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Review

Learning curve and volume outcome relationship of endoscopic *trans*-oral versus *trans*-axillary thyroidectomy; A systematic review and meta-analysis

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ABSTRACT

Background: In the modern era, minimally invasive surgery is rapidly evolving and even replacing conventional open techniques in many surgical fields. Thyroidectomy was not an exception, with the introduction of multiple endoscopic thyroidectomy techniques. *Trans*-oral endoscopic *trans*-vestibular thyroidectomy (TOT) is a novel technique with promising outcomes. We conducted this meta-analysis to compare surgical outcomes and learning curves for TOT and other endoscopic thyroidectomy techniques.
Methods: A systematic review in PubMed, MEDLINE, and EMBASE databases was conducted searching for publications on TOT versus *trans*-axillary thyroidectomy (TAT). The primary endpoint was operative (OR) time. Secondary endpoints were number of harvested lymph nodes (LNs), estimated blood loss (EBL), recurrent laryngeal nerve (RLN) injury, hoarseness, seroma, infection, chyle leak, hypocalcemia, hospital length of stay (LOS), and Cost. We also investigated the learning curve for each technique. Leave-out-out analysis, meta-regression, and subgroup analysis were used. Random effect inverse variance method was utilized.
Results: Among 3820 retrieved studies, 15 studies (10 unmatched and 5 matched), with 2173 (TOT: 1024 (47.12%) and TAT:1149(52.87%)) patients, met the inclusion criteria. The operative time and harvested L. Ns number were higher in TOT versus TAT (standard mean difference (SMD) = 0.72 [95%CI 0.07; 1.37], P = 0.029 and SMD = 0.32 [95%CI 0.02; 0.62], P = 0.036 respectively) while less EBL in TOT versus TAT (SMD = −0.26 [-0.43; −0.09], P = 0.0018). All other outcomes showed no significant difference between both groups. Weighted mean values for TOT and TAT were 158.03 vs 144.97 min for OR time, 6.33 vs 5.16 for harvested LNs, and $5,919.05 vs $6,253.79 for the cost. Statistical significance in learning curve development was noticed ranging between 6 and 15 annual cases.
Conclusion: Trans-oral thyroidectomy is a safe and reliable technique with outcomes comparable to other endoscopic techniques. It provides better access to the central compartment with a more feasible LN dissection. Improvement in surgical outcomes is expected with growing learning curve and technique mastery

1. Introduction

Over the past Century, *trans*-cervical neck incision was the gold standard approach for the removal of part or all of the thyroid gland, since it was introduced by Theodore Kocher in the 19th century [1]. Although conventional open thyroidectomy has proved to be safe, feasible, and oncologically safe, yet its visible neck scar remains a dissatisfying outcome for the surgeon and patient [2].

In recent years there have been revolutionary advances in minimally invasive surgeries and thyroid surgery was not an exception [1]. The first endoscopic thyroidectomy was performed by Huscher et al., in 1997 (3). Various endoscopic approaches have been developed since then, with the main goal being to develop port sites at hidden areas of the body such as axilla, areola, and post-auricular [4]. For more than a decade endoscopic thyroidectomy proved to be safe and efficient, yet the long-distance of tissue dissection, visible body scars, and difficult access

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to the central lymph node compartment remained major drawbacks [5].

In order to solve these surgical challenges, natural orifice transluminal endoscopic surgery (NOTES), seemed a promising approach. *Trans*-oral thyroidectomy via vestibular approach (TOT), is a convenient application, it was first described by Wang et al., 2014 [6]. With shorter flap dissection, hidden scars, and direct access to the central compartment, it is a promising upgrade for endoscopic thyroid surgery [7].

Several studies tested the efficacy and safety of TOT, comparing it to the open conventional technique, with results showing comparable outcomes in terms of safety and oncological outcomes, with even meta-analysis consolidating these results [8,9].

Recently several retrospective and prospective comparative studies have been conducted to compare the new *trans*-oral vestibular approach with various endoscopic thyroidectomy techniques, but the limited number of patients and novelty of the technique lead to inconsistency in the results of these studies [10,11].

