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CLINICAL REVIEW

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Transoral endoscopic thyroidectomy vestibular approach vs conventional open thyroidectomy: Meta-analysis

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Abstract

Background: To conduct a meta-analysis to compare the safety and efficacy of transoral endoscopic thyroidectomy vestibular approach (TOETVA) with conventional open thyroidectomy (COT).

Methods: MEDLINE, EMBASE, Science Citation Index Expanded, and the Cochrane Central Register of Controlled Trials in the Cochrane Library from January 2007 to March 2020 were searched to identify studies comparing TOETVA and COT.

Results: Six eligible nonrandomized studies involving 1151 patients were included. Meta-analysis results revealed that TOETVA group had a significantly longer operative time (weighted mean difference [WMD], 66.09; 95% confidence interval [CI], 35.22-96.96; $P < .0001$) and larger amount of drainage (WMD, 98; 95% CI, 20.14-175.86; $P = .01$). There were no significant differences in terms of postoperative outcomes.

Conclusion: TOETVA appears to be as feasible and safe as the COT for the treatment of patients with benign thyroid nodules and selected differential thyroid carcinomas.

KEYWORDS

COT, meta-analysis, minimally invasive surgery, TOETVA

1 | INTRODUCTION

Conventional open thyroidectomy (COT) has traditionally been accepted as the standard surgery for some thyroid diseases. Due to the noticeable scar on the anterior neck caused by COT and increasingly cosmetic requirements,[1,2] especially in women, a variety of endoscopic thyroidectomy (ET) approaches have been developed, such as subclavian,[3] areola,[4] breast,[5] axillary,[6] axillo-breast,[7] and dorsal approach.[8] However, concerns were also raised as these approaches may associate with an extensive flap dissection, scar hyperplasia at the incision sites, and difficulties in dissecting the lower part of central lymph node.[9,10] Along with the emergence of natural orifice transluminal endoscopic surgery (NOTES) and development of endoscopic instruments, transoral endoscopic thyroidectomy vestibular approach (TOETVA) has been rapidly developed for patients with benign thyroid nodules and selected differential thyroid carcinomas.[11] TOETVA is considered as a minimally invasive surgery with no cutaneous scar and shorter tissue dissection.[9,11]

Recently, increasing evidence has investigated the safety and feasibility of the TOETVA with a paucity of comparative studies.[9-13] Although a few studies have directly compared TOETVA and COT,[14-20] it has failed to reach a consensus whether TOETVA is safe and feasible for thyroid lesions because of small number of sample

size and assessment at a single institution. Up to the present, no meta-analysis has systematically reviewed the differences between TOETVA and COT. We therefore sought to conduct a meta-analysis to compare the intraoperative outcomes and postoperative complications of patients undergoing TOETVA and COT.

2 | PATIENTS AND METHODS

2.1 | Systematic literature search

A systematic literature search of EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials in the Cochrane Library and Science Citation Index Expanded between January 2007 and March 2020 was performed for comparing TOETVA and COT. Medical subject headings and key words were as follows: "endoscopy" and "transoral endoscopic" and "vestibular" and "thyroidectomy" or "thyroid surgery." Only human studies published in English language with full-text descriptions were considered in the analysis. Relevant studies were also identified from the reference lists of the previous articles and reviews. Final inclusion of articles was determined by consensus from two independent reviewers, when this failed, a third author was adjudicated.

2.2 | Inclusion and exclusion criteria

Two reviewers independently scanned and identified the search findings for eligible studies. Inclusion criteria for eligibility were as follows: (a) studies reported in English language; (b) clear documentation of comparison between the TOETVA and COT; (c) studies that reported on at least one of the outcomes mentioned below; (d) multiple studies were published by the same institution and/or authors, either the higher quality study or the most recent publication was included. Studies were excluded from the analysis based on the following: (a) abstracts, reviews, case reports, letters, editorials, expert opinions; (b) studies without control groups; (c) absence of clearly reported outcomes of interest.

2.3 | Outcomes of interest

Intraoperative and postoperative outcomes were evaluated to compare TOETVA and COT. Operative time and blood loss were the main intraoperative outcomes. Postoperative outcomes included transient recurrent laryngeal nerve (RLN) palsy, permanent RLN palsy, transient hypocalcaemia, permanent hypocalcaemia, number of retrieved central lymph node, number of metastatic central lymph nodes, postoperative hospital stay, hematoma, and wound infection.

