

Total endoscopic thyroidectomy versus conventional open thyroidectomy in thyroid cancer: a systematic review and meta-analysis

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Background: Despite the considerable experience gained thus far using endoscopic technologies, the role of total endoscopic thyroidectomy (ET) for papillary thyroid cancer (PTC) remains controversial. We conducted a systematic review and meta-analysis to investigate the safety and effectiveness of total ET compared with conventional open thyroidectomy (OT) in PTC.

Methods: A systematic search was conducted using the PubMed, Embase and Cochrane Library electronic databases up to March 2018. The quality of included studies was evaluated using the Newcastle–Ottawa Scale. Review Manager software version 5.3 was used for the meta-analysis.

Results: Twelve studies including 2,672 patients were ultimately included in the systematic review and meta-analysis. ET was associated with longer operative time ($P < 0.00001$), drainage time ($P < 0.00001$) and hospital stay ($P = 0.03$), higher transient recurrent laryngeal nerve (RLN) palsy rate ($P = 0.004$) and a greater amount of drainage fluid ($P < 0.0001$) compared with OT. Furthermore, no significant differences were detected between ET and OT in terms of retrieved lymph nodes ($P = 0.17$), blood loss ($P = 0.22$), transient hypocalcemia ($P = 0.84$), permanent hypocalcemia ($P = 0.58$), permanent RLN palsy ($P = 0.14$), hematoma or bleeding ($P = 0.15$) and seroma ($P = 0.54$). In addition, the rates of tumor recurrence were comparable ($P = 0.18$), whereas the proportions of stimulated thyroglobulin levels < 1 ng/mL measured after completion of thyroidectomy and radioactive iodine therapy were less ($P = 0.02$) in the ET than in the OT group.

Conclusion: ET is not superior to OT in terms of operation and drainage time, amount of drainage fluid, hospital stay or transient RLN palsy, but is comparable to OT in terms of retrieved lymph nodes and permanent complications. Despite the similar tumor recurrence rates between the two approaches, the level of surgical completeness in ET may not be as good as that for OT.

Keywords: endoscopic thyroidectomy, conventional open thyroidectomy, papillary thyroid carcinoma, meta-analysis

Background

Thyroid cancer is considered the most prevalent endocrine cancer, especially in women.^{1,2} Papillary thyroid cancer (PTC), the major histological subtype, constitutes approximately 85% of all thyroid malignancies.³ Although conventional open thyroidectomy (OT) is a standard surgery with low morbidity and minimal mortality for PTC,⁴ it requires a cervical incision in the neck. Nevertheless, the cosmetic outcome may be a particular concern, especially in young women.

The popularity of endoscopic technologies has allowed surgeons to complete resection and simultaneously deliver cosmetic results. In 1997, Hüscher et al first

performed endoscopic thyroidectomy (ET).⁵ Since then, various ET approaches have evolved, such as breast,⁶ axillary,⁷ axillobreast,⁸ submental⁹ and oral cavity approaches.¹⁰ However, endoscopic techniques present some difficulties in obtaining adequate surgical views because of the small working space and two-dimensional operative views.¹¹ In addition, surgical indications for ET remain ambiguous, and the benefits of ET are considered marginal for PTC.^{12,13} Some studies have even questioned the safety of ET for PTC and proposed that this method should be critically evaluated.^{14,15} Thus, it remains unsettled whether ET is effective and safe compared with OT.

To our knowledge, only one meta-analysis comparing outcomes between ET and OT has been published.¹⁶ However, the previous meta-analysis was conducted on five studies and focused on patients with papillary thyroid microcarcinoma (PTMC). Given the growing number of publications on this debatable subject and the extended indications for ET,⁷ it is necessary to perform a systematic meta-analysis to compare the effectiveness and safety of ET with OT in PTC patients.

Materials and methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA statement.¹⁷

Search strategy

A systematic search was conducted using the PubMed, Embase and Cochrane Library electronic databases on 15 March 2018. We used the following keywords and Medical Subject Headings (MeSH) terms: “laparoscopy” or “endoscopy” or “minimally invasive surgery” or “video-assisted surgery” and “thyroidectomy” and “thyroid cancer”. We also reviewed the reference lists from the retrieved articles.

Study selection

Two independent authors (CC and SMH) reviewed study titles and abstracts to exclude irrelevant articles, and studies meeting the inclusion criteria were selected for full-text assessment. Any discrepancy was resolved by consensus. The inclusion criteria were as follows: 1) English language; 2) comparative studies between ET and OT for patients with PTC; 3) studies comparing at least one outcome of surgery; and 4) multiple studies from the same institution were assessed and the highest quality and most up-to-date of these was retained. The exclusion criteria were as follows: 1) studies that were reviews, case reports, letters, conferences, editorials, or expert opinions; 2) studies that focused

on patients with thyroid cancer other than PTC; and 3) studies reporting on the pediatric population.

Data extraction and quality assessment

Data were extracted into prepared standardized forms by two independent reviewers.

The primary data extracted from each study included the first author, year of publication, geographical region, study type, number of patients, patient demographics, pathological characteristics of PTC, operative details (extent of thyroidectomy, surgical approach), intraoperative outcomes, postoperative outcomes and oncological outcomes (stimulated thyroglobulin [sTg], tumor recurrences). Intraoperative outcomes included operative time, blood loss and the number of retrieved lymph nodes. Postoperative outcomes included hospitalization period after the operation, volume and duration of drainage, postoperative complications (transient hypocalcemia, permanent hypocalcemia, transient recurrent laryngeal nerve [RLN] palsy, permanent RLN palsy, hematoma or bleeding, and seroma). Total thyroidectomy (TT) included near-TT and TT, whereas less than total thyroidectomy (LTT) included hemithyroidectomy and subtotal thyroidectomy. The sTg level was measured after total completion of thyroidectomy and radioactive iodine therapy and defined as <1.0 ng/mL as an indicator of surgical completeness. Any disagreement was resolved by discussion and consensus.

The quality assessment of nonrandomized studies was also performed by two independent reviewers using the Newcastle–Ottawa Scale, with some modifications to match the requirements of this study.^{18,19} The quality was assessed based on three aspects: patient selection, comparability of groups and outcome assessment. Only studies awarded six or more stars were considered as high-quality studies.

Statistical analysis

Review Manager software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) was used for data analysis. For continuous outcomes, the weighted mean differences (WMDs) with corresponding 95% CIs were calculated. For dichotomous outcomes, the ORs with corresponding 95% CIs were examined. The results were analyzed using fixed- or random-effects models, depending on the heterogeneity involved. The statistical heterogeneity was assessed by the Cochran Q test and evaluated the extent of inconsistency by the I^2 statistic, which was divided into three degrees including low (25%–49%), moderate (50%–74%) and high ($\geq 75\%$) levels.²⁰ When $P > 0.1$

and $I^2 < 50\%$, a fixed-effects model was used; otherwise, a random-effects model was applied. We used the following methods to explore sources of heterogeneity: 1) subgroup analysis (TT and LTT) and 2) sensitivity analysis conducted by excluding each of the included studies to identify which studies influenced the degree of heterogeneity. The possible presence of publication bias was estimated by Egger's test and Begg's test, investigated using STATA version 12.0 (Stata Corporation, College Station, TX, USA). P -values < 0.05 were considered statistically significant.

