Original Article

Total thyroidectomy versus less-than-total thyroidectomy for papillary thyroid carcinoma of isthmus: a systematic review and meta-analysis

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Background: Papillary thyroid carcinoma of isthmus (PTCI) has a more aggressive nature, a higher rate of lymph node metastasis and tumor recurrence. Clinicians have different preferences for the surgical approach to PTCI, but there are no definitive guidelines. The purpose of this article is to compare the oncologic outcomes and complications of total thyroidectomy and less-than-total thyroidectomy for PTCI using meta-analysis.

Methods: We searched PubMed, Embase, Cochrane Library, and Web of Science databases for articles that met the inclusion criteria, with an unlimited start date and an end date of February 19, 2023. Exclusion criteria were applied to filter out articles for further analysis. Ultimately, seven articles were used for analysis, all of which were retrospective studies. The MINORS scale was adopted to evaluate the quality of the included literature, and Review Manager 5.4 was used for data analysis.

Results: A total of 814 patients were included in the seven articles, including 401 in the less-than-total thyroidectomy group (trial group) and 413 in the total thyroidectomy group (control group). The results of the meta-analysis showed that there was no significant difference in the tumor recurrence rate between the two groups after total thyroidectomy or less-than-thyroidectomy for PTCI (odds ratio, 1.51; 95% confidence interval: 0.49, 4.65; P=0.47), and there was no statistical difference in the incidence of all postoperative complications between the two groups.

Conclusions: There may be some limitations in this analysis, such as publication bias and the fact that the included articles were all retrospective studies with a certain degree of heterogeneity. PTCI patients with early staging and no significant lymph node metastases may be able to choose a more conservative surgical approach, which is less-than-total thyroidectomy. Patients with relatively late staging and significant preoperative lymph node metastases or extra thyroidal extension may opt for total thyroidectomy plus lymph node dissection in the central region and, if necessary, lymph node dissection in the lateral cervical region.

Keywords: Papillary thyroid carcinoma (PTC); isthmus; surgical methods; tumor recurrence rate; postoperative complications

Submitted Jul 16, 2023. Accepted for publication Oct 26, 2023. Published online Nov 16, 2023.
doi: 10.21037/gs-23-300
View this article at: https://dx.doi.org/10.21037/gs-23-300

Introduction

Nowadays, the prevalence of thyroid cancer is showing a significant increase worldwide, accounting for about 1.5% of new cancers in Europe (1,2), with a male: female patient incidence ratio of about 1:3 (3). Papillary thyroid carcinoma (PTC), a pathological subtype, constitutes the predominant form of thyroid cancer, affecting approximately 80–85% of all cases (4). The prognosis of PTC is good, and the 10-year survival rate exceeds 90%. Most of it occurs in both lobes of thyroid gland, but there is also a small proportion of PTC that occurs in the isthmus. The occurrence of PTC in the isthmus is about 1–9.2% (5,6). The definition of PTC of isthmus (PTCI) is unclear. It is generally considered to be a virtual vertical line drawn from the outermost point of the trachea to the surface of the skin on both sides, with the center point of the tumor designated as the intersection of its longest and shortest diameters (*Figure 1*). And if the center point of the tumor lies between the two virtual lines, then it is an isthmus thyroid tumor, and if the postoperative pathology shows PTC, it is defined as PTCI (7). Due to the special clinicopathological manifestations of PTCI, there are some differences in preoperative diagnosis, treatment modalities, postoperative follow-up and prognosis from those of glandular lobe PTC. Some studies have shown that PTCI is more likely to cause extra thyroidal extension (ETE) than glandular lobe PTC (8,9). In addition, since the isthmus of the thyroid gland is anterior to the trachea and overlies the cervical tracheal ring, its lymphatic drainage pathway is different from that of glandular lobe PTC, so the probability of bilateral lymph node metastasis is higher. In particular, several studies in the literature have shown that PTCI has a higher probability of tumor multifocality compared to glandular lobe PTC (10-13). Therefore, some scholars believe that PTCI has a poor prognosis with a higher risk of local tumor recurrence, distant metastasis and tumor-related mortality than glandular lobe PTC (5,10,14-18).

In 2015, the American Thyroid Association (ATA) gave detailed guidelines for the treatment of PTC on the surgical approach suitable for various types of PTC, but the scope of surgery and lymph node dissection for PTCI was not clearly defined (19). Hence, in clinical practice, there are many controversies among clinicians regarding the scope of surgery for patients with PTCI. Moreover, due to the low incidence of PTCI, the number of cases selected from clinical studies is relatively small, making it difficult to make credible conclusions. The main surgical options for PTCI are total thyroidectomy, thyroid lobectomy plus isthmus resection and extended isthmusectomy (12,13). Some clinicians believe that total thyroidectomy is the ideal surgical approach for PTCI as it not only provides patients with the opportunity to be treated with I^{131} postoperatively, but also reduces the risk of tumor recurrence. Due to its large surgical extent, however, patients almost completely lose thyroid function after surgery and need to take thyroxine for a lifetime, and the surgery itself carries a high risk of postoperative complications (5,20). Thyroidectomy plus isthmusectomy is mainly used for patients with isthmus tumors on one side, when the same side of the lobe can be removed at the same time. Isthmusectomy and extended isthmusectomy can preserve the maximum possible thyroid lobes, which not only retain the patient's thyroid function, but also greatly reduce the risk of damage to the parathyroid glands and the laryngeal recurrent nerve and reduces the chance of a series of postoperative complications. However, some scholars believe that based on the fact that PTCI is more likely to have ETE, lymph node metastasis and multifocal tumor, the isthmusectomy may not be able to completely remove the lesion and therefore lead to an increased risk of tumor recurrence and secondary surgery. There are no clinical randomized controlled trials (RCTs) comparing the different surgical approaches of PTCI (9-13). The results obtained from different retrospective studies are also inconsistent (4,7,21-24).

Based on these existing clinical problems and

Highlight box

Key findings

- Papillary thyroid carcinoma of isthmus (PTCI) patients with early staging and no significant lymph node metastases may be able to choose a more conservative surgical approach, which is less than total thyroidectomy.

What is known and what is new?

- Clinicians have different preferences for the surgical approach to PTCI, but there are no definitive guidelines for the surgical approach to PTCI.
- This article is the first meta-analysis and systematic review study on the effect of surgical approaches on tumor recurrence rate and postoperative complications in patients with PTCI.

What is the implication, and what should change now?

- The implication of this paper is to provide clinicians and patients with PTCI with a new way of thinking about surgical approach selection. In the future, more reliable conclusions will be obtained if more randomized controlled trials are included or if data from individual patients are extracted for pooled data analysis.

