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REVIEW ARTICLE

Papillary Carcinoma of Thyroid Nodule if Located in Isthmus Is Associated with Greater Disease Progression: a Systematic Review and Meta-analysis

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Abstract

The aim of this study was to evaluate the clinicopathologic characteristics and pattern of lymph node (LN) metastasis in papillary thyroid cancer (PTC) located in the isthmus. A systematic review of the relevant electronic databases was conducted between January 2000 and December 2019, including Pubmed, Web of Science, and the China Journal Net. Outcomes of interest included gender, age, tumor size, multifocality, capsule invasion, extrathyroidal extension, and lymph node metastasis. We calculated the pooled odds ratios (ORs) with 95% confidence intervals (CIs) for each study using a random or fixed effect model. Nine studies with a total of 4541 patients were included. Patients with isthmic PTC were 565 (12.4%). Our meta-analysis revealed that there was a significant association between the isthmus location and multifocality (OR = 1.50; 95% CI = 1.18–1.90), capsule invasion (OR = 1.53; 95% CI = 1.17–1.99), extrathyroidal extension (ETE) (OR = 1.95; 95% CI = 1.34–2.86), and central LN metastasis (OR = 1.53; 95% CI = 1.17–1.99). For patients with solitary nodule, our meta-analysis illustrated that there was a significant association between the isthmus location and ETE (OR = 1.65; 95% CI = 1.11–2.46), and central LN metastasis (OR = 2.50; 95% CI = 1.82–3.44). However, the meta-analysis suggested that there was no correlation between the isthmus location and lateral LN involvement (OR = 1.04; 95% CI = 0.58–1.87). PTCs located in the isthmus were associated with multifocality, capsule invasion, ETE, and more likely to involve the central lymph node.

Keywords Papillary thyroid cancer · Isthmus · Lymph node dissection · Meta-analysis

Background

Thyroid cancer rarely occurs in the isthmus. The isthmus is located in front of the second and third tracheal rings connecting the two lateral lobes and has a length of about 20 mm, a width of about 20 mm, and a thickness of 2 to 6 mm [1]. The incidence of papillary carcinoma arising in the thyroid isthmus is low (1 to 9.2%) [2–5].

Previous studies have shown that papillary thyroid cancer (PTC) located in the isthmus are more likely to exhibit extrathyroidal extension and multiple lesions than those located in the other parts of the thyroid [2, 4, 6]. In addition, isthmus PTC is more strongly associate with central lymph node metastasis than lobar tumors [5].

Surgical treatment of PTCs located in the isthmus remains controversial due to its anatomical and biological characteristics. The American Thyroid Association (ATA), the British Thyroid Association (BTA), and the European thyroid Association (ETA) provided recommendations for well-differentiated thyroid cancer, but there are no accurate guidelines for the management of patients with dominant thyroid nodules of the isthmus [7–9]. To determine the optimal extent of prophylactic lymph node dissection, it is crucial to establish a pattern of lymph node metastasis in isthmus PTC.

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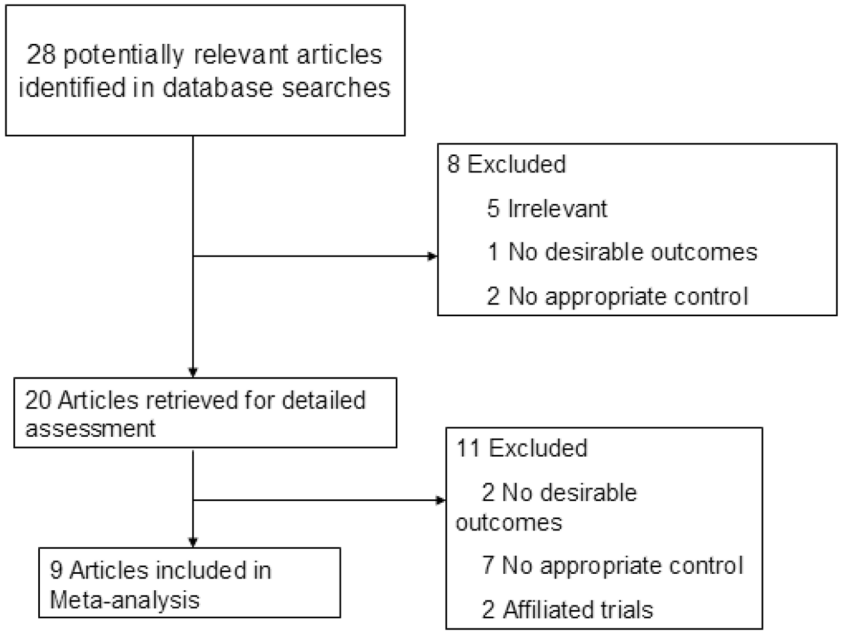

