because the heterogeneity of the data was not significant (P=0.51), and the I^2 estimate of the variance between the studies was I^2=0%. CLNM was present in 676 (33.2%) of 2036 unifocality patients and in 374 (46.3%) of 808 mutlifocaltiy patients. According to our analysis, central lymph node metastasis occurred less frequently in unifocality patients compared to mutlifocaltiy patients and the difference was significant (OR=0.55, 95% CI: 0.46-0.65, P<0.00001) (**Figure 5**).

Extrathyroid extension and CLNM: Twelve studies presented clinical data including extrathyroid extension and central lymph node metastasis. A random-effects model was adopted because the heterogeneity of the data was significant (P=0.001), and the I^2 estimate of the variance between the studies was I^2=55%. CLNM was present in 636 (44.3%) of 1435 patients with extrathyroid extension and in 570 (31.5%) of 1811 patients without extrathyroid extension. According to our analysis, central lymph node metastasis occurred more frequently in patients with extrathyroid extension than patients without extrathyroid extension and the difference was significant (OR=2.20, 95% CI: 1.67-2.90, P<0.00001) (**Figure 6**).

Tumor location and central lymph node metastasis: Four studies presented clinical data including tumor location and central lymph node metastasis. A random-effects model was adopted because the heterogeneity of the data was significant (P=0.03), and the I^2 estimate of the variance between the studies was I^2=65%. Central lymph node metastasis was present in 285 (39.3%) of 725 patients with unilateral and in 102 (51.0%) of 200 patients with bilateral. According to our analysis, central lymph node metastasis occurred less frequently in patients with unilateral than patients with bilateral but the difference was not significant (OR=1.48, 95% CI: 0.89-2.45, P=0.13) (OR=0.72, 95% CI: 0.39-1.33, P<0.29) (**Figure 7**).

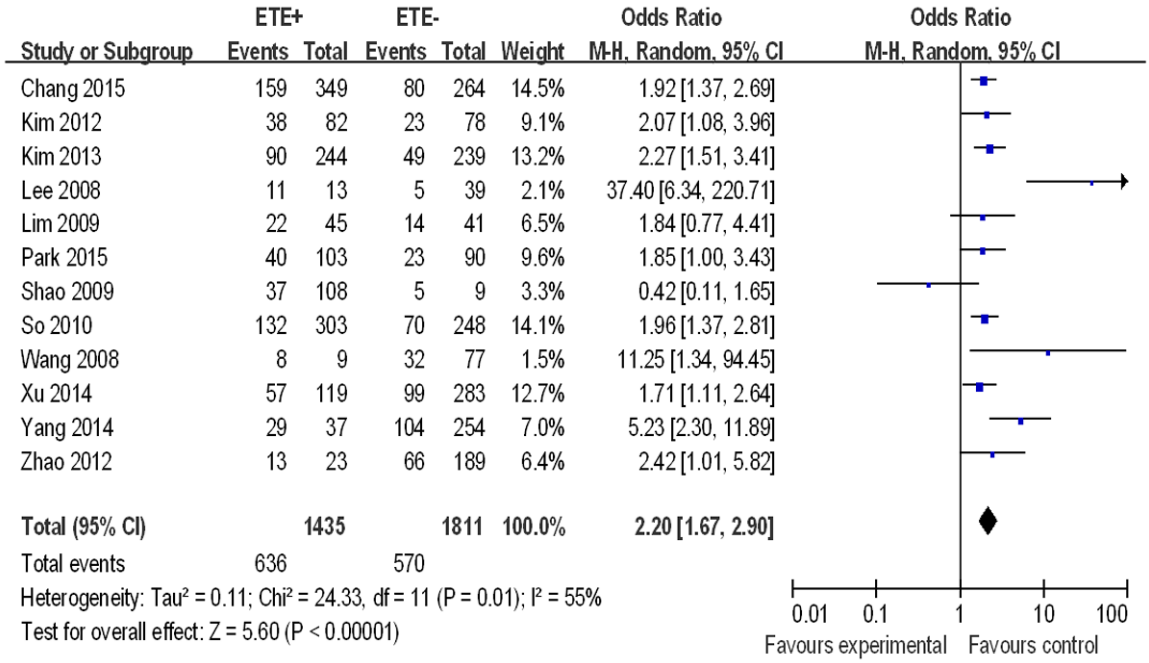

Figure 6. The odds ratios (ORs) with 95% confidence intervals (CIs) for the association between extrathyroidal extension and central lymph node metastasis. M-H, Mantel-Haenszel.