In the current study, we conducted a meta-analysis, to investigate the feasibility, efficacy, and oncological safety of *trans*-oral thyroidectomy compared to other techniques of endoscopic thyroidectomy. We systematically analyzed data from the published studies comparing the 2 groups, regarding pre-operative characteristics, intra, and postoperative outcomes. Furthermore, we assessed the learning curve among the studies included.

2. Methods

2.1. Search strategy and study selection

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Self-evaluation using AMSTAR 2 criteria using AMSTAR2 checklist revealed a high-quality review [13].

In January 2022, the PubMed, MEDLINE, and EMBASE databases were searched for publications on transoral thyroidectomy versus other techniques of minimally invasive thyroidectomy. (Full search strategy was reported in Supplementary Table 1). The references list of all studies and any published related meta-analyses were searched to identify further articles that could potentially be recruited (i.e., backward snowballing). Three authors (A. D., I.E., and E. H.) independently inspected the electronic reports identified by the searches. In case of discrepancies, they were resolved by a fourth author's (M.R.) opinion and consensus meeting. **Inclusion criteria** were full-text English articles on adult humans that compared Transoral thyroidectomy (TOT) to Other minimally invasive thyroidectomy techniques (*Trans*-axillary, *Trans*-areolar, or Combined axillo-areolar approach); labeled in our current work as *trans*-axillary thyroidectomy (TAT). In case of overlapping studies from the same centers, the study with the largest sample size was included (PRISMA flow chart was shown in Supplementary Fig. 1).

This review was registered with the PROSPERO register of systematic reviews (CRD42022321579). There was no individual patient involvement in this study; as such, institutional review board (IRB) approval was not required.

2.2. Data extraction and quality assessment

Two investigators (A.D. and I.E.) performed data extraction independently. All the following data were retrieved for each study: study characteristics (the author, publication year, study period, and institute), patients data (mean age, female percent, associated comorbidities, thyroid pathology data: benign or malignant, and nodule size), operative data: surgical technique, comparison arms, and operative time, intra-operative complications: injury of the RLN, and iatrogenic removal of the parathyroid), the amount of intraoperative blood loss, postoperative complications: unexpected hoarseness, hypocalcemia, unexpected chyle leak, wound infection and seroma, postoperative pain (assessed using the Visual Analogue Score (VAS: 0–10)) and cosmetic results. We also assessed post-operative hospital stay, post-operative pathology data, the number of harvested lymph nodes (LNs), and total costs.

The primary endpoint was operative (OR) time. Secondary endpoints were harvested LN, blood loss, RLN injury, temporary hoarseness, hoarseness, seroma, Infection, chyle leak, hypocalcemia, hospital length of stay (LOS), post-operative pain, and cost.

The quality of the included studies was assessed using the Newcastle-Ottawa scale (NOS) for observational studies and the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. ([14, 15]). Only RCTs and high-quality observational articles (defined as those with a NOS score of 7 or more) were included.

2.3. Data synthesis and statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) while categorical variables were reported as percentages (%). Standardized mean difference (SMD) and risk difference (RD) with 95% confidence intervals (95%CI) were our effect estimates for continuous and binary outcomes respectively. Risk difference was used due to the presence of zero events on both arms in some of the included studies. Weighted mean with its 95% CI was calculated for continuous variable among every single approach i.e., single-arm meta-analysis.

Inverse variance DerSimonian-Laird approach with random-effect model was used for statistical outcome pooling [16].

Threshold analysis was used to compare studies based on the annual number of cases in an ascending cut-off and its effect on different surgical outcomes (OR time, Number of harvested LNs, and intra-operative estimated blood loss) to assess the learning curve. We investigated studies that indicated a single surgeon performing all cases and assessed both groups (TOT and TAT). Each group was assessed according to its total annual number of endoscopic thyroidectomy cases, then according to the specific annual number of cases for each technique.