Results

Study selection

The initial search yielded 2,633 potentially relevant articles. Seventeen potential articles were identified after screening titles and abstracts. After full-text review, an additional five articles were excluded for the following reasons: including cases of follicular thyroid cancer ($n=1$),²¹ cohorts may have overlapped ($n=2$)^{22,23} and some conflicts in articles ($n=2$).^{24,25} Finally, 12 observational articles were obtained for final analysis (Figure 1).^{7,26-36}

Study and patient characteristics

Table 1 shows the total number of 2,672 PTC patients included, of whom 799 underwent ET and 1,873 underwent OT. Eight studies^{26-30,32-34} were performed in the Republic of Korea and four studies^{7,31,35,36} in China. All 12 studies were retrospective. In terms of surgical approach, in six studies the axillobreast approach (ABA) was performed,^{26-28,32-34}

in three studies the bilateral breast approach (BBA) was performed,^{31,35,36} in two studies the transaxillary approach (TAA) was performed,^{7,30} and in the remaining study either ABA or TAA was performed for thyroidectomy.²⁹ The pathological details of each study are summarized in Table 2.

Meta-analysis of intraoperative outcomes

Eleven studies calculated operative times for ET vs OT,^{7,26-32,34-36} and the operation time in the ET group was significantly longer than that in the OT group (WMD 50.46, 95% CI 40.50 to 60.42, $P < 0.00001$). However, there was a high level of heterogeneity among the studies ($I^2 = 87\%$, $P < 0.00001$). The meta-analysis results remained unaffected when each individual study was removed from the data set.

Ten studies presented the number of retrieved lymph nodes,^{7,27-35} and the pooled data showed no significant differences between groups (WMD -0.53 , 95% CI -1.29 to 0.22 , $P = 0.17$). Furthermore, there was a high level of heterogeneity among the studies ($I^2 = 80\%$, $P < 0.00001$). After excluding the study by Lee et al,³³ there were still no significant differences between groups (WMD -0.14 , 95% CI -0.47 to 0.20 , $P = 0.42$), but no heterogeneity was observed among the studies ($I^2 = 0\%$).

Four studies^{7,31,34,36} compared intraoperative blood loss and the pooled data showed no significant differences between groups (WMD 4.37 , 95% CI -2.62 to 11.36 , $P = 0.22$). In addition, there was a moderate level of heterogeneity

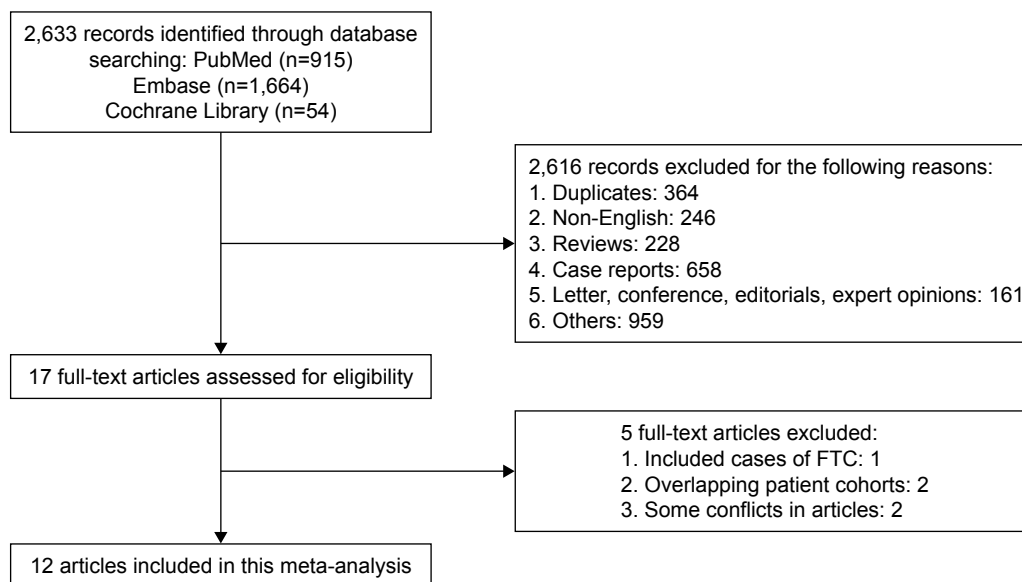


Figure 1 Flow diagram for study selection.

Abbreviation: FTC, follicular thyroid cancer.

Table 1 General characteristics of studies included in the meta-analysis

Study (first author, year)	Region	Study type	No of patients		Age (years), mean ± SD		Gender, M/F		Extent of thyroidectomy, TT/LTT		Surgical approach	Matching ^a	Quality score
			ET	OT	ET	OT	ET	OT	ET	OT			
Chung 2007 ²⁶	Korea	RS	103	198	38.2±8.2	47.2±10.2	1/102	25/173	88/15	172/26	BABA	4, 9	6
Hong 2011 ²⁷	Korea	RS	57	60	39.60±9.61	41.77±9.61	6/51	11/49	0/57	0/60	BABA/UABA	1, 2, 4, 7, 9	7
Kim 2011 ²⁸	Korea	RS	95	138	39.9±9.1	51.8±8.9	2/93	34/104	95/0	138/0	BABA	9	6
Tae 2011 ²⁹	Korea	RS	31	36	36.2±9.9	44.6±11.8	1/30	11/25	3/28	0/36	UABA/TAA	4-9	7
Lee 2012 ³⁰	Korea	RS	37	41	42.3±7.6	49.0±10.8	0/37	3/38	0/37	0/41	TAA	2, 4, 5, 7-9	7
Tan 2015 ³¹	China	RS	34	30	30 (16-44) ^b	43 (25-76) ^b	2/32	4/26	0/34	0/30	BBA	2, 4, 9	7
Huang 2016 ⁷	China	RS	75	123	37.8±10.6	39.2±11.3	16/59	31/92	75/0	123/0	TAA	1-5, 7-9	7
Kim 2016 ³²	Korea	RS	173	830	38.90 (17-57) ^b	49.53 (17-84) ^b	13/160	96/734	56/117	684/146	BABA	2	5
Lee 2016 ³³	Korea	RS	75	233	42.2±8.6	52.1±9.3	3/72	15/218	0/75	0/233	BABA/UABA	2, 4, 5, 7, 9	6
Park 2016 ³⁴	Korea	RS	50	102	38.0±9.4	50.8±11.5	4/46	14/88	50/0	102/0	UABA	2, 4-7, 9	5
Xiang 2016 ³⁵	China	RS	49	47	34.2±7.0	46.9±13.3	0/49	6/41	49/0	47/0	BBA	7, 9	6
Ren 2017 ³⁶	China	RS	20	35	36.05±5.646	36.06±5.646	0/20	0/35	0/20	0/35	BBA	1-3, 9	6

Notes: ^aFeatures matching ET and OT: 1 = age; 2 = gender; 3 = body mass index; 4 = tumor size; 5 = multiplicity; 6 = bilaterality; 7 = extrathyroidal extension; 8 = tumor stage; 9 = extent of thyroidectomy. ^bMedian (range). Abbreviations: BABA, bilateral axillobreast approach; BBA, bilateral breast approach; ET, endoscopic thyroidectomy; M, male; LTT, less than total thyroidectomy; OT, open thyroidectomy; RS, retrospective study; TAA, transaxillary approach; TT, total thyroidectomy; UABA, unilateral axillobreast approach.

among the studies ($I^2=72\%$, $P=0.01$). After removing the study by Huang et al,⁷ the results became significant (WMD 7.24, 95% CI 1.66 to 12.82, $P=0.01$) and the heterogeneity among the studies no longer existed ($I^2=0\%$) (Table 3 and Figure 2A-C).