2.4 | Data extraction and quality assessment

Two independent reviewers extracted the data from eligible studies using standardized forms. Data extracted from the selected study included: population characteristics, operative details, and postoperative outcomes. The quality of each study was evaluated using the Newcastle-Ottawa Scale with some modifications. Studies were considered as higher quality if the quality achieves six or more stars.[21]

2.5 | Statistical analysis

Meta-analysis was carried out using Review Manager software, version 5.0 (The Cochrane Collaboration, Oxford, UK). Continuous variables were performed with weighted mean difference (WMD) with corresponding 95% confidence interval (CI), whereas categorical variables were analyzed using odds ratio (OR) with corresponding 95% CI. Medians were converted to means using a previously described methodology.[22] Pooled outcome measures were calculated using fixed or random effects model, depending on the heterogeneity. Heterogeneity was assessed using chi-square test, with a P value of $<.1$ indicating significant; I^2 values were estimated for the extent of heterogeneity. [23] If the test yielded an I^2 value of $>50\%$, the random effects analysis was performed. In addition, sensitivity analyses were conducted by excluding individual studies from the data set to analyze their relative effect on the overall pooled estimates.

3 | RESULTS

3.1 | Study characteristics

There were 187 articles relevant to the search strategy. Fourteen articles were selected for further investigation. Of these, seven studies were further excluded by a close scrutiny, due to the only comparison with other operation approach, two studies had been published by the same institute and had overlapping patient populations. One study published recently was included. Therefore, six studies[15-20] matched the inclusion criteria and were included. All these studies were nonrandomized

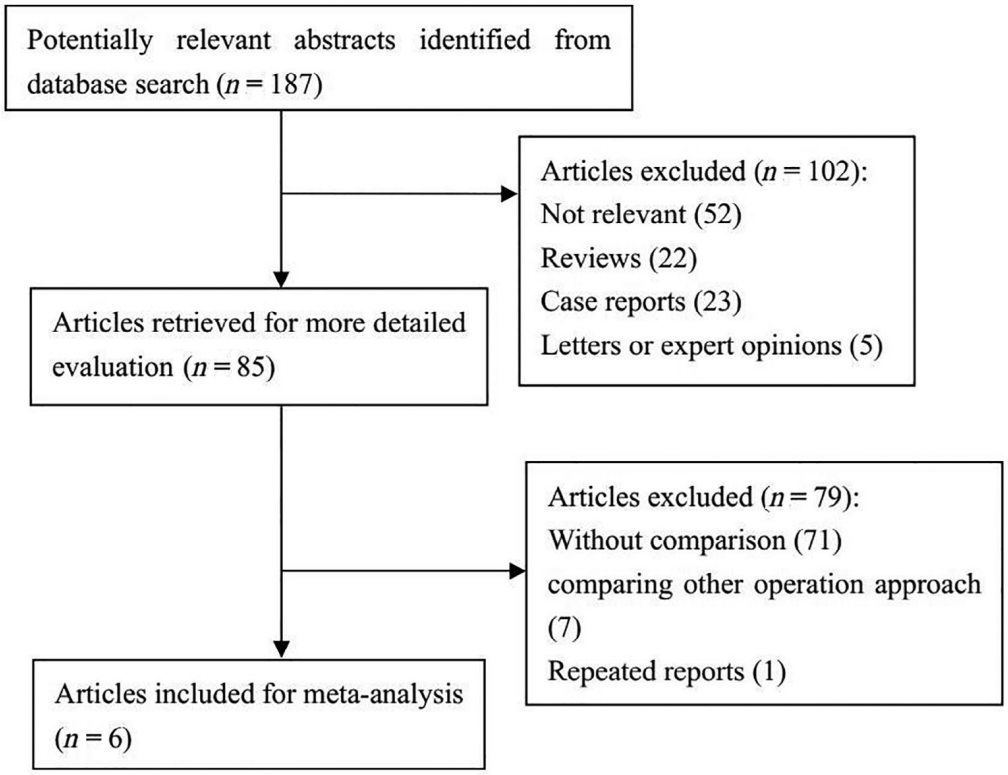

FIGURE 1 Flow diagram depicting study selection

controlled trials. A flow chart for selection of articles was shown in Figure 1.

The six articles published between 2017 and 2020 involved a total of 1151 patients: 478 in the TOETVA group and 673 patients in the COT group. The number of patients in the included studies varied from 40 to 432. Three studies were carried out in China, two in Thailand, and one in Mexico. The general characteristics and quality assessments of the studies included in the meta-analysis are summarized in Tables 1 and 2.

