

Original Article

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

Zeming Liu¹, Longqiang Wang¹, Pengfei Yi¹, Cong-Yi Wang², Tao Huang¹

¹Department of General Surgery, Affiliated Union Hospital, Tongji Medical College, Wuhan, China; ²The Center for Biomedical Research, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

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Abstract: Objective: To evaluate the risk factors of central lymph node metastasis of papillary thyroid microcarcinoma. Method: Published articles about papillary thyroid microcarcinoma were searched in PubMed, MEDLINE and EMBASE until October 2013 to examine the risky factors of central lymph node metastasis. Software RevMan 5.0 was used for meta-analysis. Results: Within the patients suffering papillary thyroid microcarcinoma underwent thyroidectomy plus prophylactic central lymph node dissection, tumor size, multifocality and capsular invasion have statistically relevant association with central lymph node metastasis, but no relation was observed associated with sex and age. Conclusion: The papillary thyroid microcarcinoma should be considered central lymph node metastasis when tumor size ≥ 0.5 cm, multifocality and have capsular invasion.

Keywords: Risk factors, central lymph node metastasis, papillary thyroid carcinoma

Introduction

Papillary thyroid microcarcinoma (PTMC), which is defined as a papillary carcinoma measuring equal or less than 10 mm in diameter according to the World Health Organization classification [1]; PTMC accounts for 38.5% of papillary thyroid cancers in the United States, 35.7% in Shanghai, China; however, it up to 48.8% in France [2-8]. Currently the surgical approach of total – thyroidectomy plus prophylactic central lymph node dissection for PTMC is still controversial and uncertain [4, 6]. And lymph node metastasis especially central lymph node metastasis is considered to be one of the most important risk factors associated with recurrence [9, 10]. Therefore, it is necessary for surgeons to assess clinical features related to central lymph node metastasis of PTMC before surgery.

Materials and methods

The literature was retrieved using PubMed, EMBASE, MEDLINE and WANFANG until October

2013 and aided by manual searching and reference backtracking. The terms “papillary thyroid microcarcinoma, occult thyroid cancer” and “central or level VI lymph node dissection or metastasis” were used as the keyword. Central lymph node dissection means dissection of the level VI lymph node which lies in central position in the neck of PTMC. Inclusion and exclusion criteria: 1) published English literature, while original and review literature are not included; 2) study object patients with PTMC; 3) all the patients with papillary thyroid microcarcinoma underwent thyroidectomy plus prophylactic central lymph node dissection and 4) the experimental design was a retrospective clinical trial and the trial should provide complete data such as the number of cases.

Statistical analysis: We used RevMan 5.0 for meta-analysis. Before combined analysis, we assessed data heterogeneity among studies. A random-effects model was used When $P < 0.1$, otherwise a fixed-model was applied. The odds ratio was calculated for dichotomous data

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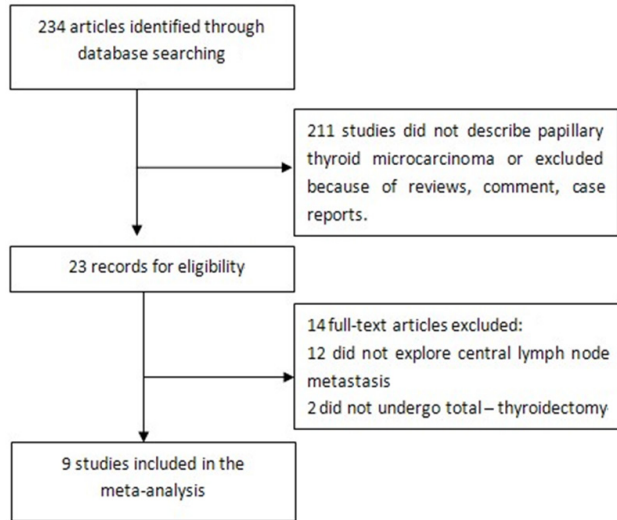


Figure 1. Flow chart for articles identified and included in the meta-analysis.

along with 95% CI, the significance level was set at 0.05.

Results

Basic information

23 studies were finally obtained after a initial screening of the 234 literatures we had retrieved, further screened according to inclusion criteria (**Figure 1**), finally we included nine studies in our analysis [7, 11-18]. All of our nine studies performed total thyroidectomy with prophylactic central neck dissection. Of these studies, three were carried out in China, four in Korea, one in Japan, and one in France. All nine studies included are retrospective trials including a total of 1928 patients. Basic information such as author, publication date, country, research design, number of cases and surgical approach is showed in **Table 1**.