Meta-analysis of postoperative outcomes

Three studies^{31,34,36} reported the duration of drainage and suggested a longer drainage period in ET than in OT (WMD 1.88, 95% CI 1.22 to 2.54, $P<0.00001$). Furthermore, this result showed a high level of heterogeneity as well ($I^2=76\%$, $P=0.01$). After removing the study by Park et al,³⁴ the significance of the result was unchanged (WMD 2.20, 95% CI 1.82 to 2.59, $P<0.00001$), but no heterogeneity existed across the studies ($I^2=0\%$).

Five studies^{28,29,31,34,36} assessed the volume of drainage and described a larger amount of drainage in the ET group (WMD 111.96, 95% CI 61.66 to 162.26, $P<0.00001$). In addition, there was a high level of heterogeneity among the studies ($I^2=95\%$, $P<0.00001$). After removing the study by Kim et al,²⁸ the previously high heterogeneity dramatically declined ($I^2=37\%$, $P=0.19$), but the significance of the result was unaffected (WMD 121.54, 95% CI 107.76 to 135.33, $P<0.00001$).

Eight studies described a hospitalization period after the operation.^{26-30,32,34,36} The combined results of these studies showed that ET had a longer hospitalization period than OT (WMD 0.65, 95% CI 0.06 to 1.24, $P=0.03$), and this result was associated with significant heterogeneity among the studies ($I^2=90\%$, $P<0.00001$). After removing the study by Hong et al,²⁷ no heterogeneity existed ($I^2=0\%$), but the significance of the result was unchanged (WMD 0.33, 95% CI 0.15 to 0.51, $P=0.0003$) (Table 3 and Figure 3A-C).

Meta-analysis of postoperative complications

Eleven studies reported the transient postoperative RLN palsy rate,^{7,26-29,31-36} whereas nine reported permanent postoperative RLN palsy rates.^{26-29,32-36} The cumulative transient RLN palsy rate was significantly higher in ET (OR 2.64, 95% CI 1.36 to 5.11, $P=0.004$), and low heterogeneity ($I^2=48\%$, $P=0.04$) was observed among the studies. The significance of the result was unchanged when removing the study by Chung et al²⁶ (OR 2.02, 95% CI 1.31 to 3.13, $P=0.002$), but the heterogeneity among studies no longer existed ($I^2=0\%$). In terms of permanent RLN palsy, no significant differences were observed between the two groups (OR 2.04,

Table 2 Pathological characteristics of studies included in the meta-analysis

Study (first author, year)	Tumor size (mm)		Multiplicity (n/N)		Bilaterality (n/N)		Extrathyroidal extension (n/N)		Positive LNs (n/N)		No of metastatic LNs	
	ET	OT	ET	OT	ET	OT	ET	OT	ET	OT	ET	OT
Chung 2007 ²⁶	<10	<10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hong 2011 ²⁷	7.25±2.30	7.10±2.65	NR	NR	NR	NR	10/57	19/60	21/57	26/60	1.30±1.83	1.43±1.87
Kim 2011 ²⁸	6.0±2.0	7.0±2.0	NR	NR	NR	NR	NR	NR	NR	NR	0.9±2.0	0.5±0.9
Tae 2011 ²⁹	7.6±4.9	6.4±2.3	2/31	2/36	0/31	0/36	2/31	1/36	4/16	2/12	NR	NR
Lee 2012 ³⁰	5.0±2.31	4.1±2.64	3/37	5/41	NR	NR	1/37	2/41	5/37	1/41	NR	NR
Tan 2015 ³¹	7.0±3.0	8.0±4.0	NR	NR	NR	NR	NR	NR	8/34	4/30	0.8±2.0	0.2±0.7
Huang 2016 ⁷	4.8±1.9	4.9±2.3	5/75	9/123	NR	NR	2/75	4/123	9/75	11/123	NR	NR
Kim 2016 ³²	NR	NR	NR	NR	NR	NR	4/173	128/830	34/173	312/830	NR	NR
Lee 2016 ³³	5.8±3.5	6.2±3.7	12/75	30/233	NR	NR	21/75	93/233	12/75	35/233	NR	NR
Park 2016 ³⁴	8.0±3.7	7.6±1.9	7/50	19/102	10/50	18/102	28/50	70/102	NR	NR	0.7±1.4	0.6±1.2
Xiang 2016 ³⁵	7.7±4.2	12.4±7.9	26/49	37/47	NR	NR	3/49	8/47	20/49	40/47	NR	NR
Ren 2017 ³⁶	<10	<10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Overall	6.4±3.2	6.7±3.7	55/317	102/582	10/81	18/138	71/547	325/1,472	113/516	431/1,376	0.9±1.8	0.7±1.3

Abbreviations: ET, endoscopic thyroidectomy; LN, lymph node; NR, not reported; OT, open thyroidectomy.

95% CI 0.80 to 5.23, $P=0.14$), and no heterogeneity existed ($I^2=0\%$).

Eight studies reported the transient postoperative hypocalcemia rate,^{26,28,29,31,32,34–36} whereas seven reported permanent postoperative hypocalcemia rates.^{26,28,29,32,34–36} No significant differences were observed between the two groups in terms of transient hypocalcemia (OR 0.93, 95% CI 0.46 to 1.87, $P=0.84$), but high heterogeneity existed ($I^2=81\%$, $P<0.0001$). The meta-analysis results remained unchanged (OR 1.26,

95% CI 0.74 to 2.16, $P=0.40$) but a moderate decline in the heterogeneity ($I^2=53\%$, $P=0.06$) was observed when the study by Kim et al was removed.³² In the case of permanent postoperative hypocalcemia, neither significant differences (OR 0.82, 95% CI 0.39 to 1.69, $P=0.58$) nor heterogeneity ($I^2=0\%$) were detected.