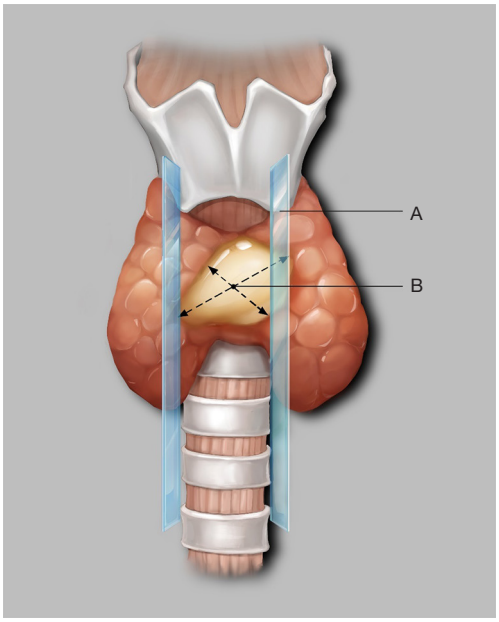

Figure 1 Anatomical schematic of the PTCI. A: the plane formed by the dotted line from the outermost part of the trachea to the skin surface on both sides. B: the center point of the tumor which is designated as the intersection of its longest and shortest diameters. PTCI, papillary thyroid carcinoma of isthmus.

controversies, we aimed to evaluate the efficiency and safety of different surgical approaches for PTCI by evaluating tumor recurrence and postoperative complications in patients with PTCI after total thyroidectomy and less-than-total thyroidectomy (including isthmusectomy, extended isthmusectomy, and thyroid lobectomy plus isthmusectomy). We present this article in accordance with the PRISMA reporting checklist (25) (available at https://gs.amegroups.com/article/view/10.21037/gs-23-300/rc).

Methods

Protocol and registration

A meta-analysis protocol registration number (INPLASY202330095) has been applied on the INPLASY website. As this study is a systematic review and meta-analysis, informed consent was not required.

Literature search strategy

We searched PubMed, Embase, Cochrane Library, and Web of Science databases for original literature reporting comparative efficiency and safety of total thyroidectomy (control group) and less-than-total thyroidectomy (trial group) in patients with PTCI. We used search terms such as "papillary thyroid carcinoma", thyroid neoplasms", "differentiated thyroid cancer", "isthmus", "isthmusectomy", "thyroidectomy", "thyroid surgery". No search start date was set, and the end date for the literature search was on February 19, 2023. The specific search formula is shown in Appendix 1.

Inclusion criteria

All included studies fulfilled the following criteria: (I) the subjects of the study were patients with differentiated isthmic thyroid cancer (meeting the criteria of the 2015 ATA guidelines for indications for surgical treatment of differentiated thyroid cancer) who were first-time surgery patients, regardless of gender and age, and all had pathologically confirmed diagnosis; (II) comparison of surgical approaches in the literature included total thyroidectomy and less-than-total thyroidectomy, including thyroidectomy plus isthmusectomy, isthmusectomy, etc.; (III) at least one of the following outcomes should be reported in the included studies: tumor recurrence rate, relative risk of tumor recurrence in each group, assessment of postoperative complications, postoperative functional recovery, and tumor outcome; and (IV) all studies must have a follow-up period of more than 2 years for retrospective or prospective studies with more than 10 cases in the trial and control groups.

Exclusion criteria

The following publications were excluded from the analysis: (I) studies evaluating patients with benign thyroid lesions; (II) studies with no control groups; (III) the literature only discussed the overall tumor recurrence/postoperative complications instead of comparing them by group; (IV) repeated studies, case reports, conference abstracts, reviews, letters or syntheses, and studies for which full text was not available; and (V) non-English literature.

Data extraction and quality assessment

Two reviewers independently extracted the following data from the included studies using a standard data extraction form. The extracted data were used after verification by the authors: (I) study characteristics: doi, main author, publication year, patient inclusion duration, number of

patients, mean patient age and male-to-female ratio, research type; (II) detailed information about different ranges of surgical procedures performed: including pre-treatment cervical lymph node metastasis, clinical stage of tumor, tumor diameter, ETE, surgical method and intraoperative lymph node dissection; and (III) surgical outcomes and follow-up: including mean follow-up duration, local tumor recurrence rate, and postoperative complication rate.

Two authors independently performed data extraction and quality assessment using the Non-Randomized Experimental Research Quality Assessment Tool [methodological index for non-randomized studies (MINORS) scale] (26). The scale consists of 12 entries, each with a score of 0–2, for a total score of 24. A score of 0 indicates not reported, 1 indicates reported but with insufficient information, and 2 indicates reported and sufficient information provided. Disagreements were also resolved through consultation with the third reviewer.

Statistical analysis

We estimated standardized mean difference (SMD) with 95% confidence interval (CI) or odds ratio (OR) with 95% CI for continuous variable and dichotomous variable, respectively. All meta-analyses in this study were performed using Review Manager (RevMan) version 5.4 and StataMP 17, and statistical tests were set to two-sided, with P values <0.05 considered statistically significant. All forest plots were generated by RevMan 5.4 and all figures for sensitivity analysis were generated by StataMP 17. A random effects model was used to assess the relative risk of tumor recurrence rate and postoperative complications in the two groups. Heterogeneity among studies was determined by the chi-square test for pooled estimates (P<0.05, indicating significant heterogeneity) and the calculation of the I^2 statistic (<25% as low heterogeneity, 25–50% as low to moderate heterogeneity, 51–75% as moderate heterogeneity, >75% as high heterogeneity). Finally, sensitivity analyses were performed to explore the quality of the study as well as the stability of the meta-analysis and to explore the sources of heterogeneity.

Results

Study selection and characteristics

Our process for inclusion in the study was strictly in accordance with the PRISMA statement (25), and 750 studies were obtained by searching four English-language databases. We imported these studies into Endnote software for de-duplication and obtained 517 studies. And then 37 potentially useful studies were obtained after two researchers independently screened by title and abstract, excluding 477 irrelevant studies and three studies for which the full text was not available. A flow-chart describing the reference selection process is illustrated in *Figure 2*.

Seven studies were included, and the basic information of the included studies is shown in *Table 1*. These seven studies met all of our inclusion criteria. All of the seven included studies were of retrospective nature and the quality of the literature was assessed using the MINORS scale and was found to have a score range of 13–18, with a mean score of 16.29. As less than 10 studies were included in this analysis, publication bias was not applied. Three studies were carried out in China, three studies in Korea, and one study in Japan. A total of 814 patients were included in the seven studies, including 401 in the less-than-total thyroidectomy group (trial group) and 413 in the total thyroidectomy group (control group). Tumor recurrence was reported in all studies, with 21 tumor recurrences and a tumor recurrence rate of 5.24% in the trial group and 14 tumor recurrences and a tumor recurrence rate of 3.90% in the control group. Five studies reported the occurrence of postoperative complications, of which a total of 154 complications were reported, 40 in the trial group and 114 in the control group. The main complications included temporary/permanent hypoparathyroidism, temporary laryngeal return nerve injury, pain, and incisional infection. The specific surgical scope of the trial group in the seven studies included: isthmusectomy, extended isthmusectomy, thyroidectomy plus isthmusectomy, and subtotal thyroidectomy. There were more females than males in all of the included studies.