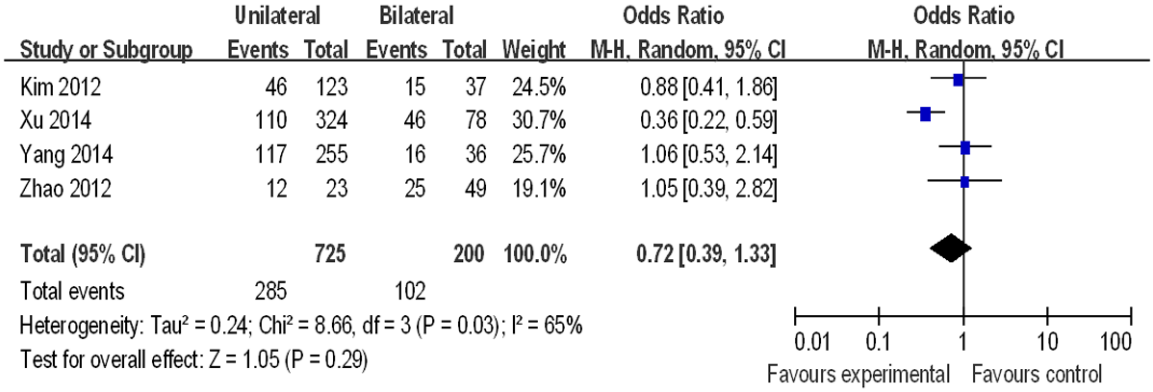

Figure 7. The odds ratios (ORs) with 95% confidence intervals (CIs) for the association between tumor location and central lymph node metastasis. M-H, Mantel-Haenszel.

Vascular invasion and CLNM: Five studies presented clinical data including vascular invasion and central lymph node metastasis. A fix-effects model was adopted because the heterogeneity of the data was not significant (P=0.66), and the I^2 estimate of the variance between the studies was I^2=0%. CLNM was present in 49 (59.0%) of 83 patients with vascular invasion and in 552 (36.3%) of 1520 patients without vascular invasion. According to our analysis, central lymph node metastasis occurred more frequently in patients with vascular invasion than patients without vascular invasion and the difference was significant (OR=15.85, 95% CI: 0.85-295.85, P<0.00001) (**Figure 8**).

Combined hashimoto and CLNM: Six studies presented clinical data including combined hashimoto and central lymph node metastasis. A random-effects model was adopted because the heterogeneity of the data was significant (P=0.05), and the I^2 estimate of the variance between the studies was I^2=54%. CLNM was present in 244 (39.9%) of 612 patients with u combined hashimoto and in 494 (51.0%) of

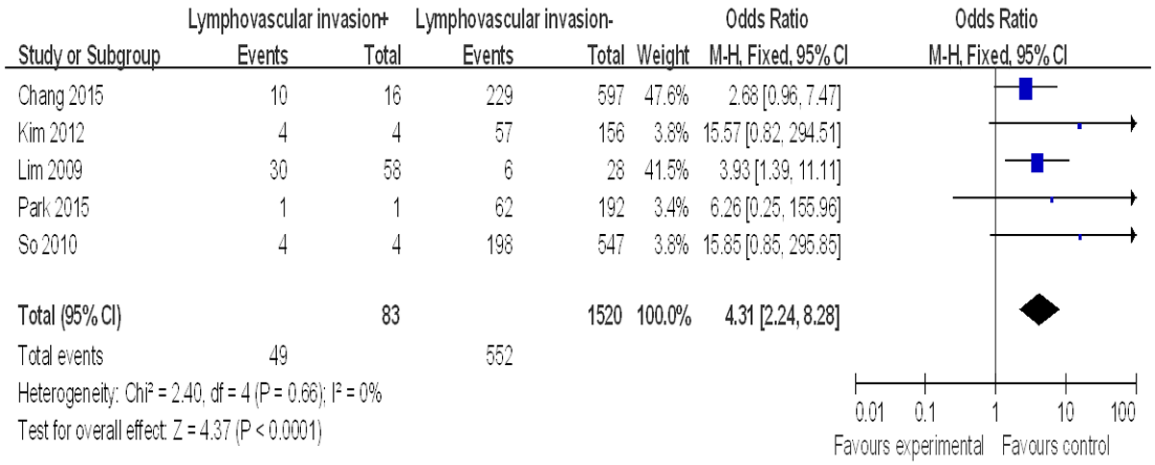

Figure 8. The odds ratios (ORs) with 95% confidence intervals (CIs) for the association between vascular invasion and central lymph node metastasis. M-H, Mantel-Haenszel.