Fig. 1 Flowchart of the results of the literature search

In the present study, we analyzed the clinicopathologic features in patients with papillary carcinoma of the thyroid isthmus and compared the findings with those for patients with tumors in other parts of the thyroid.

Materials and Methods

Search Strategy

Pubmed, Web of science, and the China Journal Net were searched for publications from January 2000 to December 2019. The search terms used were "Papillary Thyroid Cancer," "Isthmus," and "Clinicopathologic Characteristics." The reference lists of relevant studies were checked manually to locate any missing studies.

Inclusion and Exclusion Criteria

Criteria for eligibility of a study included in this meta-analysis were as follows: (1) Detection of the papillary thyroid cancer in the isthmus. (2) The studies were published in English, Chinese, and Korean. (3) When several studies were reported from the same authors or organizations, the meta-analysis enrolled the most recent or highest quality study only if the most recent one did not fit the inclusion criteria. Studies were excluded if (1) studies were case reports, letters, and reviews without original data; animal or laboratory studies; (2) the studies without

Table 1 Overview of the reviewed studies

Author, Year	Country	No. of patients	Sex (male/female)	Patient source	Mean age		Tumor size (cm)	
					Isthmus	Non-isthmus	Isthmus	Non-isthmus
Chang 2018 [11]	Korea	282	22/260	Korea University Anam Hospital	43.2	45.6	1.2	1.4
Karatzas 2015 [5]	UK	575	121/454	Laikon General Hospital	53.00	49.66	1.21	1.01
Lee 2016 [10]	Korea	190	45/145	Kyung Hee University	51.6	50.4	1.54	1.39
Song 2015 [12]	Korea	194	39/155	Hanyang University	46.84	49.27	1.22	1.16
Li 2017 [13]	China	94	21/73	West China Hospital of Sichuan University	41.3	38.6	1.31	1.44
Lee 2010 [2]	Korea	1973	288/1685	Gangnam Severance Hospital	47.6	47.7	1.02	1.13
Choi 2010 [15]	Korea	70	7/63	Kangdong Sacred Heart Hospital	45.2	46.2	1.5	1.2
Xiang 2014 [14]	China	949	207/742	Zhejiang University		43.8		0.6
Hahn 2014 [6]	Korea	144	–	Sungkyunkwan University School		47.6		1.2

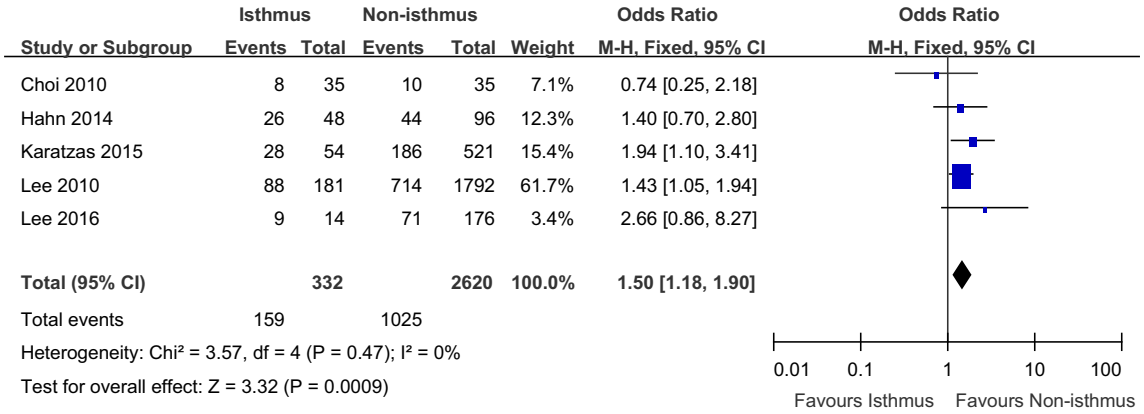

Fig. 2 Fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) for patients with multifocality in isthmus PTC vs. in non-isthmus PTC

control data were excluded; (3) repeated studies were based on the same database or patients.