Tumor recurrence rate

Sugenoya's 1993 study reported on tumor recurrence in PTCI patients 5–24 years after surgery, and none of the 19 patients included had tumor recurrence (23). The articles by Gui, Lei, Lim, and Zhang mentioned median follow-up times, with the longest being Zhang's study in 2021 with a median follow-up time of 67.5 months (8,24,27). The analysis showed (*Figure 3*) that there was low to moderate heterogeneity (P=0.14; I^2=40%). The included articles were imported into Stata 17 and the OR values were analyzed using the Influence Analysis, metan-based (metaninf) panel

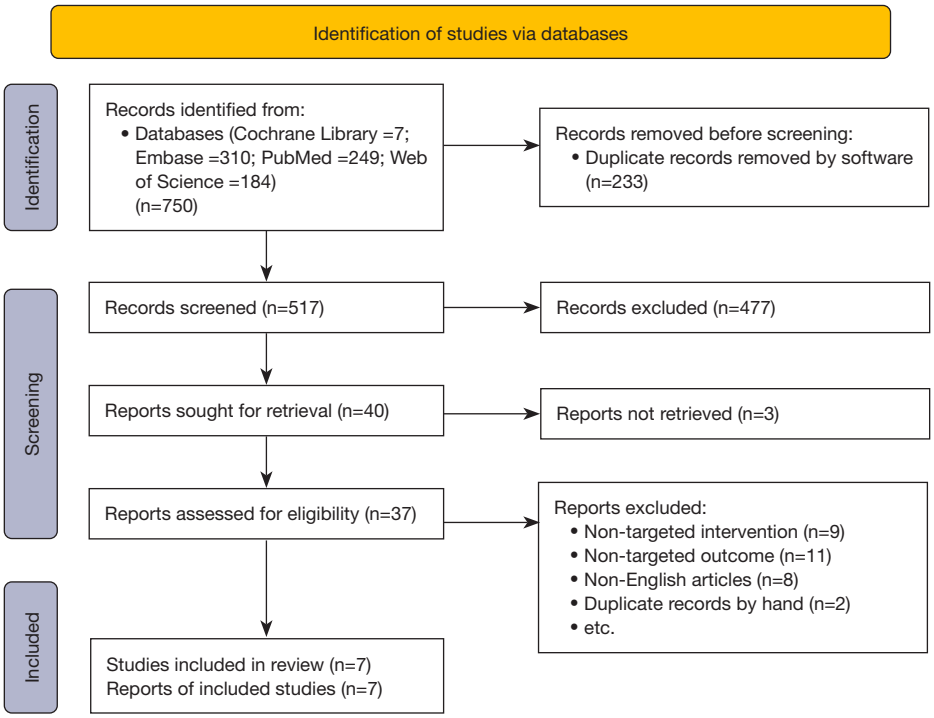

Figure 2 Article selection process flowchart (based on PRISMA).

and the Random, Mantel-Haenszel method was selected. As shown (*Figure 4*), the results showed that the 95% CI crossed the null line after removing any of the articles, indicating that the study had high stability despite low to moderate heterogeneity. The results showed similar tumor recurrence rates in the trial and control groups with no statistical difference (OR, 1.51; 95% CI: 0.49, 4.65; P=0.47).

Comparison of tumor recurrence rates between thyroid lobectomy plus isthmusectomy and total thyroidectomy

In this study, five articles provide detailed information about the number of patients who underwent thyroid lobectomy plus isthmusectomy and their postoperative recurrence rates. Among the 491 patients analyzed, 18 experienced tumor recurrence following thyroid lobectomy plus isthmusectomy, resulting in an 8.7% recurrence rate. In contrast, only eight patients experienced tumor recurrence after undergoing total thyroidectomy, yielding a tumor recurrence rate of 2.8%. The analysis, performed using a random-effects model with low heterogeneity (I^2=0%), revealed a significantly higher tumor recurrence rate in the thyroid lobectomy plus isthmusectomy group (OR, 2.49; 95% CI: 1.03, 6.01; P=0.04) when compared to the total thyroidectomy group (*Figure 5*). This difference was statistically significant.

Comparison of recurrence rates between extended isthmusectomy and total thyroidectomy

In this study, only two articles reported the number of individuals who underwent extended isthmusectomy and the number of those who experienced postoperative tumor recurrence. In the articles published by Sugenoya *et al.* in 1993, there were no cases of postoperative tumor recurrence in either group (23). This absence of recurrence prevented the conduct of a meta-analysis, resulting in the absence of reliable data analysis results.

Comparison of recurrence rates between isthmusectomy and total thyroidectomy

Four articles in this study provide detailed information about the individuals who underwent isthmusectomy and their postoperative recurrence rates. Out of 322 patients, just one experienced tumor recurrence after isthmusectomy, while five patients faced tumor recurrence after total thyroidectomy. The results of the analysis, using a random-effects model, indicated no significant difference between the two groups in terms of postoperative tumor recurrence incidence (OR, 2.85; 95% CI: 0.06, 131.73;

Table 1 Main characteristics of the included studies

Study, year	Inclusion cycle	Follow-up time	Number of patients	Prevalence of females (%)	Patient age (years)[†,‡]	Tumor size (cm)[†,‡]	Tumor staging[†]	Lymph node dissection status[§]	Tumor recurrence rate (%)[†]	Postoperative complication rate (%)[†]	MINORS score
Gui, 2020, (27)	2012–2019	Median: 41.5 m	47/23	63/70, 90.0	47	1.12	–	A: 69, C: 1	4.26 (2/47); 0 (0/23)	–	16
Kwon, 2021, (21)	2009–2018	32.1±14.2 m	90/64	124/154, 80.5	46.4±11.8/ 47.8±12.3	0.76±0.39/ 0.76±0.36	I: 77, II: 13/ I: 54. II: 10	A: 154	0 (0/90); 3.1 (2/64)	6.67 (6/90); 67.19 (43/64)	17
Lei, 2016, (22)	2009–2015	Median: 22 m	18/85	80/103, 77.7	43.2±14.6/ 44.4±15.4	1.22±1.09/ 1.44±0.89	–	A: 11, B: 56, C: 18	16.67 (3/18); 2.35 (2/85)	11.11 (2/18); 17.65 (15/85)	17
Lim, 2016, (7)	1997–2011	Median: 64.34 m	126/97	201/223, 90.1	46.17±9.70/ 50.11±11.84	0.77±0.52/ 1.07±0.69	cT1N0M0	A: 126, B: 97	11.11 (14/126); 2.06 (5/97)	–	18
Seo, 2020, (4)	2003–2019	55.8±32.8 m	51/70	93/121, 76.9	47.2±12.4/ 49.1±13.8	0.78±0.3/ 1.2±0.6	I: 48, II: 3/ I: 68, II: 2	A: 104, C: 17	2.0 (1/51); 1.4 (1/70)	9.8 (5/51); 57.14 (40/70)	17
Sugenoya, 1993, (23)	1967–1986	Range, 5–24 y	13/6	15/19, 78.9	47.9	0.5–5	–	A: 9, B: 3, C: 7	0 (0/13); 0 (0/6)	0 (0/13); 33.33 (2/6)	13
Zhang, 2021, (24)	2001–2017	Median: 67.5 m	56/68	100/124, 80.6	46.49±9.93/ 42.44±11.03	0.99±0.53/ 0.89±0.57	cT1N0M0	A: 56, B: 68	1.79 (1/56); 5.88 (4/68)	48.21 (27/56); 20.59 (14/68)	16

[†], less-than-total thyroidectomy/total thyroidectomy group; [‡], data are presented as median, mean ± SD, or range; [§], A: unilateral central, B: bicentral, C: other. MINORS, methodological index for non-randomized studies; m, months; y, years; SD, standard deviation.