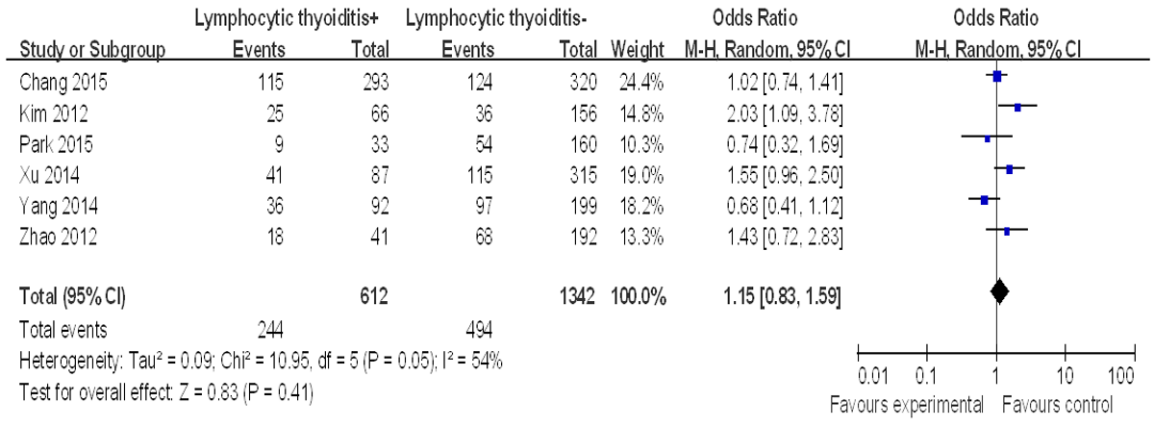

Figure 9. The odds ratios (ORs) with 95% confidence intervals (CIs) for the association between combined hashimoto and central lymph node metastasis. M-H, Mantel-Haenszel.

1342 patients without combined hashimoto. According to our analysis, central lymph node metastasis occurred more frequently in patients with combined hashimoto than patients without combined hashimoto but the difference was not significant (OR=1.15, 95% CI: 0.83-1.59) (**Figure 9**).

Sensitivity and subgroup analyses of risk factors of CLNM

Our meta-analysis showed that the effects of the heterogeneity of age, sex, tumor size, extrathyroidal extension, tumor location, and combined Hashimoto's disease on CLNM were significant (all P<0.1). Subgroup analysis was further conducted according to the country of the studies in order to investigate the potential sources of heterogeneity and to assess whether the effects of the investigated clinicopathological features on CLNM of PTMC were associated with geographic regions (**Table 2**).

According to our subgroup analysis, the I^2 estimates of the variance in the different factors were still over 50%, but had decreased significantly. Therefore, one of the heterogeneity sources may be due to the different countries of the studies.

In addition, we performed sensitivity analysis for the effect of tumor size on the presence of CLNM in PTMC patients. When we excluded the study of Vergez, the heterogeneity was significantly decreased (**Figure 10**). One reason may be due to the included patients having clinically

Table 2. Subgroup analyses of risk factors for central lymph node metastasis in PTMC patients. PTMC: papillary thyroid microcarcinoma

Subgroup	OR	OR (95% CI)	I^2 (%)	Model Used
Age				
Korea (6 studies)	1.16	0.94-1.43	0	Fix-effects
China (4 studies)	1.61	1.08-2.39	54	Random-effects
Sex				
Korea (7 studies)	1.78	1.14-2.78	54	Random-effects
China (4 studies)	1.11	0.37-3.31	94	Random-effects
Tumor Size				
Korea (6 studies)	0.29	0.17-0.49	77	Random-effects
France (1 study)	4.66	1.83-11.84	-	-
China (4 studies)	0.56	0.43-0.73	31	Fix-effects
Japan (1 study)	0.53	0.30-0.94	-	-
Extrathyroidal extension				
Korea (7 studies)	2.14	1.62-2.81	45	Random-effects
China (5 studies)	2.29	1.06-4.91	70	Random-effects
Combined Hashimoto				
Korea (3 studies)	1.17	0.70-1.95	59	Random-effects
China (3 studies)	1.13	0.65-1.97	67	Random-effects

negative CLNM, and lymph node metastasis, especially CLNM, may not have been easily detected easily before operation. Therefore, the risk of CLNM in patients with a small tumor size was higher than in those with lager tumor size in that study.

Discussion

CLNM occurs in for 31-61% of PTMC cases [7, 9]. The risk factors of CLNM have been reported by many recent studies; however, they remain controversial [7, 12, 13, 19]. Moreover, the previous studies were conducted in PTMC patients of different ethnicities, and it can be speculated that this is the reason for the varying frequencies of CLNM between the studies. Therefore, we performed this meta-analysis to determine the associations of CLNM with various clinicopathological characteristics in PTMC patients.

PCLND is known to reduce the recurrence rate and improve the survival of PTMC patients [5, 7]; however, not all authors recommend PCLND for all PTMCs, as PCLND may increase the risk of perioperative lesions such as hypoparathyroidism and laryngeal nerve injury [9, 20]. Therefore, it is necessary to elucidate the clinicopathological characteristics associated with a high risk of CLNM in order to establish the most reasonable surgical approach for PTMCs.