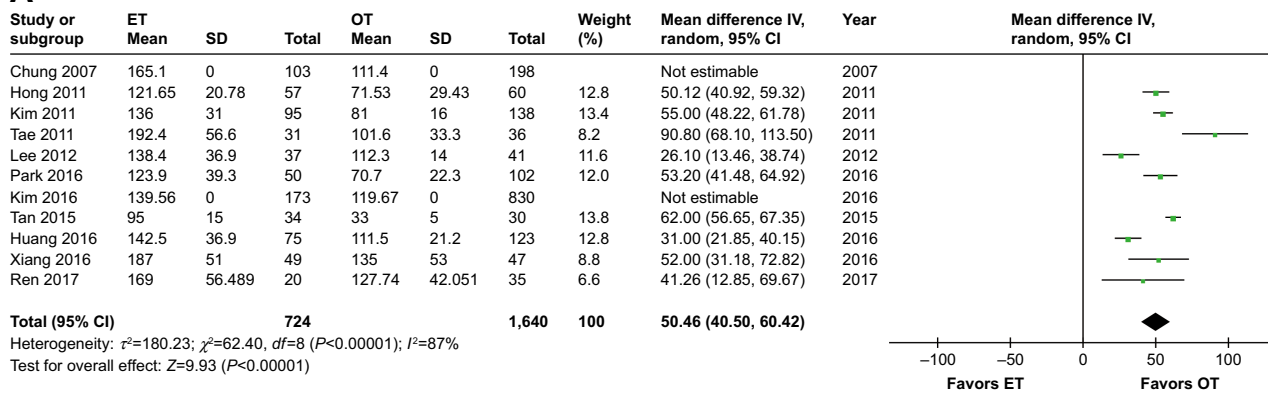
Regarding other complications, such as postoperative hematoma or bleeding (OR 1.76, 95% CI 0.81 to 3.81, $P=0.15$) and postoperative seroma (OR 1.33, 95% CI 0.53

Table 3 Outcomes of meta-analysis comparing ET vs OT

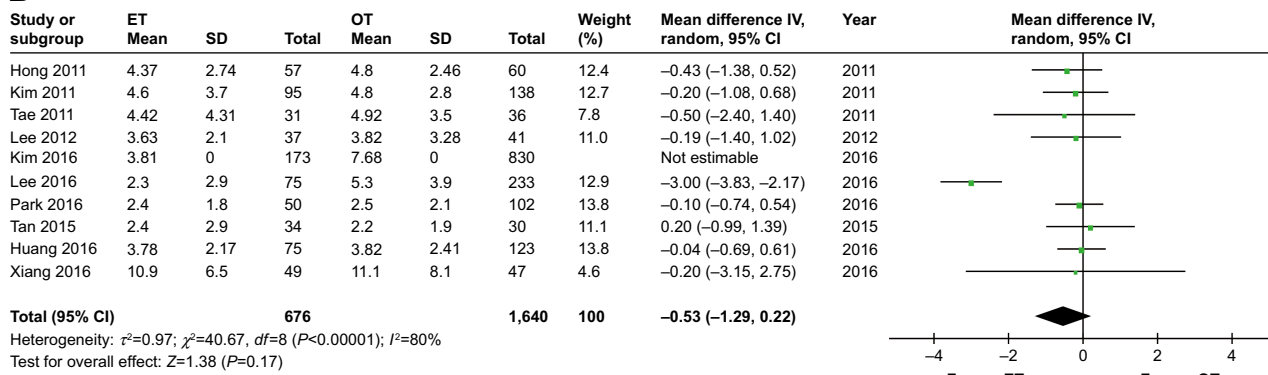
Outcomes	No of studies	No of patients		OR/WMD	95% CI	P-value	I ² (%)
		ET	OT				
Intraoperative outcomes							
Operative time	11	724	1,640	50.46	40.50, 60.42	<0.00001	87
No of retrieved LNs	10	676	1,640	-0.53	-1.29, 0.22	0.17	80
Blood loss	4	179	290	4.37	-2.62, 11.36	0.22	72
Postoperative outcomes							
Duration of drainage	3	104	167	1.88	1.22, 2.54	<0.00001	76
Volume of drainage	5	230	341	111.96	61.66, 162.26	<0.0001	95
Hospitalization period	8	566	1,440	0.65	0.06, 1.24	0.03	90
Transient RLN palsy	11	762	1,832	2.64	1.36, 5.11	0.004	48
Permanent RLN palsy	9	653	1,679	2.04	0.80, 5.23	0.14	0
Transient hypocalcemia	8	555	1,416	0.93	0.46, 1.87	0.84	81
Permanent hypocalcemia	7	521	1,386	0.82	0.39, 1.69	0.58	0
Hematoma or bleeding	10	674	1,538	1.76	0.81, 3.81	0.15	0
Seroma	4	258	357	1.33	0.53, 3.34	0.54	0
Oncological outcomes							
sTg <1.0 ng/mL	2	29	343	0.33	0.13, 0.81	0.02	0
Tumor recurrences	6	398	1,170	0.54	0.22, 1.32	0.18	0

Abbreviations: ET, endoscopic thyroidectomy; LN, lymph node; OT, open thyroidectomy; RLN, recurrent laryngeal nerve; sTg, stimulated thyroglobulin; WMD, weighted mean difference.

A



B



C

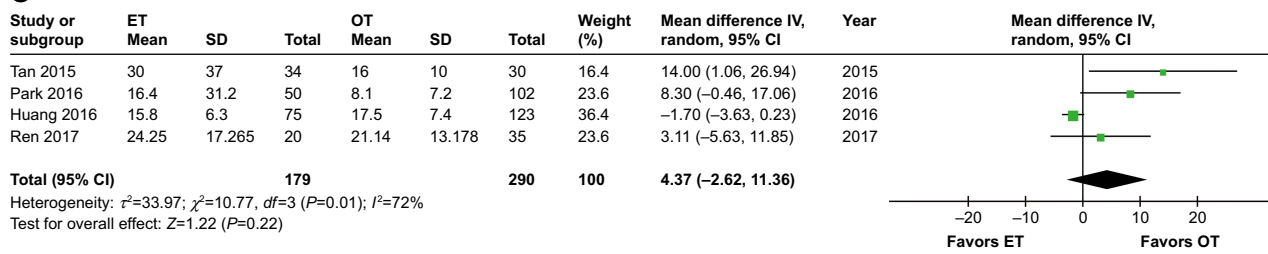


Figure 2 Forest plot and meta-analysis of (A) operative time; (B) number of retrieved lymph nodes; (C) blood loss. **Abbreviations:** ET, endoscopic thyroidectomy; OT, open thyroidectomy.

to 3.34, $P=0.54$), no heterogeneity existed across studies ($I^2=0\%$), and no significant differences between the ET and OT groups were observed (Table 3 and Figure 4A–F).

Meta-analysis of oncological results

The sTg levels were available in two studies.^{26,32} The ET group had lower proportions of having sTg <1.0 ng/mL (OR 0.33, 95% CI 0.13 to 0.81, $P=0.02$). No heterogeneity among studies existed ($I^2=0\%$).

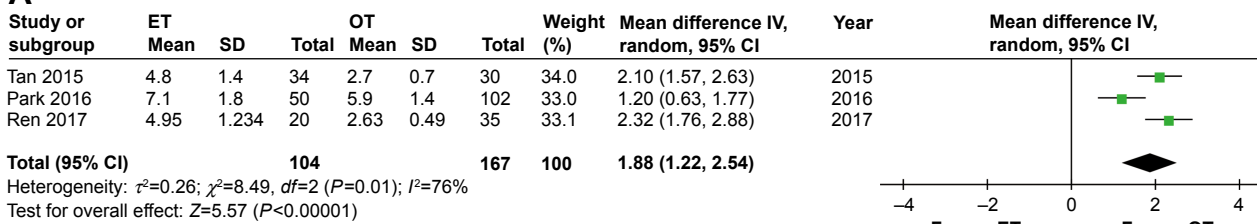
Six studies recorded tumor recurrences,^{26,29–32,36} and three studies reported no tumor recurrences during the follow-up period. Analysis of the pooled data showed that the two

groups did not differ significantly (OR 0.54, 95% CI 0.22 to 1.32, $P=0.18$). No heterogeneity among studies was observed ($I^2=0\%$) (Table 3 and Figure 5).