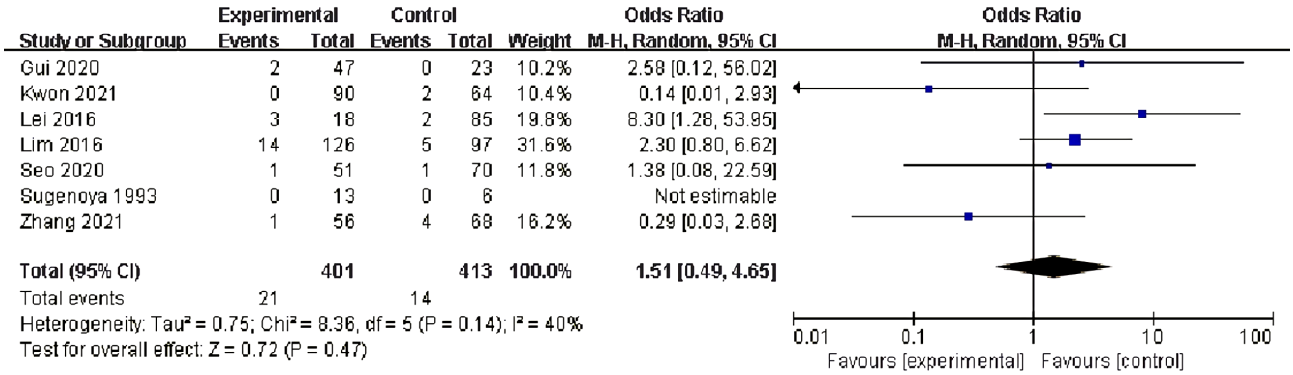

Figure 3 Meta-analysis of tumor recurrence rate. M-H, Mantel-Haenszel; CI, confidence interval.

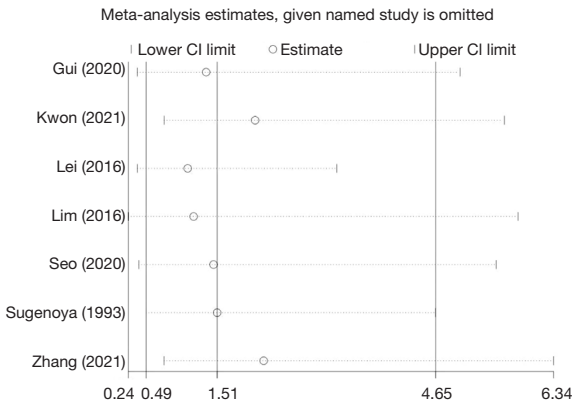

Figure 4 Sensitivity analysis of tumor recurrence rate. X-axis represents the OR. CI, confidence interval; OR, odds ratio.

P=0.59). The analysis displayed a moderate to high degree of heterogeneity (I^2=76%) (*Figure 6*). We conducted a sensitivity analysis of tumor recurrence rates in both groups using Stata and observed that the inclusion of Lei's article influenced overall homogeneity, reducing I^2 to 30% after its removal (22) (*Figure 7*).

Tumor recurrence rate after adjustment for tumor staging

In this study, two articles described in detail the tumor-node-metastasis (TNM) staging of patients before surgery, with the study by Lim 2016 and the study by Zhang 2021 both selecting patients with cT1N0M0 staging before surgery, for a total of 347 patients (8,24). There were

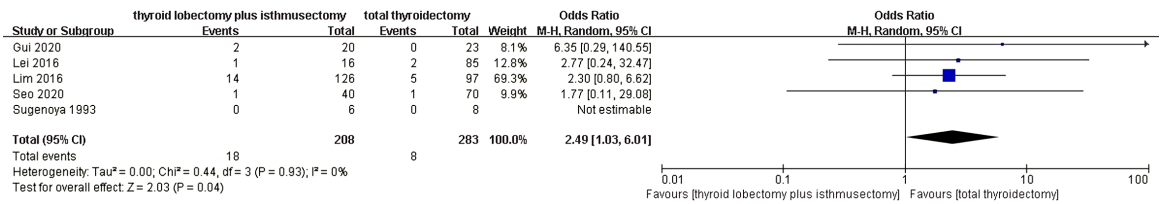

Figure 5 Meta-analysis of tumor recurrence rates between thyroid lobectomy plus isthmusectomy and total thyroidectomy. M-H, Mantel-Haenszel; CI, confidence interval.

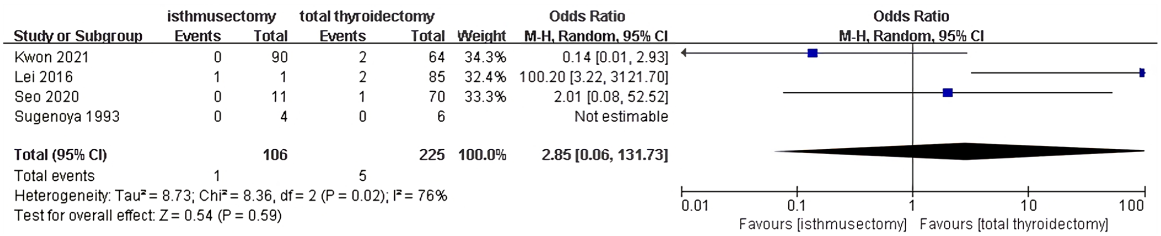

Figure 6 Meta-analysis of recurrence rates between isthmusectomy and total thyroidectomy. M-H, Mantel-Haenszel; CI, confidence interval.

15 tumor recurrences in the trial group and nine tumor recurrences in the control group. The analysis showed (*Figure 8*) that there was significant study heterogeneity (P=0.10; I^2=63%). The combined effect resulted in an OR of 1.04 (95% CI: 0.14, 7.51), indicating no significant difference in tumor recurrence rates between the trial and control groups (P=0.97).

Incidence of complications

Among them, the article published by Lei in 2016 did not elaborate on the complications, we sought the original data from the authors and entered it into our original data table for further analysis after obtaining their consent (22). The statistics showed that the postoperative complication rates ranged from 0% to 48.21% in the trial group and from 17.65% to 67.19% in the control group. And the opposite results were obtained in all four studies except for Zhang's study in which less-than-total thyroidectomy patients had a higher complication rate than total thyroidectomy patients (24).

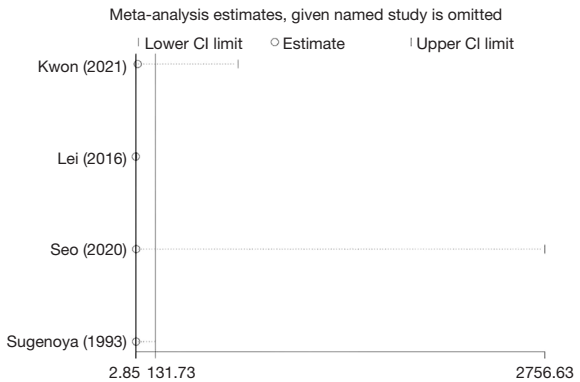

Figure 7 Sensitivity analysis of recurrence rates between isthmusectomy and total thyroidectomy. X-axis represents the OR. CI, confidence interval; OR, odds ratio.

There was significant heterogeneity in the studies (P<0.00001; I^2=94%). Applying sensitivity analysis, the results are shown in *Figure 9*. None of the included studies affected the overall results and therefore the overall results can be considered stable and reliable. Using a random effects model analysis, the combined effect results OR, 0.22, 95% CI: 0.03, 1.92, and the incidence of complications was similar between patients in the trial and control groups, with no statistical difference (P=0.17) (*Figure 10*).

Transient parathyroidism

We analyzed the rate of transient parathyroidism using a random effects model, and the results showed (*Figure 11*) that there was no significant difference in the rate of transient parathyroidism between the trial and control groups (OR, 0.24; 95% CI: 0.02, 2.32). The *Z* test showed the *Z* value to be 1.23, P>0.05, and the difference was not statistically significant. It should be noted that the analysis was highly heterogeneous, with I^2>75%. Sensitivity analysis of transient parathyroidism using Stata revealed that Zhang's article had a significant effect on overall heterogeneity (24), with I^2=0 after removing this article (*Figure 12*).