Data Extraction

Two review authors (L.Y. and L.H.) independently selected studies for inclusion and extracted the data. A third researcher (X.J.) arbitrated in the event of any disagreement. The decision for inclusion in the analysis was made by consensus. Full-text copies of potentially relevant studies were obtained. The following variables were recorded: authors, sex, number of patients, age of patients, and clinicopathological characteristics. The dominant nodule was considered as the primary carcinoma when multifocal disease was found. Patients with dominant nodule in isthmus were classified as isthmus group, and patients with dominant nodule located in lobes were classified as the non-isthmus group.

Statistical Analysis

A formal meta-analysis was made for all studies. The statistical analysis was carried out using the Review Manager 5.0. Pooled estimates of the complications were calculated using a fixed effects model, but a random effects model was used according to heterogeneity. The test of effect homogeneity was performed using χ^2 tests, with $p \leq 0.05$ indicating significant heterogeneity. When the hypothesis of homogeneity was not rejected, the fixed effects model was used to estimate the pooled effect of the outcomes; when the reverse was true, the random effects model was also calculated. For the pooled analysis of the correlation between isthmus location and clinicopathological features (sex, tumor size, multifocality, capsule invasion, presence of extrathyroidal extension, lymph node metastasis), odds ratios (ORs) and 95% CIs were combined to estimate the effect.

Results

Study Selection

We identified 19 potentially relevant articles (Fig. 1). After exclusion of duplicate references, non-relevant literature, and those manuscripts that did not satisfy the inclusion criteria, 9

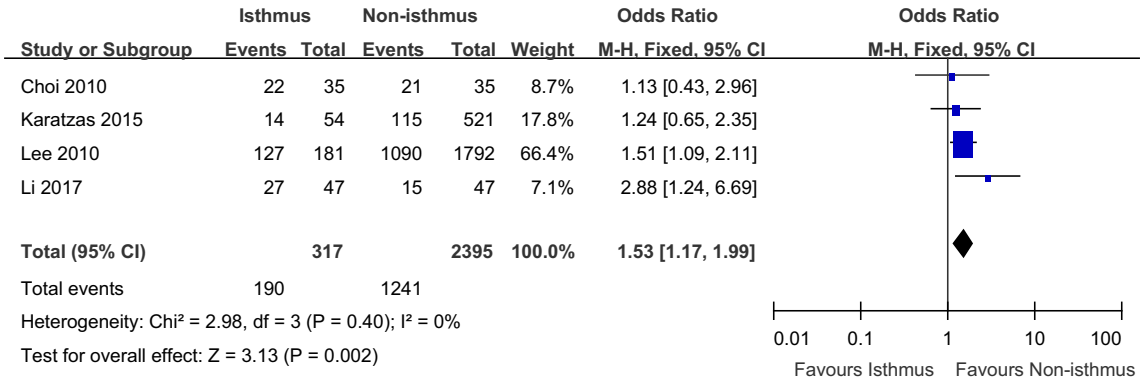

Fig. 3 Fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) for patients with capsule invasion in isthmus PTC vs. in non-isthmus PTC