Sensitivity analysis using "leave-one-out analysis" and meta-regression were performed for mean age, female percent, nodule size, publication year, study period(months), annual endoscopic thyroidectomy, annual TOT thyroidectomy, annual TAT thyroidectomy, number of institutions (single or multiple) and number of surgeons (single or multiple). Meta-regression results were reported as regression coefficient (i.e., Beta) with its p-value. Funnel plots and Egger's test were used for the assessment of publication bias for the primary outcome.

Hypothesis testing for statistical homogeneity was based on the Cochran Q test, with I^2 values of 0–25%, 26–50%, and 51–100% representing low, moderate, and high heterogeneity, respectively [17]).

Two-sided significance testing was used and a P-value for significance was set at 0.05. All analyses were performed using R (version 4.1.1 R Project for Statistical Computing) within RStudio.

3. Results

3.1. Eligible studies and characteristics of studies

For clinical outcomes, 3820 studies were identified. After the removal of duplicates, 2177 studies were screened. 468 full-text articles were assessed for eligibility. Among them 15 studies [6,7,10,11,18–28] (10 unmatched and 5 PSM studies) (see Table 1) met the inclusion criteria. An outline of the PRISMA flowchart for clinical outcomes is shown in (Supplementary Fig. 1).

For the overall quality of the included studies check Supplementary Table 2. For the 11 retrospective studies, 3 studies had a NOS score of 9/9, 5 studies had a score of 8/9, and only 3 studies had a score of 7/9. The quality of the Prospective studies was assessed using the Cochrane collaboration tool.

Of the 2173 patients included, 1024 (47.12%) underwent *trans*-oral thyroidectomy and 1149 (52.87%) underwent *trans*-axillary thyroidectomy.

Table 1
Criteria of included studies and Patients' demographics, NR: Not reported R = Retrospective, P=Prospective, RCT = Randomized Controlled Trial.