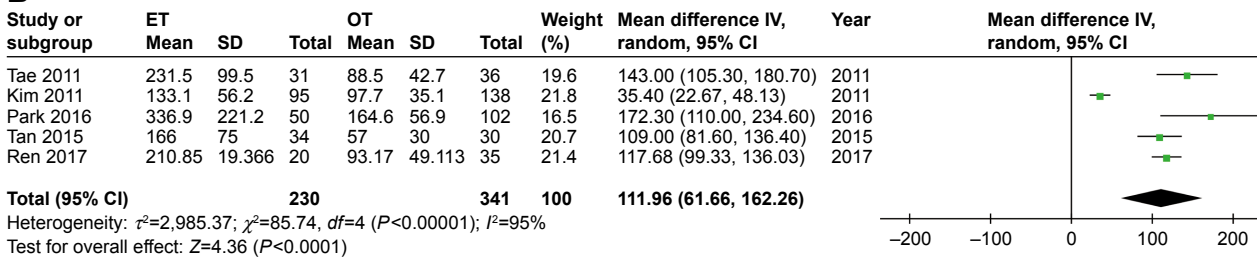
Subgroup analysis

We conducted a subgroup analysis according to the extent of thyroidectomy. The results of the subgroup analysis were roughly consistent with the previous outcomes. However, the volume of drainage (WMD 100.31, 95% CI –33.67 to 234.29, $P=0.14$) and transient RLN palsy (OR 1.58, 95% CI 0.66 to 3.79, $P=0.31$) were comparable between the ET and OT groups in TT. In addition, the hospitalization period

A



B



C

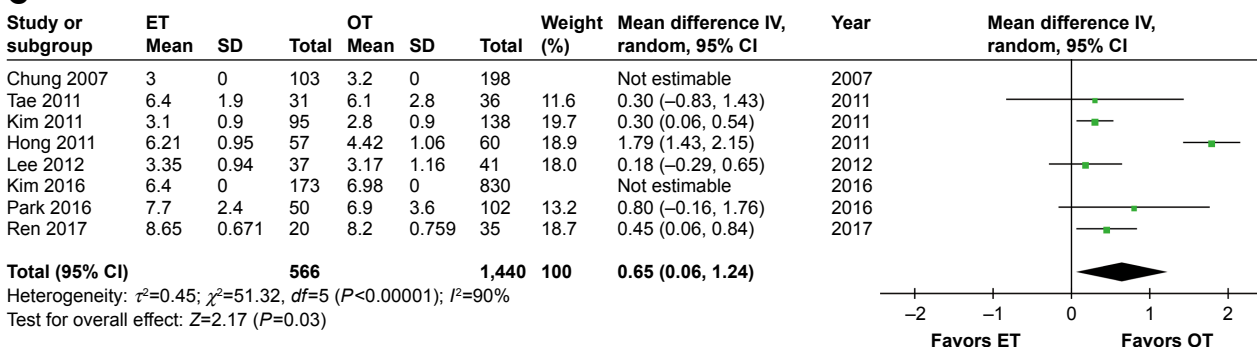


Figure 3 Forest plot and meta-analysis of (A) duration of drainage; (B) volume of drainage; (C) hospitalization period. **Abbreviations:** ET, endoscopic thyroidectomy; OT, open thyroidectomy.

was comparable between the two groups in LTT (OR 0.81, 95% CI -0.19 to 1.82, $P=0.11$). The concrete results of the subgroup analysis are summarized in Table 4.

Pooled surgical outcomes

Table 5 shows the pooled surgical outcomes of patients between ET and OT groups from all eligible studies.

Publication bias

Figure 6 shows a funnel plot of the studies reporting on transient RLN palsy. Begg’s test ($P=0.276$) and Egger’s test ($P=0.753$) showed no statistical publication bias in the studies reporting on transient RLN palsy.

Discussion

PTC is a subtype of differentiated thyroid cancer and surgery remains the primary therapeutic method for thyroid cancer.

However, an obvious scar on the neck left after conventional OT causes psychological concerns in patients. With the popularity of endoscopic instruments, ET has been an attractive alternative to open surgery for the treatment of PTC. Owing to the limited number of studies comparing the outcomes between ET and OT, the general application of ET for PTC remains controversial. Unlike the previous meta-analysis, which included patients with PTMC only,¹⁶ our study also recruited patients with tumor sizes larger than PTMC. Furthermore, many new studies with a greater number of patients have been published in recent years. Therefore, we aimed to perform a comprehensive systematic review and meta-analysis to identify the clinical value of ET in adult patients with PTC.

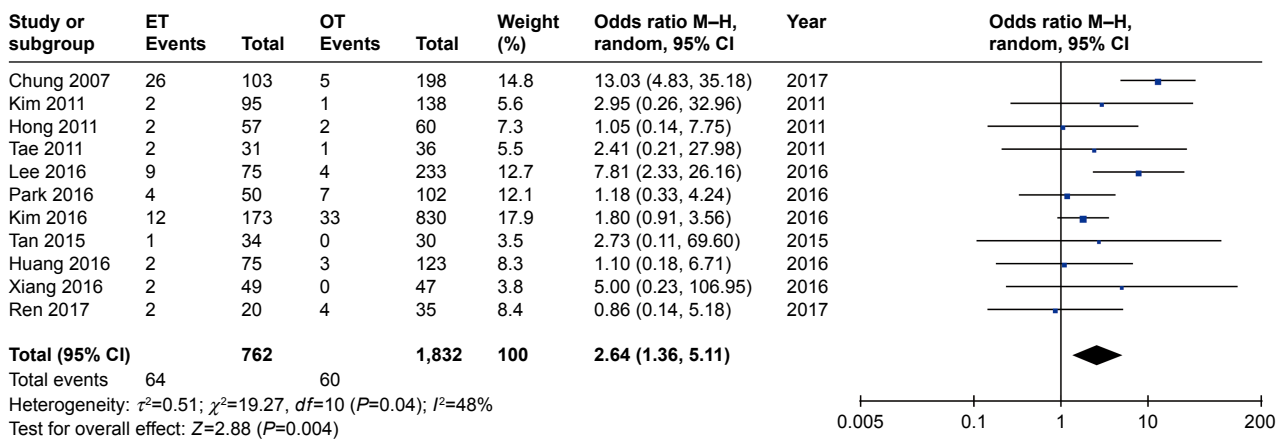
The results of our meta-analysis showed that the operative time in the ET group was longer than that in the OT group. This may be attributed to three reasons. First, more time is

needed to create the skin flap.^{31,32} Second, the meticulous bleeding control and careful lymph-node dissection require longer operation times.^{7,30} Third, surgeon experience and skills affect the operation times.^{19,29,37} The volume of fluid drainage and the time taken to remove the drainage tube in the ET group were much greater than in the OT group. It has been