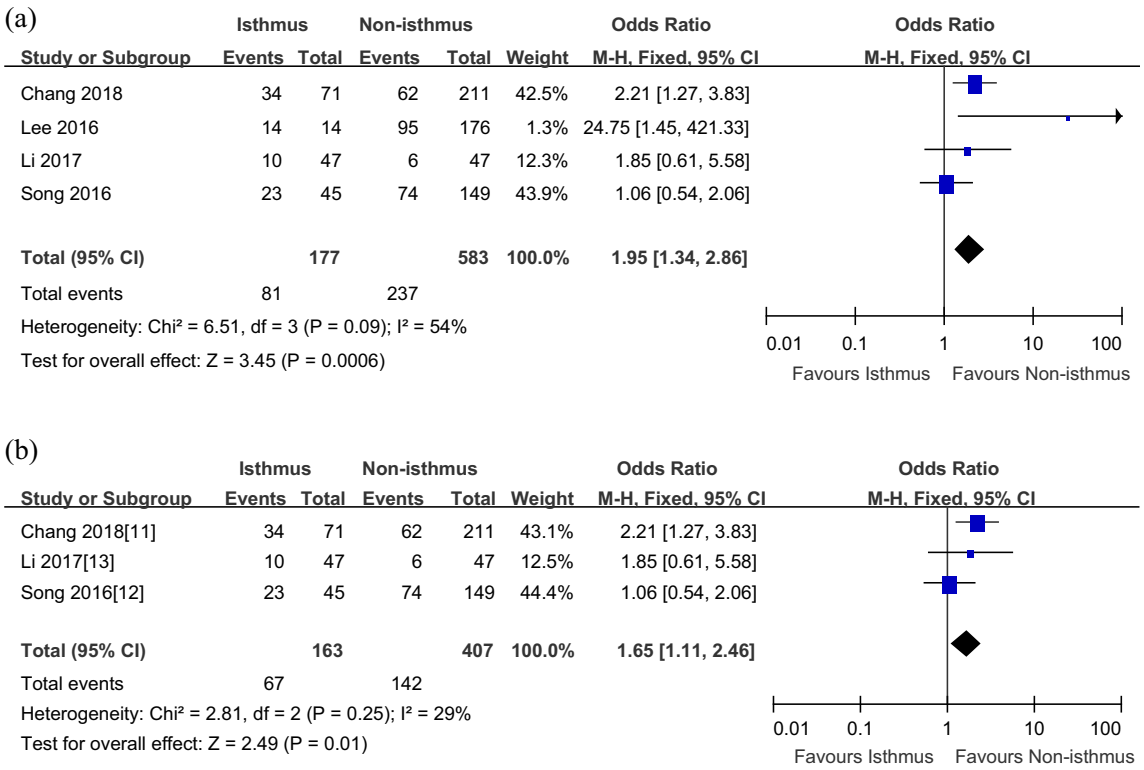

Fig. 4 Fixed effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) for patients with extrathyroidal extension. **a** Isthmus PTC vs. non-isthmus PTC. **b** Isthmus PTC with solitary nodule vs. non-isthmus PTC with solitary nodule