They divided the PTCI patients into four groups (group A: total thyroidectomy + unilateral central neck dissection; group B: total thyroidectomy + bilateral central neck dissection; group C: less-than-total thyroidectomy + unilateral central neck dissection; group D: less-than-total thyroidectomy + bilateral central neck dissection). They concluded from a pairwise comparison of the four groups that patients with PTCI who underwent total thyroidectomy + bilateral central neck dissection were more likely to suffer from transient parathyroidism than patients who underwent less-than-total thyroidectomy + bilateral central neck dissection, similar to the results of other studies. For better analysis, we combined group A with group B and group C with group D, and came to an opposite conclusion to the original article, that less-than-total thyroidectomy was more likely to occur with transient

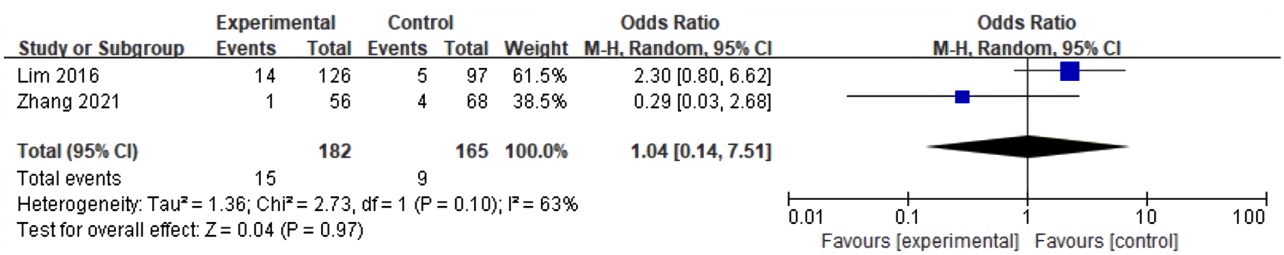

Figure 8 Meta-analysis of tumor recurrence rate after adjusting tumor stage. M-H, Mantel-Haenszel; CI, confidence interval.

parathyroidism. This may be the reason for the greater effect of Zhang's article on overall heterogeneity (24).

Permanent parathyroidism

Similarly, we analyzed the rate of permanent parathyroidism using the random effects model, and five studies described the number of PTCI patients with permanent parathyroidism in each group. The analysis showed (*Figure 13*) that there was no significant difference in the rate of permanent parathyroidism between the trial and control groups (OR, 0.18; 95% CI: 0.02, 1.37). The *Z* test showed *Z* value of 1.66, P>0.05, and the difference was not statistically significant. This analysis had moderate to high heterogeneity with an I^2>50%. Performing the sensitivity analysis, we found that Zhang's literature influenced the overall homogeneity (24), and after removing this literature, I^2=0 (*Figure 14*).

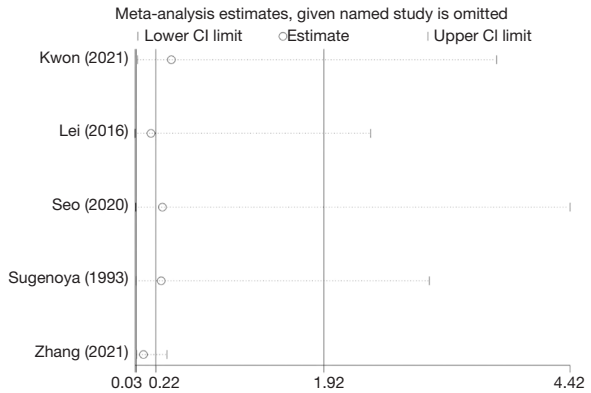

Figure 9 Sensitivity analysis of complications rate. X-axis represents the OR. CI, confidence interval; OR, odds ratio.

Transient laryngeal recurrent nerve injury

A total of four articles reported detailed data on the occurrence of transient laryngeal recurrent nerve injury in postoperative patients with a total of 502 patients, of which 10 and 12 cases of postoperative transient laryngeal recurrent nerve injury occurred in the control and trial groups, respectively. In the Kwon 2021 study, the rate of transient laryngeal recurrent nerve injury was 0 in both groups (21). We used a random-effects model with a combined-effects outcome OR, 1.72, 95% CI: 0.41, 7.18, and the rate of postoperative transient laryngeal recurrent nerve injury was similar in the trial and control groups with

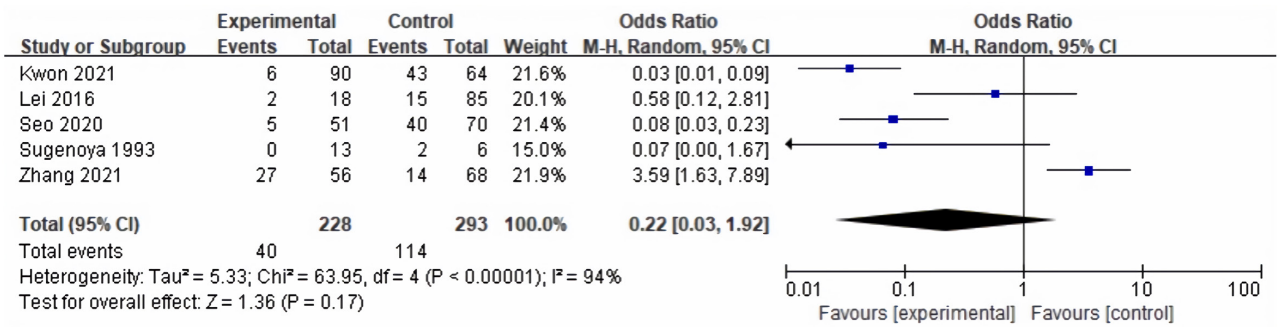

Figure 10 Meta-analysis of the incidence of complications. M-H, Mantel-Haenszel; CI, confidence interval.

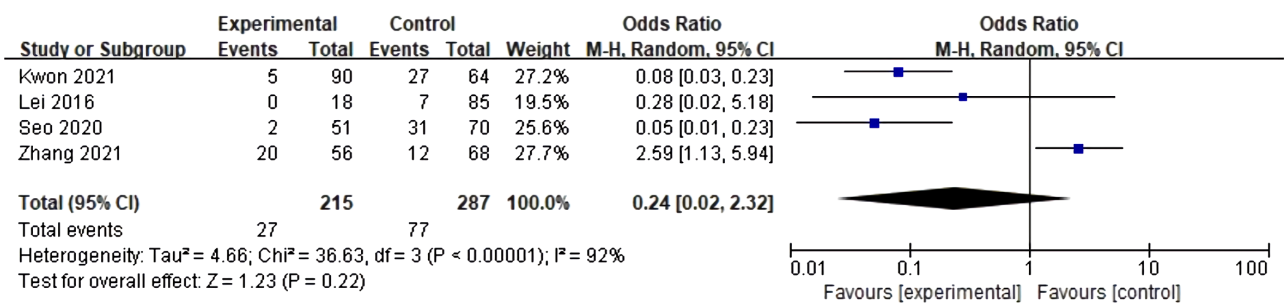

Figure 11 Meta-analysis of transient parathyroidism rate. M-H, Mantel-Haenszel; CI, confidence interval.

no statistical difference (P=0.19) (*Figure 15*).

Permanent laryngeal recurrent nerve injury

Of the seven included studies, no patients had permanent laryngeal recurrent nerve injury after surgery, except for the study by Sugenoya and Gui *et al.* (23,27), in which the occurrence of permanent laryngeal recurrent nerve injury was not described in detail, so no meta-analysis was performed for this complication outcome in this paper.