3.2 | Intraoperative outcomes

All the results of the analyses are summarized in Table 3. All studies explicitly provided information on operative time. Meta-analysis showed that TOETVA group was associated with a significant increase in the operative time (WMD, 66.09; 95% CI, 35.22-96.96; $P < .0001$) (Figure 2A). Five studies revealed no statistically significant difference in the blood loss between the two groups (WMD, 0.93; 95% CI, −1.54 to 3.39; $P = .46$) (Figure 2B).

3.3 | Postoperative outcomes

Two studies reported on amount of drainage between the two groups and showed a larger amount of drainage in the TOETVA group (WMD, 98; 95% CI, 20.14-175.86; $P = .01$) (Figure 2C). Three studies revealed no significant difference in the number of retrieved central lymph node between the two groups (OR: 0.29; 95% CI: −1.35 to 1.93, $P = .73$) (Figure 2D). Furthermore, analysis of the pooled data from two studies revealed that the two groups did not differ significantly in the number of metastatic central lymph nodes (OR: 0.32; 95% CI: −0.00 to 0.65, $P = .05$) (Figure 2E).

No significant differences were observed between the two operative methods in terms of transient RLN palsy (OR, 1.01; 95% CI, 0.52-1.93; $P = .98$) (Figure 2F), permanent RLN palsy (OR, 3.04; 95% CI, 0.12-75.69; $P = .50$), transient hypocalcaemia (OR, 0.96; 95% CI, 0.56-1.65; $P = .89$) (Figure 2G), permanent hypocalcaemia (OR, 0.32; 95% CI, 0.01-8.26; $P = .49$), hematoma (OR, 7.93; 95% CI, 0.97-65.12; $P = .05$) (Figure 2H), wound infection (OR, 3.15; 95% CI, 0.12-82.16; $P = .49$), and postoperative hospital stay (WMD, 0.02; 95% CI, −0.50 to 0.54; $P = .94$).

3.4 | Sensitivity and subgroup analyses

Sensitivity analyses were carried out by excluding each individual study from each outcome measure. These exclusions did not change the overall results of cumulative analyses. Subgroup analyses were conducted according to high-quality studies and studies only including patients with papillary thyroid carcinoma. The results of the analyses were consistent with the previous

TABLE 1 General characteristics of included studies

Reference	Year	Country	Design	Group	No. of patients	Age (years)	Male/female	Matching[a]	Type of procedure	Pathological diagnosis, PTC/BTN
Anuwong et al[15]	2018	Thailand	Rtro	TOETVA COT	216 216	35.1 ± 11.9 35.3 ± 12.1	20/199 19/197	1-4	$a = 133$, $b = 86$ $a = 132$, $b = 84$	NA NA
Bian et al[16]	2018	China	Rtro	TOETVA COT	30 30	24.0 (17-41) 26.5 (17-44)	1/29 0/30	1, 4, 10	$f = 30$ $f = 30$	30/0 30/0
Pérez-Soto et al[17]	2019	Mexico	Rtro	TOETVA COT	20 20	48.10 ± 15.67 45.55 ± 14.42	2/18 34/104	1, 3-7	$a = 3$, $b = 13$, $c = 2$, $d = 1$, $e = 1$ $a = 3$, $b = 16$, $c = 1$	18/2 18/2
Wang et al[18]	2019	China	Rtro	TOETVA COT	80 80	31.48 ± 6.60 32.59 ± 5.18	13/179 53/213	1, 2, 4, 8, 9	$f = 80$ $f = 80$	80/0 80/0
Sun et al[19]	2020	China	Rtro	TOETVA COT	100 289	29.65 ± 6.57 45.18 ± 11.47	14/86 124/165	1, 2, 4, 8	$f = 100$ $f = 289$	100/0 289/0
Kasemsiri et al[20]	2020	Thailand	Pro	TOETVA COT	32 38	38.3 ± 11.3 46.7 ± 10.9	0/32 4/34	1, 2, 4, 7	$a = 32$ $a = 38$	1/31 0/38

Note: a: hemithyroidectomy; *b*: total thyroidectomy; *c*: near total thyroidectomy; *d*: subtotal thyroidectomy; *e*: total thyroidectomy plus central neck dissection; *f*: hemithyroidectomy plus central neck dissection.

Abbreviations: BTN, benign thyroid nodule; NA, not available; Pro, prospective; PTC, papillary thyroid carcinoma; Rtro, retrospective.