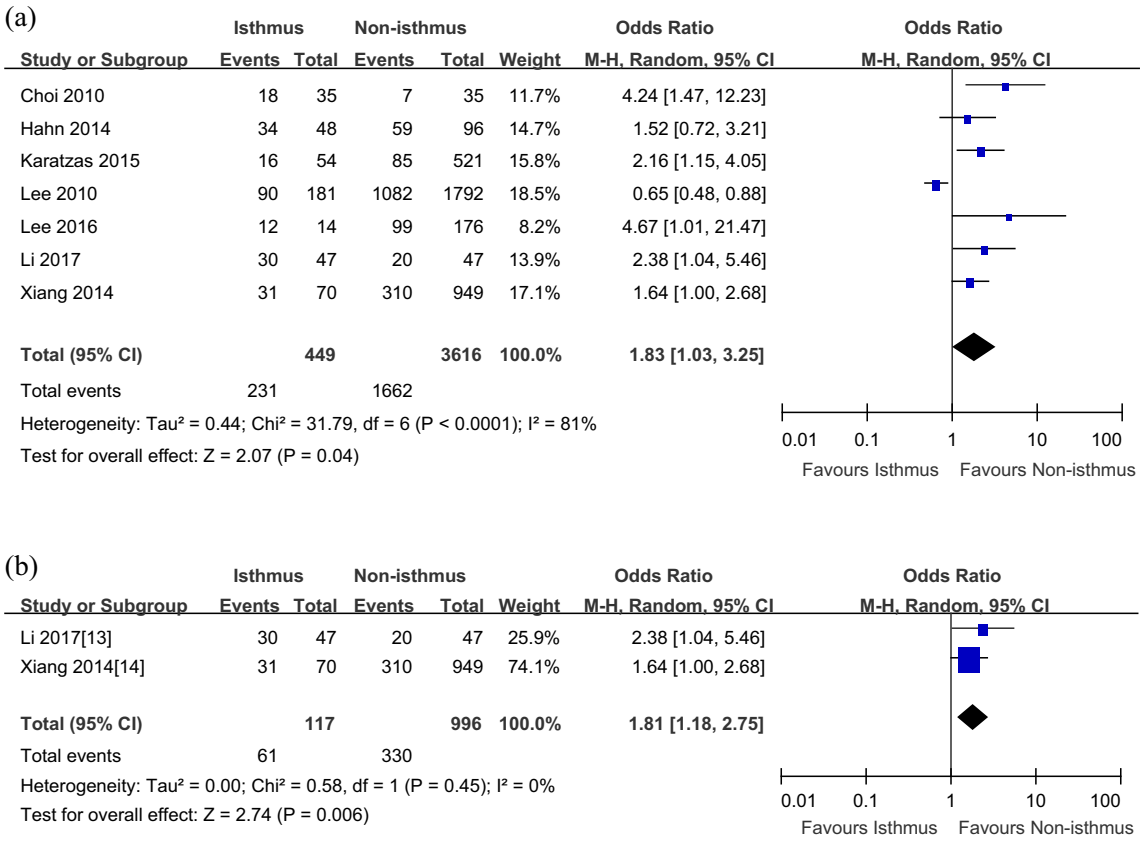

Fig. 5 Random effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) for patients with lymph node metastasis. **a** Isthmus PTC vs. non-isthmus PTC. **b** Isthmus PTC with solitary nodule vs. non-isthmus PTC with solitary nodule

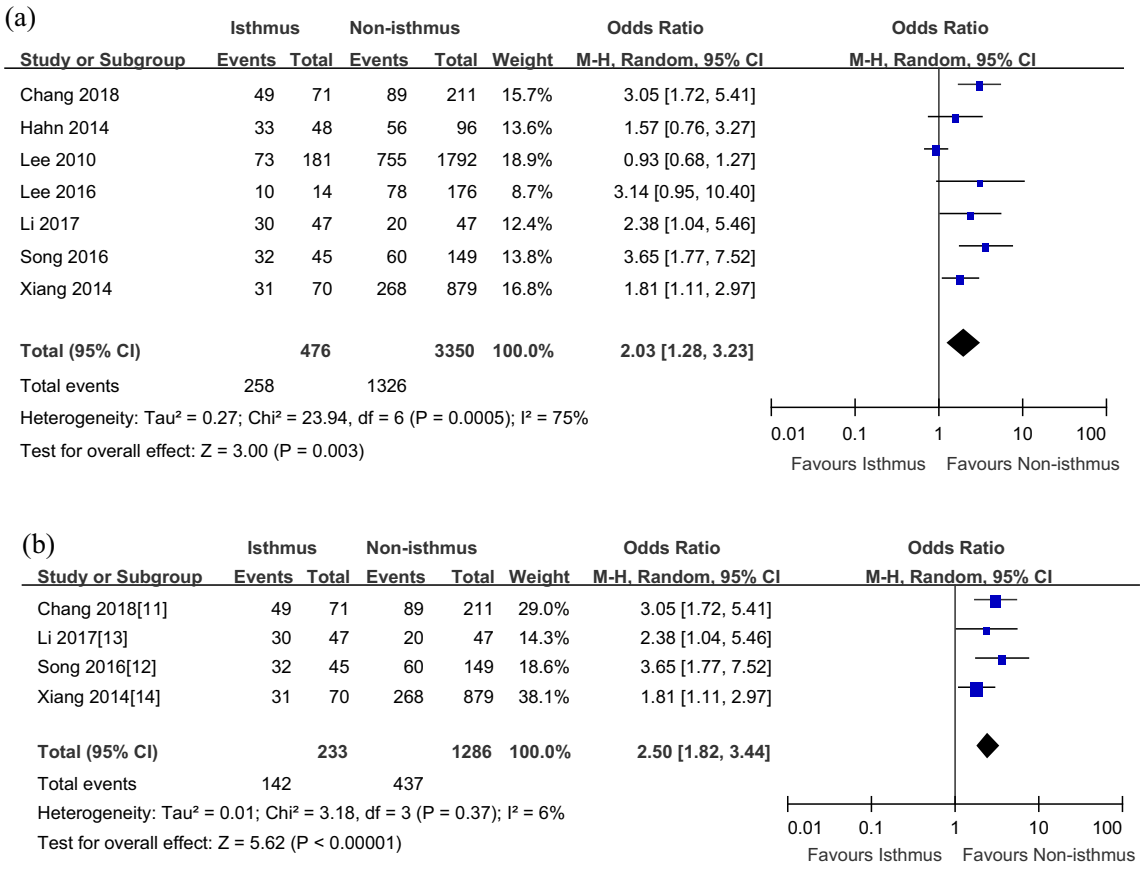

Fig. 6 Random effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) for patients with central lymph node metastasis. **a** Isthmus PTC vs. non-isthmus PTC. **b** Isthmus PTC with solitary nodule vs. non-isthmus PTC with solitary nodule

candidate articles [2, 5, 6, 10–15] were considered for the meta-analysis. The study characteristics are summarized in Table 1.