Postoperative infections

Two articles reported in detail on the data of the occurrence of postoperative infections of a total of 227 patients, including 153 in the control group with 1 case of postoperative infection and 74 in the trial group, also with only one case of postoperative infection. The exact number of wound infections was not mentioned in detail in the Lei 2016 literature, and we obtained details of the occurrence of postoperative complications by contacting the authors (22). Since no significant heterogeneity existed (P=0.70; I^2=0%), fixed-effects model was used. The combined effect results OR, 2.51, 95% CI: 0.28, 22.20, the incidence of infection was similar in the trial and control groups with no statistical difference (P=0.41) (*Figure 16*).

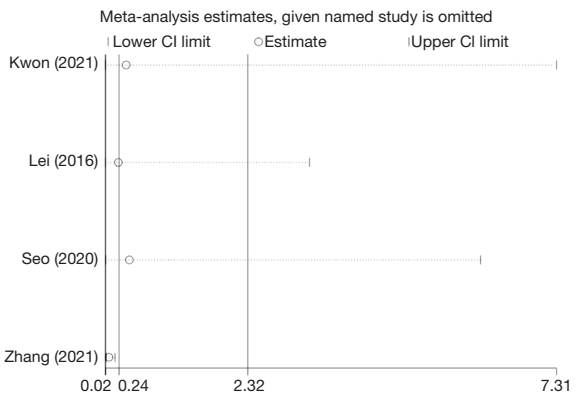

Figure 12 Sensitivity analysis of temporary parathyroidism rate. X-axis represents the OR. CI, confidence interval; OR, odds ratio.

Comparison of postoperative complications between thyroid lobectomy plus isthmusectomy and total thyroidectomy

Among the three articles included in this study, which specifically reported the total number of patients who underwent thyroid lobectomy plus isthmusectomy and the number of those who experienced postoperative complications, Lei's 2016 article was derived from original data provided by the authors. Four patients in the thyroid lobectomy plus isthmusectomy group experienced postoperative complications, yielding a complication rate of 7% (22). In the total thyroidectomy group, postoperative complications affected 57 patients, resulting in a complication rate of 35.4%. The results, analyzed using a random-effects model, revealed that the rate of postoperative complications in the thyroid lobectomy plus isthmusectomy group was significantly lower than in the total thyroidectomy group (OR, 0.10; 95% CI: 0.04, 0.29; P<0.0001), and this difference was statistically significant. The analysis exhibited low heterogeneity, with I^2 at 0% (*Figure 17*).

Comparison of postoperative complications between extended isthmusectomy and total thyroidectomy

In this study, only two articles provided specific information about the number of patients who underwent extended isthmusectomy and the number of those who experienced postoperative complications. Out of 100 enrolled patients, postoperative complications were observed in only one patient in the extended isthmusectomy group and nine

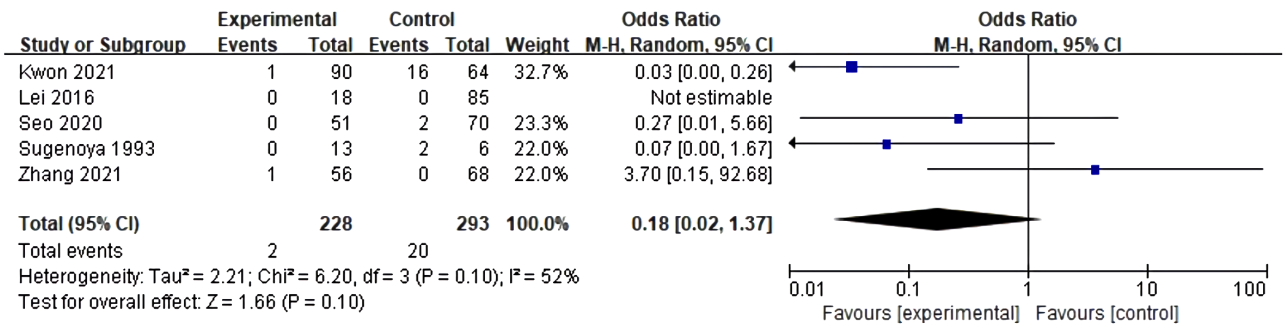

Figure 13 Meta-analysis of permanent parathyroidism rate. M-H, Mantel-Haenszel; CI, confidence interval.

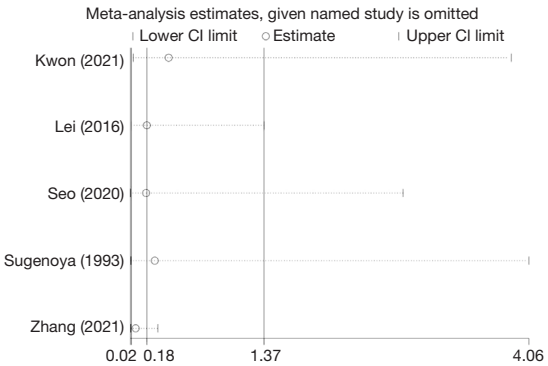

Figure 14 Sensitivity analysis of permanent parathyroidism rate. X-axis represents the OR. CI, confidence interval; OR, odds ratio.

patients in the total thyroidectomy group. Analysis of the results using a random-effects model indicated no significant difference in the likelihood of postoperative complications between the two groups (OR, 1.20; 95% CI: 0.01, 143.63; P=0.94). It is important to note that this analysis displays high heterogeneity with I^2>75% (*Figure 18*).

Comparison of postoperative complications between isthmusectomy and total thyroidectomy

In this study, four articles provide detailed information about the individuals who underwent isthmusectomy and the incidence of postoperative complications. Out of 331 patients, eight experienced postoperative complications in

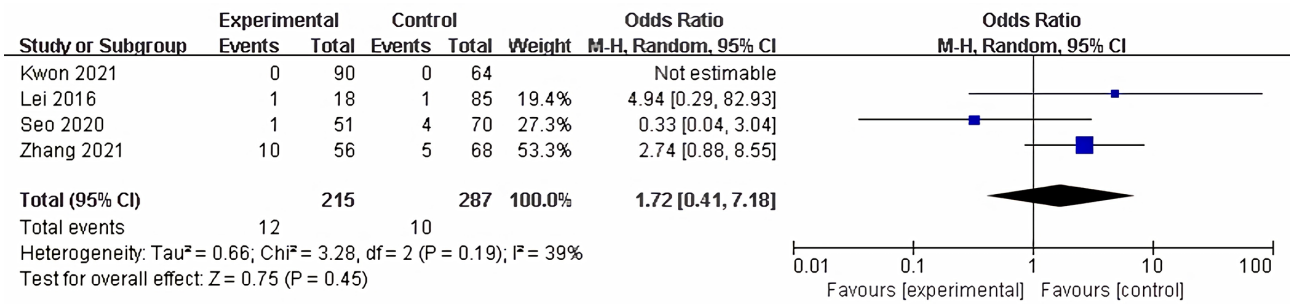

Figure 15 Meta-analysis of transient laryngeal recurrent nerve injury rate. M-H, Mantel-Haenszel; CI, confidence interval.