[a]1 = age; 2 = gender; 3 = type of procedure; 4 = tumor size; 5 = body mass index; 6 = length of stay;7 = pathological diagnosis; 8 = multiplicity 9 = bilateral PTC; 10 = T-classification stage.

TABLE 2 Newcastle-Ottawa scoring system for nonrandomized comparative studies

References	Selection star	Comparability star	Outcome star	Total star
Anuwong et al[15]	3	2	1	6
Bian et al[16]	2	2	0	4
Pérez-Soto et al[17]	3	1	0	4
Wang et al[18]	2	2	2	6
Sun et al[19]	3	2	2	7
Kasemsiri et al[20]	3	1	2	6

Note: Comparability variables include age, gender, type of procedure, tumor size, multiplicity, and pathological diagnosis.

TABLE 3 Meta-analysis of the subgroups for studies comparing TOETVA and COT

Outcomes	No. of studies	No. of patients	OR/WMD	95% CI	*P* value	I^2 (%)
High-quality studies						
Operative time(min)	4	1051	57.80	22.27, 93.33	.001	98
Blood loss (mL)	3	662	1.38	−1.46, 4.23	.34	0
Transient RLN palsy	4	1051	0.89	0.45, 1.76	.74	0
Permanent RLN palsy	2	592	3.04	0.12, 75.69	.50	-
Tansient hypocalcemia	2	592	1.05	0.58, 1.88	.88	0
No. of retrieved central lymph node	2	549	−0.17	−3.04, 2.70	.91	86
No. of metastatic central lymph nodes	2	549	0.32	−0.00, 0.65	.05	0
Amount of drainage	2	549	98.00	20.14, 175.86	.01	99
Studies only including PTC						
Operative time (min)	3	609	90.44	76.21, 104.67	<.00001	78
Blood loss (mL)	2	220	1.56	−1.25, 4.38	.28	0
Transient RLN palsy	3	609	0.75	0.26, 2.15	.59	0
No. of retrieved central lymph node	3	609	0.29	−1.35, 1.93	.73	73
No. of metastatic central lymph nodes	2	549	0.32	−0.00, 0.65	.05	0
Amount of drainage	2	549	98	20.14, 175.86	.01	99

Abbreviations: CI, confidence intervals; COT, conventional open thyroidectomy; OR, odds ratios; PTC, papillary thyroid carcinoma; RLN, recurrent laryngeal nerve; TOETVA, transoral endoscopic thyroidectomy vestibular approach; WMD, weighted mean differences.

outcomes when all studies were considered. These results are illustrated in Table 3.

3.5 | Publication bias

The funnel plot of the studies based on the transient RLN palsy is shown in Figure 3. A somewhat asymmetric distribution around the vertical axis indicates moderate publication bias. However, the result needs to be interpreted with caution, due to the limited numbers of the included studies.

4 | DISCUSSION

ET is currently considered as an alternative to the COT for thyroid diseases. TOETVA, as a new endoscopic approach, not only caters for the higher esthetic requirement of women, but also provides easy access to the bilateral thyroid and central compartment.[11] Since the successful report of TOETVA by Nakajo et al[24] and Wang et al[25] in 2013, the benefits afforded by TOETVA, such as cutaneous scar-free and minimally invasive surgery,[11] have led to its increased application in thyroid surgery. Five published systematic reviews[26-30]have investigated