A total of 4541 patients who underwent thyroidectomy due to papillary thyroid cancer (PTC) were enrolled. Of them, most cases of PTC were located in the lobe ($n = 3976$, 87.6%), and a total of 565 PTC cases had tumors located at the isthmus. The patient demographics for the 9 studies are presented in Table 1. All papers were retrospective chart reviews. The publication dates ranged from 2010 to 2018. The study sizes ranged from 70 to 1973 patients.

Five studies demonstrated that there was a significant association between the isthmus location and multifocality (OR = 1.50; 95% CI = 1.18–1.90) (Fig. 2). Except this abovementioned parameter, controversies also existed on the correlation among capsule invasion, extrathyroidal extension, and lymph node metastasis. Four studies including 2712 patients were analyzed for the association between the isthmus location and capsule invasion. There was a significant association between the isthmus location and capsule invasion (OR = 1.53; 95% CI = 1.17–1.99) (Fig. 3). Four studies including 760 patients were analyzed for the association between the isthmus location and extrathyroidal extension (ETE). There was a significant association between the isthmus location and extrathyroidal extension (OR = 1.95; 95% CI = 1.34–2.86) (Fig. 4a). In addition, there was a significant correlation between the isthmus location and lymph node metastasis (OR = 1.83; 95% CI = 1.03–3.25) (Fig. 5a) and central lymph node metastasis (OR = 2.03; 95% CI = 1.28–3.23) (Fig. 6a). However, the meta-analysis suggested that there were no correction between the isthmus location and lateral lymph node involvement (OR = 1.04; 95% CI = 0.58–1.87) (Fig. 7a). When we focused on the solitary thyroid nodule, we also discovered that there was a significant association between the isthmus location and extrathyroidal extension (OR = 1.95; 95% CI = 1.34–2.86) (Fig. 4b), lymph node metastasis (OR = 1.81; 95% CI = 1.18–2.75) (Fig. 5b), and central lymph node metastasis (OR = 2.50; 95% CI = 1.82–3.44) (Fig. 6b). On the contrary, there were no significant differences between the isthmus location and lateral lymph node involvement for solitary isthmus nodule (OR = 1.53; 95% CI = 0.87–2.71) (Fig. 7b).

Discussion

A solitary PTC of the isthmus is an uncommon lesion and requires surgical evaluation. Despite its low incidence,