Risk factors for central lymph node metastasis

Tumor size and central lymph node metastasis: Tumor size was reported in 8 studies, a random-effects model was adopted as there was a significant heterogeneity between tumor size <0.5 cm and tumor size >0.5 cm ($P<0.00001$, $I^2=81\%$). Tumor size >0.5 cm resulted in a higher incidence of central lymph node metastasis compared with Tumor size <0.5 cm (OR=2.31, 95% CI: 1.29-4.13; $P=0.005$; as shown in **Figure 2**).

Foci number and central lymph node metastasis: Foci number was reported in 7 studies, a fix-effects model was adopted as there was no significant heterogeneity between unifocal and multifocal ($P=0.40$, $I^2=3\%$). T multifocal resulted in a higher incidence of central lymph node metastasis compared with unifocal (OR=1.75, 95% CI: 1.39-2.18; $P<0.00001$; as shown in **Figure 3**).

Age and central lymph node metastasis: Age of PTMC was reported in 5 studies, a random-effects model was adopted as there was a significant heterogeneity between tumor age <45 years and age >45 years ($P=0.09$, $I^2=50\%$). No significant difference was observed between the age <45 years group and age >45 years group (OR=1.46, 95% CI: 0.93-2.31; $P=0.10$; as shown in **Figure 4**).

Sex and central lymph node metastasis: Gender of PTMC was reported in 7 studies, a random-effects model was adopted as there was a significant heterogeneity between male ground and female group ($P<0.00001$, $I^2=88\%$). No significant difference was observed between the male ground and the female ground (OR=1.03, 95% CI: 0.40-2.67; $P=0.96$; as shown in **Figure 5**).

Capsulate invasion and central lymph node metastasis: Capsulate invasion of PTMC patients was reported in 7 studies, a random-effects model was adopted as there was a significant heterogeneity between capsulate invasion and non-capsulate invasion ($P=0.002$, $I^2=72\%$). Capsulate invasion resulted in a higher incidence of central lymph node metastasis compared with non-capsulate invasion (OR=2.84, 95% CI: 1.60-5.06; $P=0.0004$; as shown in **Figure 6**).

Discussion

Rates of extrathyroid extension, capsule invasion, lymph node metastases, and distant metastases at presentation in patients with PTMC have been as great as 21%, 20%, 26%, and 3%, respectively [19-21]. The incidence of CLNM in patients with papillary thyroid microcarcinoma was reported from 31% to 61% [7, 11, 14]. In our studies, the frequency of LNM in PTMCs varied by ethnicity; the mean frequency

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Table 1. Basic information of the studies

Authors	Year	Country	Research design	Case number	Surgical approach
Lim [15]	2009	Korea	Retrospective clinical study	86	TT+PCLND
S. vergez [20]	2010	France	Retrospective clinical study	82	TT or NTT+PCLND
Zhao [7]	2012	China	Retrospective clinical study	212	TT+PCLND
Kim [16]	2013	Korea	Retrospective clinical study	483	TT or NTT+PCLND
So [17]	2010	Korea	Retrospective clinical study	551	TT+PCLND
Wada [12]	2003	Japan	Retrospective clinical study	259	TT or NTT+PCLND
Lee [13]	2008	Korea	Retrospective clinical study	52	TT or NTT+PCLND
Shao [18]	2009	China	Retrospective clinical study	117	TT or NTT+PCLND
Wang [19]	2008	China	Retrospective clinical study	86	TT or NTT+PCLND

TT: total thyroidectomy, NTT: near-total thyroidectomy, PCLND: prophylactic central lymph node dissection.

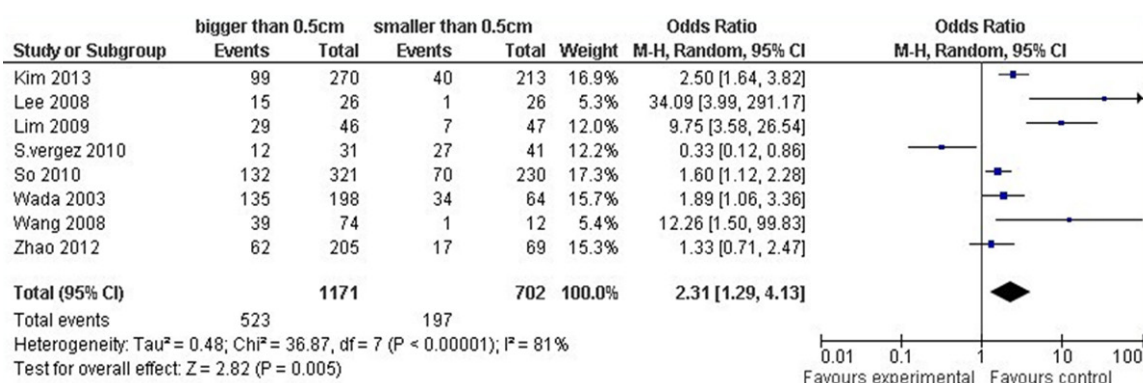


Figure 2. Tumor size and central lymph node metastasis.