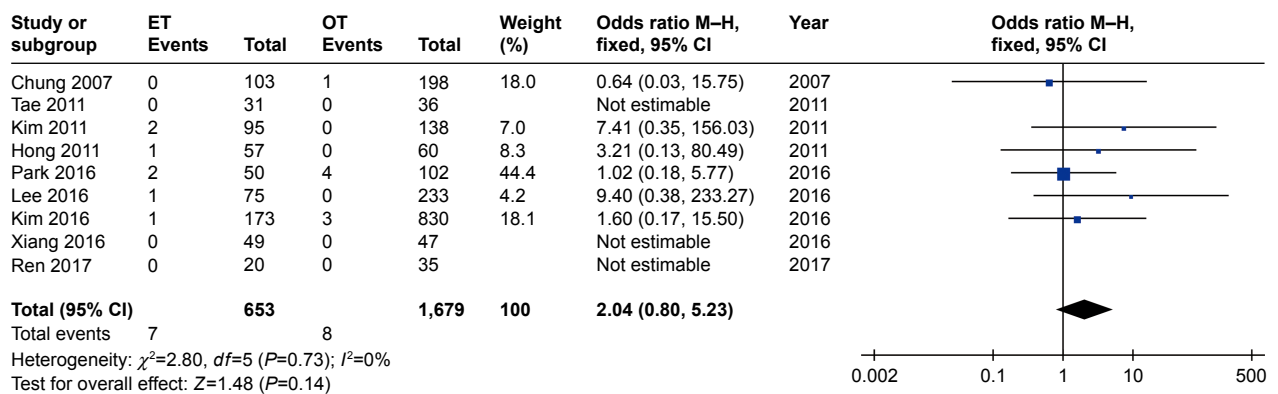
suggested that more dissection is needed to achieve the necessary working space.²⁸ Furthermore, the longer postoperative hospitalization period in ET suggests a longer recovery period than for OT, especially when performing TT.

In terms of the number of lymph nodes dissected, our meta-analysis demonstrated that there was no significant

A



B



C

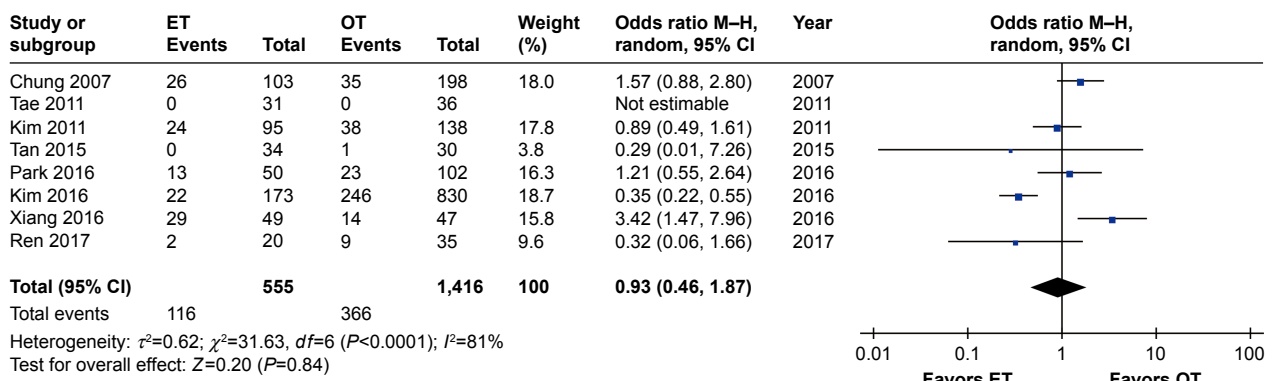
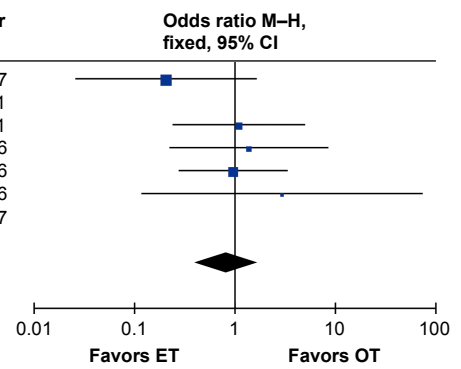


Figure 4 (Continued)

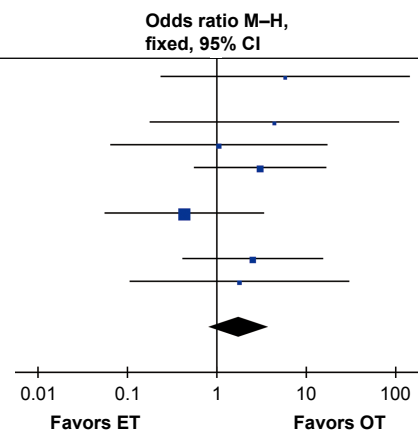
D

Study or subgroup	ET Events	Total	OT Events	Total	Weight (%)	Odds ratio M-H, fixed, 95% CI	Year
Chung 2007	1	103	9	198	36.5	0.21 (0.03, 1.65)	2007
Tae 2011	0	31	0	36		Not estimable	2011
Kim 2011	3	95	4	138	18.9	1.09 (0.24, 5.00)	2011
Park 2016	2	50	3	102	11.3	1.38 (0.22, 8.50)	2016
Kim 2016	3	173	15	830	30.4	0.96 (0.27, 3.35)	2016
Xiang 2016	1	49	0	47	3.0	2.94 (0.12, 73.94)	2016
Ren 2017	0	20	0	35		Not estimable	2017
Total (95% CI)		521		1,386	100	0.82 (0.39, 1.69)	
Total events	10		31				
Heterogeneity: $\chi^2=2.81$, $df=4$ ($P=0.59$); $I^2=0\%$							
Test for overall effect: $Z=0.55$ ($P=0.58$)							



E

Study or subgroup	ET Events	Total	OT Events	Total	Weight (%)	Odds ratio M-H, fixed, 95% CI	Year
Chung 2007	1	103	0	198	3.7	5.81 (0.23, 143.88)	2007
Tae 2011	0	31	0	36		Not estimable	2011
Kim 2011	1	95	0	138	4.3	4.40 (0.18, 109.09)	2011
Hong 2011	1	57	1	60	10.3	1.05 (0.06, 17.25)	2011
Lee 2012	5	37	2	41	17.7	3.05 (0.55, 16.76)	2012
Tan 2015	0	34	0	30		Not estimable	2015
Kim 2016	1	173	11	830	40.8	0.43 (0.06, 3.38)	2016
Xiang 2016	0	49	0	47		Not estimable	2016
Huang 2016	3	75	2	123	15.7	2.52 (0.41, 15.45)	2016
Ren 2017	1	20	1	35	7.5	1.79 (0.11, 30.27)	2017
Total (95% CI)		674		1,538	100	1.76 (0.81, 3.81)	
Total events	13		17				
Heterogeneity: $\chi^2=3.32$, $df=6$ ($P=0.77$); $I^2=0\%$							
Test for overall effect: $Z=1.43$ ($P=0.15$)							