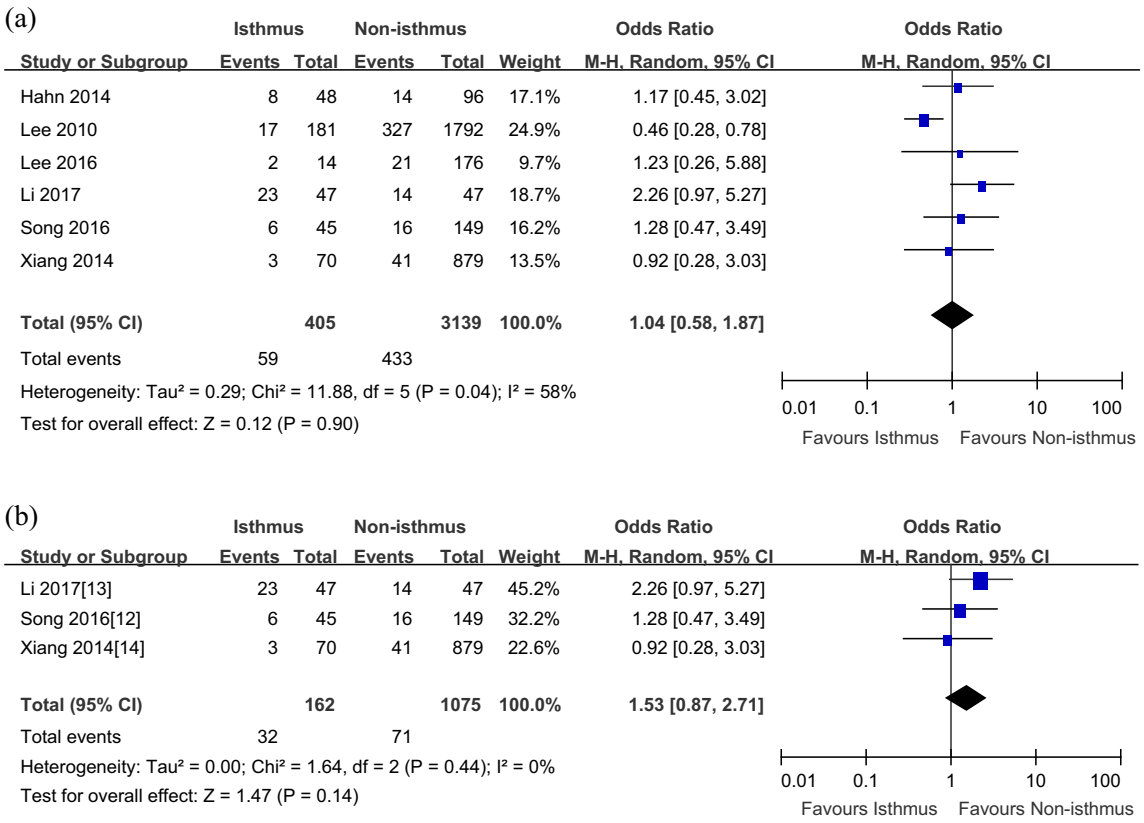

Fig. 7 Random effects model of the odds ratios (ORs) with 95% confidence intervals (CIs) for patients with lateral lymph node metastasis. **a** Isthmus PTC vs. non-isthmus PTC. **b** Isthmus PTC with solitary nodule vs. non-isthmus PTC with solitary nodule

isthmic PTC is associated with more aggressive clinical and pathological features. Previous studies have indicated that PTCs located in the isthmus are more likely be multifocal compared with PTC located in other parts of the gland [4, 16]. Arora [17] have reported that multifocal tumors are common in PTC, and their incidence is not related to tumor size. The multifocality seems to be related to the midline position of the tumors, which easily spreads to the thyroid bilobes.

The capsule invasion rate was 59.9% in the isthmic PTC group, which was significantly higher than the 51.8% rate reported in the control group. The main reason for this difference might be the special anatomical structure with tissue that is 2 to 6 mm thick and is covered by strap muscles [3], even with smaller tumors, the isthmic PTC is more likely to invade the capsule, and capsule invasion cases are more likely to invade the surrounding tissue, which translates into a higher rate of extrathyroidal extension.

Several reports have suggested that tumor location is associated with neck metastasis [18–20]. However, the controversy remains regarding whether PTC located in the isthmus is correlated with central lymph node or lateral lymph node metastasis. In our results, isthmus PTC were more likely to involve the central lymph nodes, and there was no significant difference in the frequency of lateral lymph node involvement. This result seems to be due to differences in the lymphatic system according to the anatomical locations of the thyroid gland. Although the isthmus has poor lymphatic channels, lymphatics from the isthmus usually drain into the prelaryngeal and pretracheal regions [2].

Prelaryngeal LN are also called Delphian, from "the Oracle of Delphi," a Greek legend, predicting an unfavorable prognosis [21]. Furthermore, prelaryngeal lymph node metastasis in PTC has been associated with poor prognostic markers, such as higher rates of extrathyroidal extension, capsule invasion, and multifocality [22–24]. Lateral node involvement was also commonly observed with isthmus PTC in our study at 14.6% (59/405), which is comparable with other previous studies [25]. However, there was no significant difference in the frequency of lateral LN involvement. This difference may be explained by differences in the extent of neck dissection performed.

There are some limitations in our meta-analysis. Firstly, the pooled studies differed in inclusion and exclusion criteria. These may be the major source of heterogeneity. Second, the data included in some studies may have been too crude and also subject to measurement error. Finally, the sample size of the included studies was too small to exclude beta error. Hence, our findings must be interpreted with caution.

Conclusions

The location of the cancer in the isthmus was associated with multifocality, capsule invasion, ETE, and central lymph node metastasis at the time of diagnosis. Thus, patients with PTC originating in the isthmus should be performed with total thyroidectomy and possible central node dissection.

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