Lim et al. reported that there was no statistically significant difference in the risk of CLNM according to the age and sex of PTMC patients [12], whereas Zhao et al. suggested that age and sex were significantly associated with CLNM [7]. In terms of multifocality, Pitt et al. reported that, even in patients with a tumor size of <0.5 cm, multifocality was still a significant risk factor for contralateral PTMCs [21], while Lim et al. found that CLNM was not associated with multifocality [12]. Similar discrepancies also exist in terms of the roles of vascular invasion [7, 12], extrathyroidal extension [8, 10], vascular invasion [3, 12], tumor size [5, 7], and the presence of combined Hashimoto's disease on the risk of CLNM [13, 15]. In the present meta-analysis, we found that CLNM was associated with age, tumor size, multifocality, extrathyroidal extension, and vascular invasion, whereas there was no association with sex, tumor location, and combined Hashimoto's disease. Our findings may be of great value in evidence-based clinical decision-making. For example, cases at high risk of CLNM, such as patients aged <45 years and patients with tumor size >5 mm, multifocality, extrathyroidal extension, and vascular invasion detected pre- or intraoperatively may require aggressive surgical treatment such as PCLND.

Our analysis should be interpreted with caution because of the observed heterogeneity in the data, which is a major limitation. Possible explanations for this heterogeneity include differences in the patient demographics, ethnicities, surgical approach, and pathological detection, as well as in the approaches used for lymph node dissection. The current study population included patients from Korea, China, Japan, and France, and the heterogeneity was decreased in our subgroup analysis by different countries.

Another limitation is that the number of included articles was relatively small, and relevant unpublished data could not be obtained for fur-

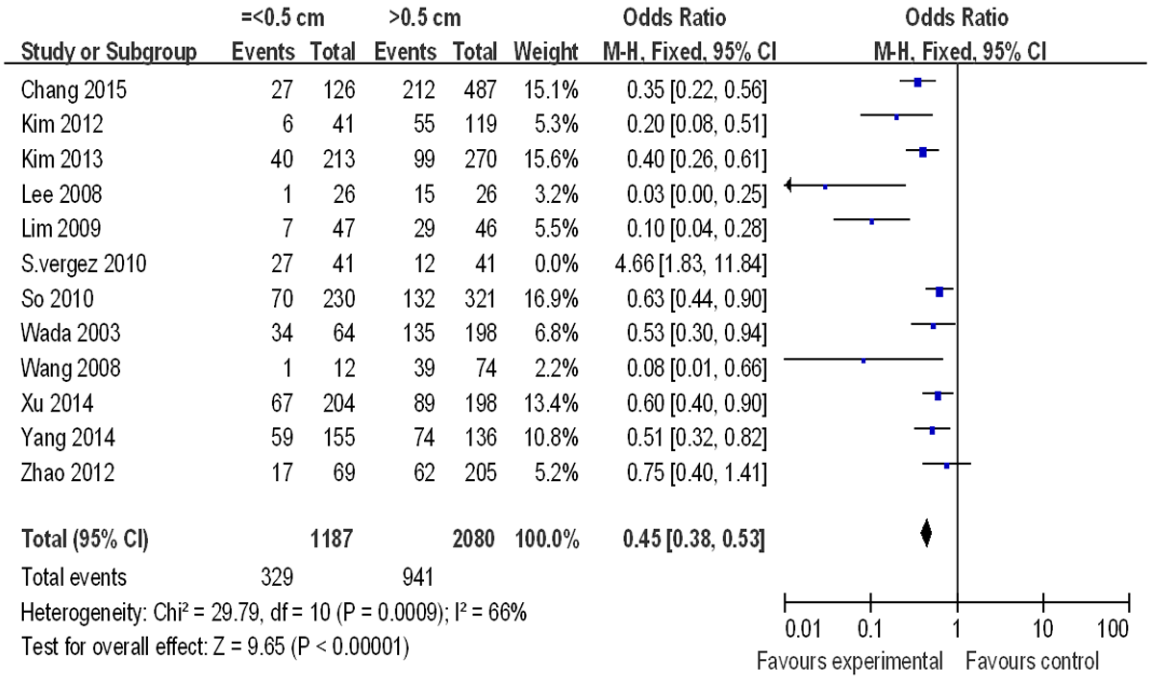

Figure 10. Heterogeneity was significantly decreased after excluding the study of Vergez (2010).

ther analysis. Therefore, our conclusions should be interpreted cautiously. Larger studies would be helpful to definitely address the clinicopathological risk factors and their role in the development of CLNM in PTMC patients.

Conclusion

Our meta-analysis summarized the common clinicopathological factors that predict the risk of CLNM in patients with PTMC; however, further international, large-scale, multicenter, randomized, prospective researches are needed to confirm these findings.

Disclosure of conflict of interest

None.

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