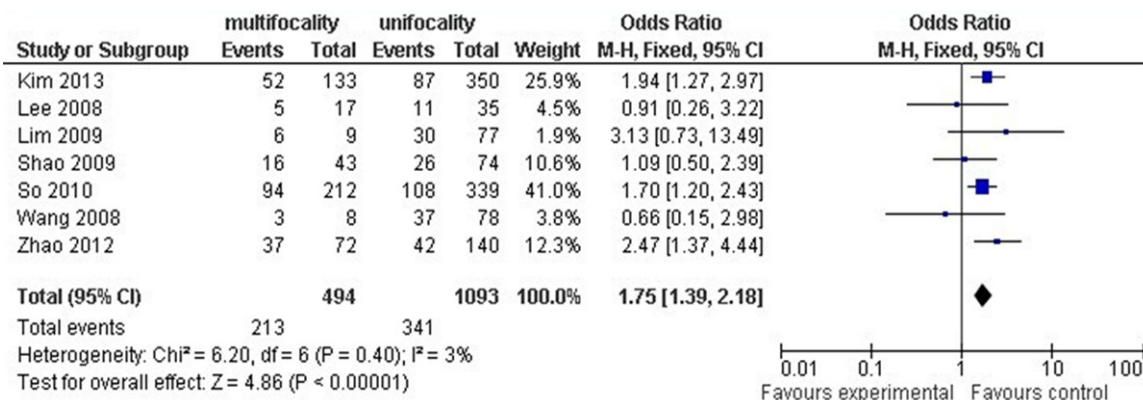


Figure 3. Foci number and central lymph node metastasis.

in Asians was 38.2%, whereas in whites it was 47.6%.

It remains controversial whether patients with PTMC need PCLND or not. Some surgeons advocate that PCLND is not recommended in patients with PTMC for its less aggressive form and CLND may increase the rate of periopera-

tive lesion such as hypoparathyroidism, laryngeal nerve injury [11, 22, 23]; While others suggest PCLND for it may reduce the recurrence rate and improve the survival [24-28]. And some clinical features for patients with PTMC are still much debated too. For example, zhao [7]'s results support the idea that age and gender are significantly different associated with

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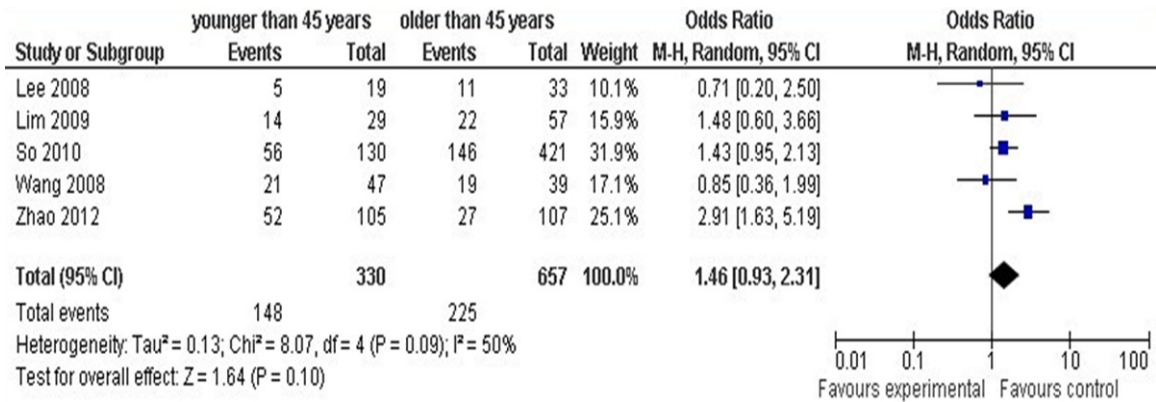


Figure 4. Age and central lymph node metastasis.