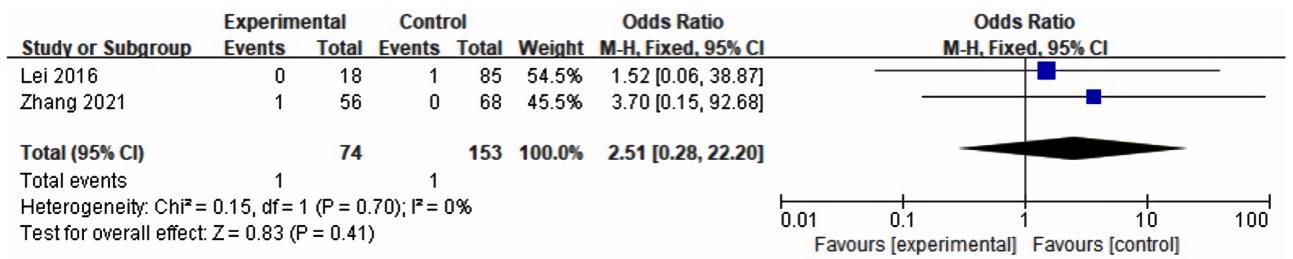

Figure 16 Meta-analysis of postoperative infection rate. M-H, Mantel-Haenszel; CI, confidence interval.

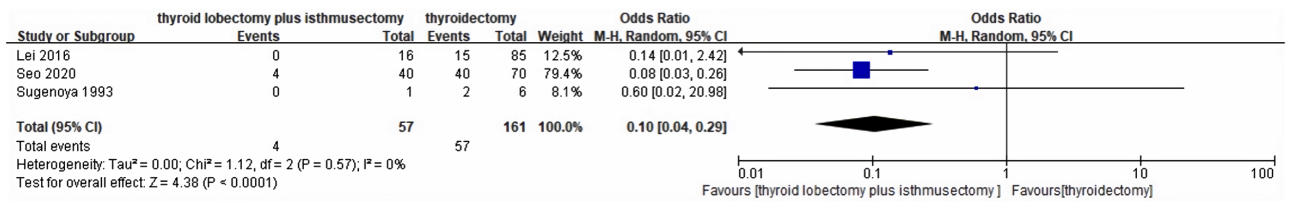

Figure 17 Meta-analysis of postoperative complications rates between thyroid lobectomy plus isthmusectomy and total thyroidectomy. M-H, Mantel-Haenszel; CI, confidence interval.

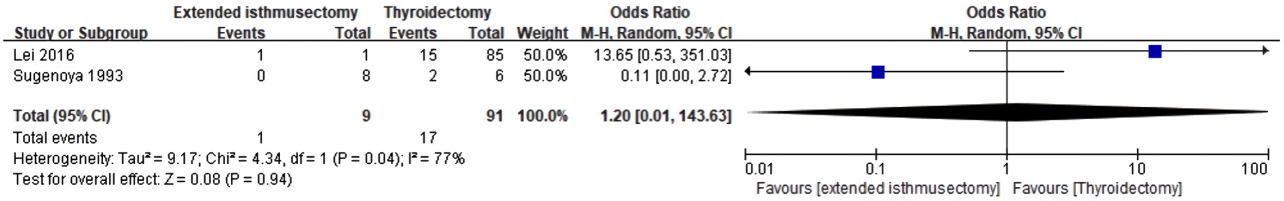

Figure 18 Meta-analysis of postoperative complications rates between extended isthmusectomy and total thyroidectomy. M-H, Mantel-Haenszel; CI, confidence interval.

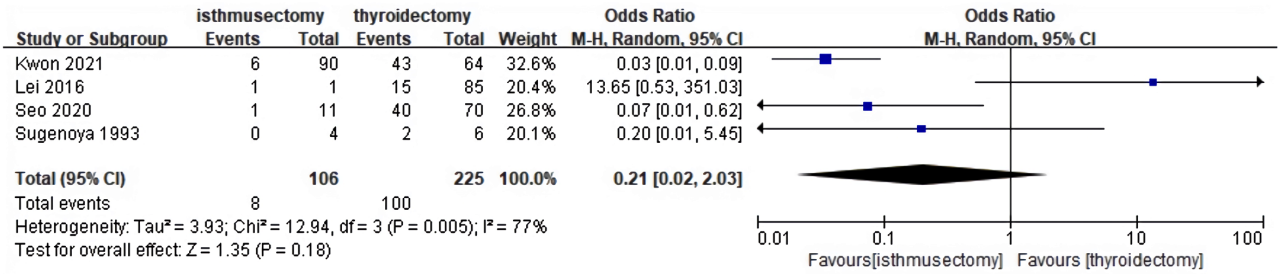

Figure 19 Meta-analysis of postoperative complications rates between isthmusectomy and total thyroidectomy. M-H, Mantel-Haenszel; CI, confidence interval.

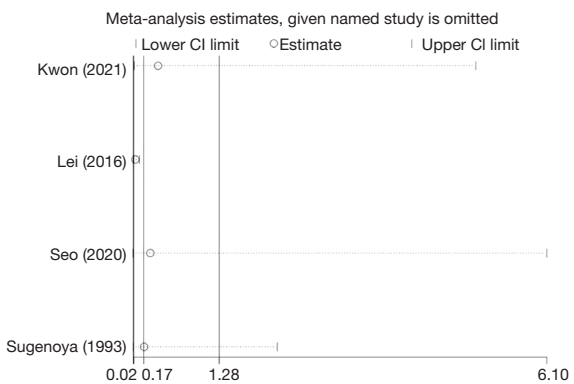

Figure 20 Sensitivity analysis of postoperative complications rates between isthmusectomy and total thyroidectomy. X-axis represents the OR. CI, confidence interval; OR, odds ratio.

the isthmusectomy group, while 100 patients in the total thyroidectomy group had postoperative complications. Analysis using a random-effects model revealed no significant difference in the likelihood of postoperative complications between the two groups (OR, 0.21; 95% CI: 0.02, 2.03; P=0.18) (*Figure 19*). This analysis exhibited high heterogeneity, with I^2>75%. We conducted a sensitivity analysis of postoperative complications in both groups using Stata and observed that the inclusion of Lei's article influenced overall homogeneity (22), reducing I^2 to 0% after its removal (*Figure 20*).

Discussion

In this study, we performed a systematic review and meta-analysis of articles published up to 2023 on comparing the clinical outcomes of different surgical approaches in the treatment of PTCI. We mainly compared the tumor recurrence rate and the rate of various complications between total thyroidectomy and less-than-total thyroidectomy (including isthmusectomy, extended isthmusectomy, and thyroid lobectomy plus isthmusectomy). Owing to the scarcity of articles comparing the effectiveness of surgical treatments for PTCI and the predominance of retrospective studies with limited quality of evidence, considerable controversies persist regarding the selection of surgical approaches for PTCI patients in both China and internationally. To our knowledge, this is the first systematic review and meta-analysis comparing total thyroidectomy with less-than-total thyroidectomy for PTCI.

The discussion of which surgical procedure should be performed for PTCI has been ongoing since the late 20th century. Authoritative associations such as the ATA

and the European Thyroid Association (ETA) have not clearly recommended the extent of surgical resection for PTCI (19,28). However, there seems to be consensus on the biological characteristics and clinical features that distinguish PTCI from PTC, i.e., PTCI has a higher rate of perineural invasiveness, ETE, multifocality, and lymph node metastasis (8,9,16,29). The choice of surgical scope for PTCI can be divided into two groups of researchers, one supporting total thyroidectomy and the other favoring less-than-total thyroidectomy.

During 2015–2016, there was a majority of studies supporting total thyroidectomy, such as Karatzas' study showing that total thyroidectomy and central lymph node dissection can be considered as suitable treatment modalities for PTCI regardless of tumor size (5). Wang recommended total thyroidectomy and prophylactic bilateral central neck dissection for male PTCI patients who were under 38 years old and had tumors larger than 0.6 cm (30). In the largest retrospective study of PTCI surgical approaches to date, Lim concluded that patients with tumor size greater than 1 cm who underwent total thyroidectomy had a better prognosis (7). In addition to this, other scholars have come to the same conclusion by studying the clinicopathological features and surgical outcomes of PTCI, that total thyroidectomy seems to be the appropriate surgical option for PTCI (3,8,15,18,22,31).