F

Study or subgroup	ET Events	Total	OT Events	Total	Weight (%)	Odds ratio M-H, fixed, 95% CI	Year
Tae 2011	2	31	1	36	11.0	2.41 (0.21, 27.98)	2011
Kim 2011	0	95	1	138	15.5	0.48 (0.02, 11.91)	2011
Hong 2011	7	57	5	60	54.4	1.54 (0.46, 5.16)	2011
Huang 2016	1	75	2	123	19.0	0.82 (0.07, 9.17)	2016
Total (95% CI)		258		357	100	1.33 (0.53, 3.34)	
Total events	10		9				
Heterogeneity: $\chi^2=0.83$, $df=3$ ($P=0.84$); $I^2=0\%$							
Test for overall effect: $Z=0.62$ ($P=0.54$)							

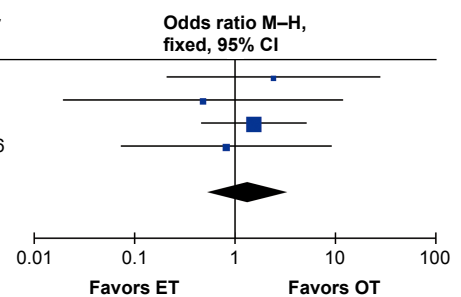


Figure 4 Forest plot and meta-analysis of (A) transient RLN palsy; (B) permanent RLN palsy; (C) transient hypocalcemia; (D) permanent hypocalcemia; (E) hematoma or bleeding; (F) seroma.

Abbreviations: ET, endoscopic thyroidectomy; M-H, Mantel-Haenszel; OT, open thyroidectomy; RLN, recurrent laryngeal nerve.

difference between the ET and OT groups. This finding may indicate that the clearance of lymph nodes is comparable between the two groups. The previous meta-analysis showed that the number of lymph nodes dissected is less in the ET group, but no significant difference existed in the subgroup analysis,¹⁶ which is in concordance with our result.

RLN palsy and hypocalcemia are the major complications of thyroid surgery. Our meta-analysis showed that ET was associated with a significantly greater risk of transient RLN palsy than OT, which was not consistent with the previous meta-analysis.¹⁶ In the sensitivity analysis, the significant difference still existed. It is worth noting that endoscopic

magnification with high-definition monitors is better for detecting the RLN. However, the similar or even worse risk of transient RLN palsy in ET relative to OT remains disappointing.^{12,38} Chung et al reported that 25.2% (26/103) of patients experienced transient RLN palsy and proposed that thermal damage caused by the ultrasonic scalpel may injure the RLN.²⁶ Tan et al adopted the same viewpoint.³¹ Another reason may be that ET represents a different anatomic surgery approach, which is not familiar to traditional thyroid surgeons.^{39,40} Sun and Dionigi proposed that surgeons must have an excellent understanding of the RLN in terms of identification and suggested that intraoperative neural

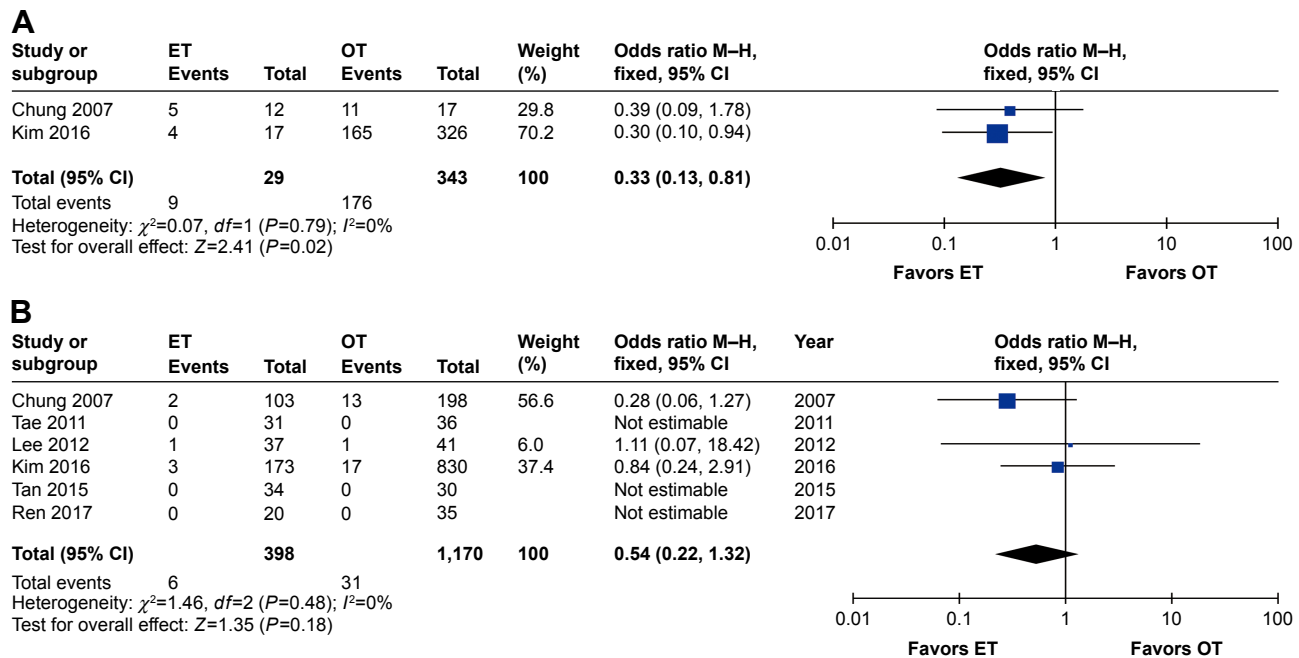


Figure 5 Forest plot and meta-analysis of (A) number of sTg < 1 ng/mL; (B) number of tumor recurrences. **Abbreviations:** ET, endoscopic thyroidectomy; M-H, Mantel-Haenszel; OT, open thyroidectomy; sTg, stimulated thyroglobulin.

monitoring may be a good choice to avoid RLN palsy.⁴¹ It was an interesting finding that in the subgroup analysis, transient RLN palsy was comparable between the two groups in TT, but not in LTT. We consider that the risk of transient

RLN palsy can be greatly reduced as long as the surgeon is experienced in ET, and good exposure and protection of the RLN are achieved during surgery. In addition, there were no significant differences between the two groups in terms of