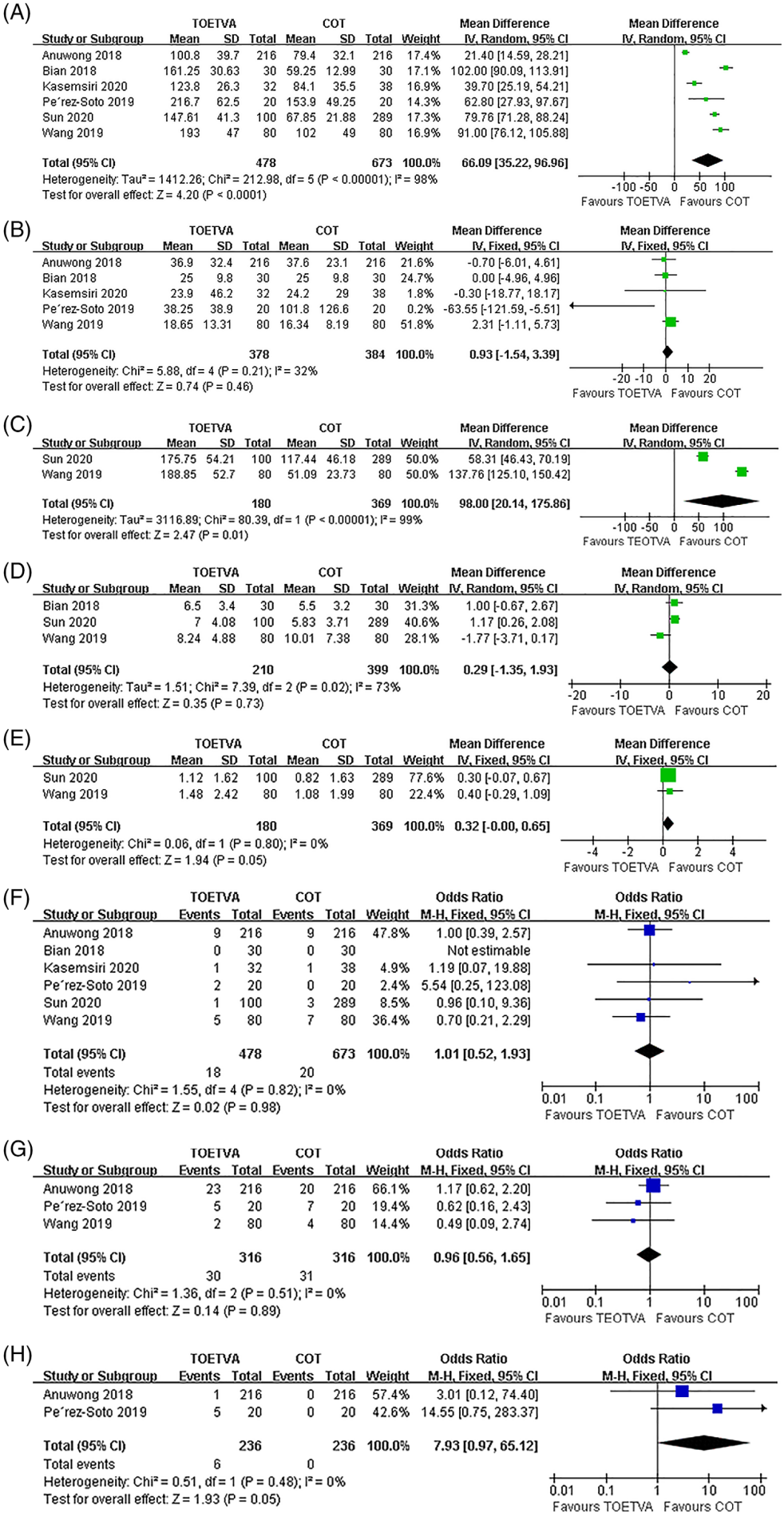

FIGURE 2 A, Forest plots displaying operative time comparing TOETVA vs COT. B, Forest plots displaying blood loss comparing TOETVA vs COT. C, Forest plots displaying amount of drainage comparing TOETVA vs COT. D, Forest plots displaying number of retrieved central lymph node comparing TOETVA vs COT. E, Forest plots displaying number of metastatic central lymph nodes comparing TOETVA vs COT. F, Forest plots displaying transient RLN palsy comparing TOETVA vs COT. G, Forest plots displaying transient hypocalcaemia comparing TOETVA vs COT. H, Forest plots displaying hematoma comparing TOETVA vs COT. CI, confidence intervals; COT, conventional open thyroidectomy; RLN, transient recurrent laryngeal nerve; TOETVA, transoral endoscopic thyroidectomy vestibular approach [Color figure can be viewed at wileyonlinelibrary.com]

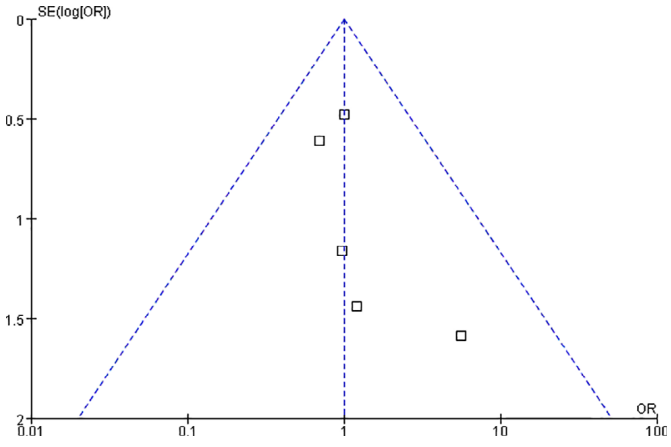

FIGURE 3 Funnel plot to investigate publication bias. OR, odds ratio [Color figure can be viewed at wileyonlinelibrary.com]