Conversely, other researchers have suggested that more conservative operations are appropriate for PTCI. For example, earlier, it was demonstrated that isthmusectomy was effective and safe for patients with PTCI (24,32). In 2011, Nixon concluded in a small case study that thyroidectomy may be an adequate treatment for PTCI patients without lymph node metastases, with 100% 10-year survival and 100% local and regional 10-year recurrence-free survival in 19 patients (33). In 2016, Lim *et al.* also recommended thyroid lobectomy + isthmusectomy for PTCI patients with tumor size less than 1 cm in the aforementioned retrospective study (7). Also in 2016, the ATA issued new guidelines for the treatment of thyroid nodules, with the option of lobectomy plus isthmusectomy for patients with T1b and T2 and negative lymph nodes (19). In contrast, the 2009 ATA guidelines for these patients recommend total thyroidectomy (34).

Since the publication of the new guidelines, thyroid surgery has favored a more conservative surgical approach to reduce trauma and postoperative complications. Interestingly, we found that most of the articles in support of less-than-total thyroidectomy for PTCI was published in the last 3 years. For example, in 2020, Seo *et al.* studied 121 PTCI patients, and they found no difference in tumor recurrence and survival rates between the three groups of patients who underwent total thyroidectomy, thyroid lobectomy + isthmusectomy, and isthmusectomy, with thyroid isthmus resection being an effective treatment for small unilateral isthmus PTC (4). In the same year, Gui *et al.* investigated patients with isthmus PTMC and came to the same conclusion that conservative surgery should be performed when possible (27). Park *et al.* confirmed that isthmusectomy was an acceptable procedure for PTCI patients with low- and intermediate-risk (32). In 2021, Kwon recommended isthmus resection combined with prophylactic central compartment neck dissection as the preferred surgical approach for PTCI (21). Zhang *et al.* proposed less-than-total thyroidectomy for PTCI patients with cT1N0M0 and less-than-total thyroidectomy + central lymph node dissection for patients with tumor size ≥0.55 cm and age >55 years who were prone to central occult lymph node metastasis (24). Seven studies were included in this study for the primary outcome, and the results showed no significant difference in the effect of total thyroidectomy and less-than-total thyroidectomy on the rate of tumor recurrence in PTCI. It is important to note that the underlying conditions of the patients included in these studies varied widely. For instance, Lim and Zhang's study strictly limited the TNM stage of patients, and they included only patients with cT1N0M0, while other studies may have included patients with more advanced stages (7,24). Different staging will directly affect the tumor recurrence rate and prognosis of patients, and the follow-up time, patient age, tumor size, tumor multifocality, and preoperative lymph node metastasis, which are all factors influencing the tumor recurrence rate, vary between studies. Therefore, there is no way to prove that a certain surgical approach is suitable for all PTCI patients, and it is more reasonable to choose the surgical approach on an individual basis. The choice of surgical modality for PTCI patients with specific different stages still requires more studies for subgroup analysis. Furthermore, we conducted an additional analysis to determine if there were differences in tumor recurrence rates among the three less-than-total thyroidectomy surgical approaches compared to total thyroidectomy. Extended isthmusectomy could not be compared to total thyroidectomy. The results indicated that there was no significant difference in the tumor recurrence rate when comparing the isthmusectomy to total thyroidectomy. Nevertheless, the tumor recurrence rate

was higher in the thyroid lobectomy plus isthmusectomy group compared to the total thyroidectomy group. We hypothesize that this might be due to the choice of a more conservative surgical approach by some high-risk recurrence patients.

Rather dubiously, our analysis of postoperative complications revealed no statistical difference between the trial and control groups in terms of overall complications and each postoperative complication. By broad consensus and experience, the complication rate due to total thyroidectomy should be higher than that due to less-than-total thyroidectomy (35-37). Hence, we conducted a further comparison of postoperative complication rates among the three less-than-total thyroidectomy surgical approaches in relation to total thyroidectomy, with the goal of investigating the potential impact of different surgical techniques on our findings. The results indicated that only the thyroid lobectomy plus isthmusectomy group exhibited a significantly lower postoperative complication rate compared to the total thyroidectomy group, while the complication rates of the other two surgical approaches did not show significant differences from those of total thyroidectomy. We believe that the occurrence of postoperative complications is not only related to the surgical approach. Experienced surgeons and intraoperative monitoring may help to reduce the occurrence of complications. Also, it is possible that hospitals have a reporting bias in reporting the number of patients with postoperative complications.

We acknowledge that there are several limitations that should be considered when interpreting our current meta-analysis. First, only four English databases were searched in this study, and for technical reasons, not all gray literature, including conference abstracts, letters, and unpublished data, was retrieved, which may lead to publication bias. Second, the articles we included were retrospective studies, and there was certain heterogeneity in the studies. In the future, more reliable conclusions will be obtained if more RCTs are included or if data from individual patients are extracted for pooled data analysis. Third, in the study of complications, postoperative complication rates were low in most articles, which may make it difficult to show differences in complications between the two groups. Fourth, the number of articles meeting the inclusion criteria for this study was limited. Furthermore, when narrowing down the surgical modalities for analysis, the number of eligible articles further decreased, and some elements could not be analyzed due to missing data. Nevertheless, the conclusions obtained in this study should be taken into account, namely, that for PTCI patients, a certain surgical approach cannot be uniformly adopted due to their unique biological characteristics and clinical features, and individualized surgery is more worthy of consideration.

Conclusions

PTCI patients with earlier staging and no significant lymph node metastases may be able to choose a more conservative surgical approach, i.e., less-than-total thyroidectomy (including isthmusectomy, extended isthmusectomy, isthmusectomy plus lobectomy, etc.). In contrast, patients with relatively late staging and significant preoperative lymph node metastases or ETE may opt for total thyroidectomy + lymph node dissection in the central region.

Acknowledgments

We are grateful to Dr. Jianyong Lei of the Division of Thyroid & Parathyroid Surgery, Department of General Surgery, West China Hospital Sichuan University, who provided the original data of his study (Surgical procedures for papillary thyroid carcinoma located in the thyroid isthmus: an intention-to-treat analysis) for us to analyze. We sincerely thank Hiru M, West China School of Medicine, Sichuan University, for her invaluable linguistic editorial contribution to this article.

Funding: This article was financially supported by the Science & Technology Department of Sichuan Province (No. 2021YFS0103 to Anping Su), the Health Commission of Sichuan Province (No. 20PJ057 to Anping Su), and the China Health Promotion Foundation (No. HX22-228/HX-H2204083 to Anping Su).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-300/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-300/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-300/

coif). A.S. was supported by research grants from the Science & Technology Department of Sichuan Province (No. 2021YFS0103), the Health Commission of Sichuan Province (No. 20PJ057), and the China Health Promotion Foundation (No. HX22-228/HX-H2204083). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. As this study is a systematic review and meta-analysis, informed consent was not required.

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Cite this article as: Gong H, Jiang Y, Su A. Total thyroidectomy versus less-than-total thyroidectomy for papillary thyroid carcinoma of isthmus: a systematic review and meta-analysis. Gland Surg 2023;12(11):1525-1540. doi: 10.21037/gs-23-300