Table 4 Meta-analysis of the subgroups according to the extent of thyroidectomy

Outcomes	No of studies	No of patients		OR/WMD	95% CI	P-value	I ² (%)
		ET	OT				
TT							
Operative time	4	269	410	47.40	34.18, 60.61	<0.00001	84
No of retrieved LNs	4	269	410	-0.10	-0.50, 0.30	0.63	0
Blood loss	2	125	225	2.35	-7.27, 11.97	0.63	79
Volume of drainage	2	145	240	100.31	-33.67, 234.29	0.14	94
Hospitalization period	2	145	240	0.33	0.10, 0.56	0.005	0
Transient RLN palsy	4	269	410	1.58	0.66, 3.79	0.31	0
Permanent RLN palsy	3	194	287	1.89	0.49, 7.33	0.36	20
Transient hypocalcemia	3	194	287	1.48	0.68, 3.20	0.32	70
Permanent hypocalcemia	3	194	287	1.35	0.46, 3.99	0.58	0
Hematoma or bleeding	3	219	308	2.93	0.61, 14.02	0.18	0
Seroma	2	170	261	0.67	0.10, 4.55	0.68	0
LTT							
Operative time	4	148	166	45.96	29.33, 62.59	<0.00001	90
No of retrieved LNs	4	203	364	-0.89	-2.48, 0.70	0.27	90
Blood loss	2	54	65	6.52	-0.72, 13.76	0.08	46
Duration of drainage	2	54	65	2.20	1.82, 2.59	<0.00001	0
Volume of drainage	2	54	65	114.99	99.74, 130.24	<0.00001	0
Hospitalization period	3	114	136	0.81	-0.19, 1.82	0.11	95
Transient RLN palsy	4	186	358	2.83	1.26, 6.36	0.01	44
Permanent RLN palsy	3	152	328	5.29	0.54, 52.22	0.15	0
Transient hypocalcemia	2	54	65	0.31	0.07, 1.36	0.12	0
Hematoma or bleeding	4	148	166	2.20	0.62, 7.84	0.22	0

Abbreviations: ET, endoscopic thyroidectomy; LN, lymph node; LTT, less than total thyroidectomy; OT, open thyroidectomy; RLN, recurrent laryngeal nerve; TT, total thyroidectomy; WMD, weighted mean difference.

Table 5 Pooled surgical outcomes between ET and OT groups from all eligible studies

Outcomes	ET	OT	References
Intraoperative outcomes			
Operative time (minutes)	142.0±45.9	92.3±36.6	7, 27–31, 34–36
No of retrieved LNs	4.3±4.1	4.7±4.0	7, 27–31, 33–35
Blood loss (mL)	19.6±24.5	14.5±9.8	7, 31, 34, 36
Postoperative outcomes			
Duration of drainage (days)	5.9±1.9	4.6±2.0	31, 34, 36
Volume of drainage (mL)	202.3±142.0	112.7±56.9	28, 29, 31, 34, 36
Hospitalization period (days)	5.3±2.5	4.8±2.9	27–30, 34, 36
Transient RLN palsy, n (%)	64 (8.3)	60 (3.3)	7, 26–29, 31–36
Permanent RLN palsy, n (%)	7 (1.1)	8 (0.5)	26–29, 32–36
Transient hypocalcemia, n (%)	116 (20.9)	366 (25.8)	26, 28, 29, 31, 32, 34–36
Permanent hypocalcemia, n (%)	10 (1.9)	31 (2.2)	26, 28, 29, 32, 34–36
Hematoma or bleeding, n (%)	13 (1.9)	17 (1.1)	7, 26–32, 35, 36
Seroma, n (%)	10 (3.9)	9 (2.5)	7, 27–29
Oncological outcomes			
sTg <1.0 ng/mL, n (%)	9 (31.0)	176 (51.3)	26, 32
Tumor recurrences, n (%)	6 (1.5)	31 (2.6)	26, 29–32, 36

Abbreviations: ET, endoscopic thyroidectomy; LN, lymph node; OT, open thyroidectomy; RLN, recurrent laryngeal nerve; sTg, stimulated thyroglobulin.

permanent RLN palsy, transient hypocalcemia, permanent hypocalcemia, hematoma or seroma.

Oncological outcomes, such as tumor recurrences and completeness of thyroid resection, are highly valued by surgeons. According to the American Thyroid Association guidelines, sTg may be helpful in predicting disease status.⁴² Only two studies recorded the number of patients with sTg <1 ng/mL,^{26,32} and our results demonstrated that the OT group may be associated with cleaner resection. Similarly, Kim et al found that the ET group showed higher postoperative thyroglobulin levels (2.4±6.3 ng/mL) than the OT group (0.8±2.0 ng/mL).²⁸ This indicates that OT is superior to ET in sTg levels presenting completeness of thyroid resection. In contrast, Jeong et al enrolled 275 PTMC patients who underwent ET and reported that all

thyroidectomized patients had <1 ng/mL of postoperative serum thyroglobulin.²⁴ With regard to tumor recurrences, the results showed no significant differences between the two groups, and three studies reported no tumor recurrences during the follow-up period.^{29,31,36} However, the results should be interpreted with caution. This is because, first, there were still insufficient available data on sTg levels. Second, data on postoperative follow-up were lacking and follow-up times were too short, because most PTCs have a slow progression and a good prognosis, with a 10-year survival rate of more than 90%.⁴³ Third, tumor characteristics such as tumor size were not well matched between the two groups. Thus, unlike surgical-related outcomes, oncological outcomes are difficult to compare. Randomized controlled trials with long-term follow-up assessment are needed to further evaluate oncological outcomes.

There are several limitations in our meta-analysis. First, all studies included were non-randomized controlled trials, which could lead to a higher risk of potential selection and reporting bias than randomized controlled trials. Second, some heterogeneity was observed for certain results. This may be related to differences among patient and tumor characteristics, the surgeons' experience and the surgical approaches. Third, transoral endoscopic thyroidectomy (TOET) has received attention in recent years, but no reports have compared OT with TOET in total thyroid cancer. Most patients who undergo TOET have benign lesions,⁴⁴ and many reports are on initial experiences^{45,46} or robot-assisted surgery.^{47,48} In addition, cosmetic results and quality of life are difficult to assess because of the few well-accepted tools available to study such outcomes.⁴⁰

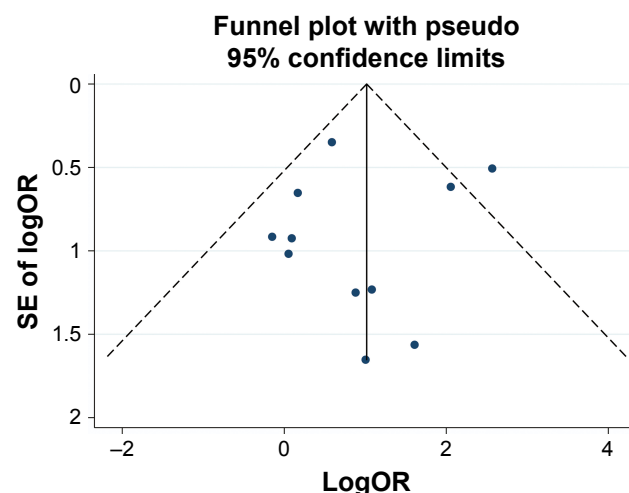


Figure 6 Funnel plot of transient recurrent laryngeal nerve palsy in all included studies.

Conclusion

Compared with OT, ET is disappointing in terms of operation and drainage time, amount of drainage fluid, hospital stay and transient RLN palsy, whereas other complications appear comparable. In addition, despite the similar tumor recurrence rates, the level of surgical completeness in ET may not be as good as that in OT. Therefore, the application of ET for patients with PTC should be conducted carefully, and further prospective studies with longer follow-up are needed to evaluate the oncological effectiveness of ET.

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Author contributions

J Zhou and L Wang designed the study; J Zhou and C Chen wrote the manuscript; C Chen, S Huang, A Huang, Y Jia and J Wang analyzed the data and interpreted the results. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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