the safety and feasibility of the TOETVA for thyroid disease. These systematic reviews have reported that TOETVA was feasible and safe for the treatment of selected thyroid disease. However, controversy remains about whether TOETVA is appropriate for thyroid diseases, particularly for thyroid carcinoma.[18] To the best of our knowledge, this is the first comprehensive meta-analysis aimed at comparing TOETVA vs COT for patients with thyroid lesions.

Based on our analysis, we found operating time was significantly longer in TOETVA group compared to COT group, which can be explained by the additional time for ports insertion and creation of working space.[14,18,26] Operative time in TOETVA group may decrease with the increased endoscopic surgery training and experience.[15,31] Wang et al[18] demonstrated that TOETVA was associated with equivalent central lymph node dissection time as compared with that of COT. Our analysis also found that the amount of drainage in the TOETVA group was significantly greater than that in the COT group, which might be due to the requirement for larger subcutaneous flaps.[18] Further analysis revealed no significant difference in intraoperative blood loss and postoperative hospital stay within the two groups.

With regard to the postoperative complications, our results revealed no significant difference in the incidence rates of transient RLN palsy, permanent RLN palsy, transient hypocalcemia, permanent hypocalcemia, and hematoma between the TOETVA and COT groups. This result might be attributed to the endoscopic magnification providing a better view of the RLN and parathyroid gland.[18,19] In addition, intraoperative neuromonitoring for TOETVA can help prevent RLN injury by identifying RLN and confirming its integrity.[32]

New specific complications brought by TOETVA include increased risk of wound infection and mental nerve injury. Of the studies included in this analysis, three studies[15-17]reported wound infection and mental nerve injury. Concern for higher risk of wound infection occurred due to clean-contaminated procedure in TOETVA.[33] However, our results reveal no significant difference in the wound infection between the TOETVA and COT groups, possibly due to the prophylactic use of intravenous antibiotics and oral sterilization perioperatively for TOETVA.[9,34] In terms of mental nerve injury introduced only by transoral vestibular approach TOETVA, Anuwong et al[15] reported a 1.4% transient mental nerve injury incidence rate for TOETVA. Bian et al[16] reported 17 patients experienced transient mental nerve injury. Pérez-Soto et al[17] reported three patients presented transient mental nerve injury.

It is evident that that lymph node metastasis affected oncologic outcomes and was related to a higher patient mortality.[35,36] Prophylactic ipsilateral central lymph node dissection was recommended for all papillary thyroid carcinoma patients based on the current Chinese guidelines. In our meta-analysis, three studies reported the number of retrieved central lymph node. The pooled data of retrieved central lymph node revealed no significant difference between TOETVA and COT group, which may indicate that the clearance of central lymph node is comparable within the two groups. Of the three studies included in this analysis, only one study[18] demonstrated that TOETVA had equivocal number of positive central lymph nodes to COT.

The review has several limitations and hence the results should be interpreted cautiously. First, relatively small number of the studies with short-term follow-up data were included in the meta-analysis. Second, all the studies included were nonrandomized trials, which might over/under estimate the measured effect. Third, this study failed to analyze important outcomes including cosmetic results and oncological outcome due to lack of available data. Furthermore, some heterogeneity was observed in certain outcome measures. This might be explained by differences in patient selection, surgical procedure, and surgeons' experience. Therefore, well-designed randomized controlled trials with emphasis on evaluating important outcomes and adequate follow-up are required to clarify ambiguities surrounding the use of TOETVA.

5 | CONCLUSIONS

This systematic review demonstrates that TOETVA is as feasible and safe as the COT for the treatment of patients with benign thyroid nodules and selected differential thyroid carcinomas, although TOETVA is not superior to

conventional techniques with respect to operative time. Further larger randomized controlled trials with longer follow-up are still needed to confirm the clinical and oncological effectiveness of TOETVA.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Tao Wei, Jingqiang Zhu, and Zhihui Li designed the research. Yichao Wang, Shengliang Zhou, and Shu Rui developed the literature search. Yichao Wang and Xueting Liu carried out statistical analysis of the studies. Yichao Wang drafted the article. All authors read and approved the final manuscript.

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