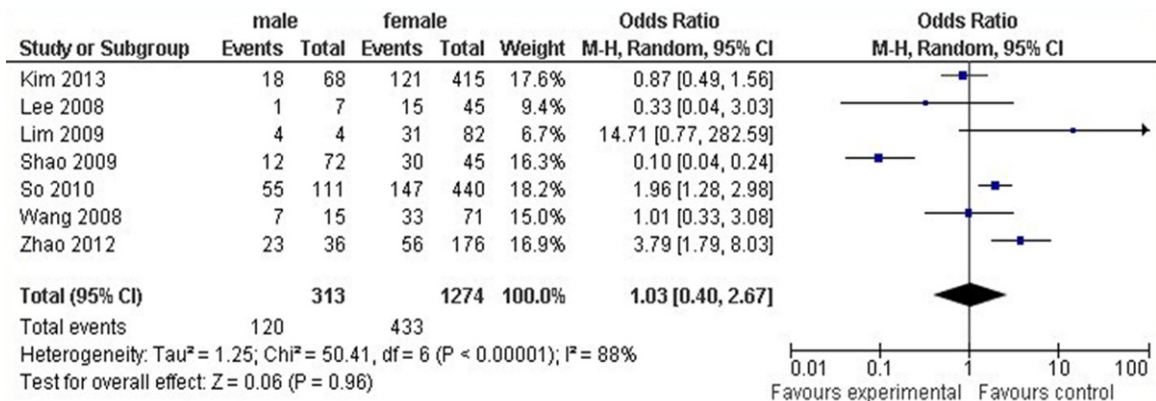


Figure 5. Sex and central lymph node metastasis.

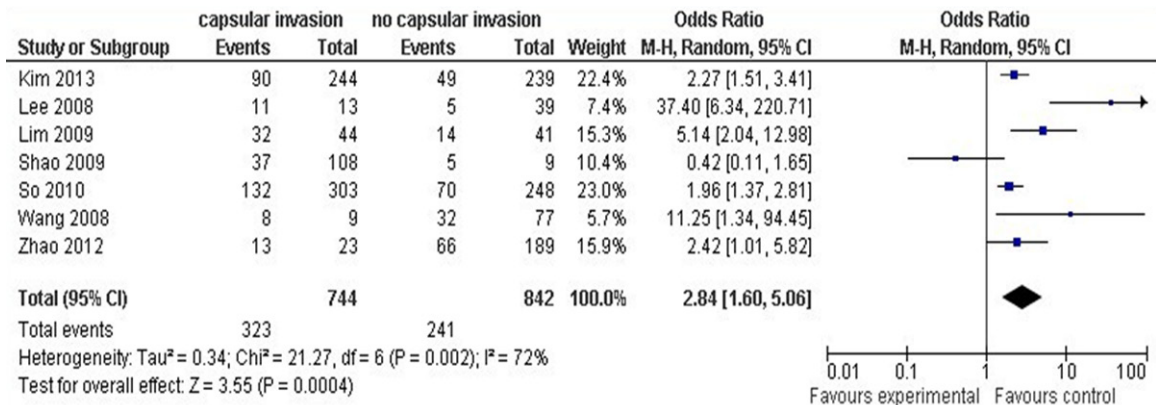


Figure 6. Capsulate invasion and central lymph node metastasis.

CLNM; yet Lim [14] demonstrated that there are no statistically significant between age and gender with CLNM. Lee [13] found extracapsular spread was significantly associated with CLNM (p=0.14, OR=1.987); but zhao et al. [7]

found that the difference between CLNM with or without capsular invasion (p=0.043, OR=2.4) was not so dramatic. Recent research has shown that tumors from multifocal PTC arise from independent clonal origins of distinct

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tumor foci [29]. And Pitt SC [30] have reported that in patients with primary tumors <1 cm even <0.5 cm, multifocal disease is a significant risk factor for contralateral tumors; but Lim YC [14] suggesting that central lymph node involvement is not associated with multifocality.

According to the above results and analysis, we found out that CLNM was significantly more likely to occur in patients with tumor size >0.5 cm, multifocality and capsular invasion, but there was no significant differences associated with sex and age. Central Lymph node metastasis are confirmed to be an independent and the most important predictors of disease relapse [20]. So prophylactic central lymph node dissection may be not recommended if the patients with clinicopathologic features such as tumor size <0.5 cm, tumor unifocality, no capsular invasion, but PCLND should be considered in patients with big tumor size (>0.5 cm), multifocal lesions or capsular invasion.

In general, this meta-analysis summarizes the common clinical factors to predict the risk of CLNM in patients with PTMC; however, there are still several limitations to this study. First of all, the studies we chose were not randomized case-control trial; so they only reflect PTMC patients with surgery approach of TT+PCLND. Furthermore, due to lacking follow-up data, only one study from Europe [13], more studies and researches are need to confirm CLNM model in PTMC patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Tao Huang, Department of General Surgery, Affiliated Union Hospital, Tongji Medical College, Wuhan, China. Tel: +8613807112766; E-mail: huangtaowh@163.com

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