Author/year	Study Design	COUNTRY	TOT TOTAL	TAT TOTAL	PERIOD MONTHS	TOT GENDER (Female %)	TAT GENDER (Female %)	TOT AGE	TAT AGE	TOT SIZE (NODULE) CM	TAT SIZE (NODULE) CM	No. of Centers	No. of SURGEONS	PATHOLOGY	Laparoscopic vs robotic	TYPE OF NECK DISSECTION	Procedure	Cosmetic Satisfaction (TOT)	Cosmetic satisfaction (TAT)
Chae 2020 (23)	R	Korea	14	56	122	78.57%	89.29%	38.69 ± 9.21	40.02 ± 9.37	0.76 ± 0.29	0.75 ± 0.35	Single	Single	Malignant	Robotic	Central	Total thyroidectomy	NR	NR
Kumar 2021 (18)	P	India	10	10	21	100%	100%	33.2 ± 10.42	28.2 ± 8	2.7 [2,3]	3 (2.25–3.9)	Single	Single	Benign	Endoscopic	Central	Hemithyroidectomy	4 [4,5] (Likert)	4.5 [4,5]
Chai 2018 (10)	R	Korea	50	50	96	94.00%	92.00%	39.5 ± 10.4	41.2 ± 9.4	1 ± 0.6	1.1 ± 0.8	Single	Single	Benign & malignant	Robotic	Central	Total, subtotal and hemi thyroidectomy	NR	NR
Jonathan 2019 (27)	R	USA	92	70	66	NR	NR	NR	NR	NR	NR	Multiple	Multiple	Benign	Robotic and endoscopic	NR	Total and hemi thyroidectomy	NR	NR
Wang 2013 (44)	RCT	China	12	12	8	83.30%	83.3	24 ± 6.49	25.67 ± 6.24	3.26 ± 1.03	2.84 ± 1.31	Single	Single	Benign	Endoscopic	Central	Hemi and subtotal thyroidectomy	1.58 ± 0.79 (Questionnaire)	2.33 ± 0.65
Yang 2020 (19)	R	Korea	248	316	120	83.10%	90.50%	40.62 ± 10.9	40.03 ± 9.7	0.96 ± 0.95	0.86 ± 0.91	Single	Single	Benign & malignant	Robotic	Central	Total and Hemi thyroidectomy	NR	NR
Li 2021 (17)	R	China	60	65	23	91.60%	100%	22.2 ± 3.00	23.7 ± 3.8	3.1 ± 0.5	3.3 ± 0.6	Single	NR	Benign	Endoscopic	Central	Total thyroidectomy	9.8 ± 0.5 (VAS (0–10))	9.4 ± 0.9
Xu 2019 (20)	R	China	48	44	16	91.60%	88.60%	30.46 ± 6.93	33.3 ± 6.94	NR	NR	Single	Single	Malignant	Endoscopic	Central	Hemi-thyroidectomy	9.2 ± 0.7 (SSSQ)	7.7 ± 1.3
Guo 2020 (22)	R	China	40	40	11	100%	100%	29.8 ± 0.96	33.75 ± 1.19	0.608 ± 0.034	0.582–0.034	Single	NR	Malignant	Endoscopic	Central	Total thyroidectomy	8.59 ± 1.59 (VAS)	5.56 ± 1.83
Nguyen 2021 (25)	P	Vietnam	51	50	12	90.20%	96.70%	45.1 ± 11.8	34.5 ± 8.4	2.29 ± 0.89	2.18 ± 0.88	Single	Single	Benign	Endoscopic	Central	Total and Hemi thyroidectomy	50 (98.03%) satisfied (Fischer exact test)	48 (96%) satisfied
Zhang 2021 (38)	R	China	45	50	11	80%	100%	33.4 ± 6.87	34.44 ± 7.65	0.66 ± 0.31	0.61 ± 0.31	Single	Single	Malignant	Endoscopic	Central	Total and Hemi thyroidectomy	NR	NR
Zheng 2021 (26)	R	China	150	150	30	90%	84.60%	35.3 ± 10.0	37.4 ± 10.7	0.8 ± 0.5 [0.2–3]	0.6 ± 0.3	Multiple	Multiple	Benign & malignant	Endoscopic	Central	Total and Hemi thyroidectomy	97.2% very satisfied (Questionnaire)	99.3% very satisfied
Kim 2018 (24)	P	Korea	47	43	9	93.60%	95.30%	39.4 ± 9.4	39.8 ± 10.7	0.7 ± 0.4	0.9 ± 0.5	Single	Single	Benign & malignant	Robotic	Central	Total and Hemi thyroidectomy	3.68 ± 0.52 (Satisfaction Score (0–5))	3.40 ± 0.76
Shen 2021 (21)	R	China	57	74	12	63.20%	64.90%	37.8 ± 12.4	41.2 ± 11.9	2.5 (2.95)	2.6 (3.15)	Single	Multiple	Benign	Endoscopic	Central	Hemi thyroidectomy	NR	NR
Sun 2020 (11)	R	China	100	119	18	86.60%	86%	29.65 ± 6.57	34.59 ± 7.69	0.71 ± 0.38	0.67 ± 0.31	Single	NR	Malignant	Endoscopic	Central	Hemithyroidectomy	NR	NR

3.2. Meta-analysis of intra- and post-operative outcomes

Primary outcome: Operative time (Reported in 15 studies), including a total of 2173 patients. The operative time was higher in TOT compared to TAT. (SMD = 0.72 95% CI [0.07; 1.37], P = 0.03). Heterogeneity was (97.7%, P < 0.001). (Fig. 1, Table 2).

4. Secondary outcomes

1) The number of harvested LNs was reported in 9 studies with 1610 patients included. Our meta-analysis showed that the number of harvested LNs was more in TOT compared to TAT (SMD = 0.32 [0.02; 0.62], P = 0.03), however; heterogeneity was high with I^2 of 84.9%. The weighted mean of harvested LNs was 6.33 and 5.16 nodes in TAT and TOT respectively. Tables 2 and 4
2) The amount of estimated blood loss (EBL) was reported in 7 studies, including a total of 567 Patients. TOT showed less intra-operative blood loss compared to TAT (SMD = −0.26 [-0.43; −0.09], P = 0.001). No heterogeneity among the included studies (I^2 = 0.0%). The weighted mean of EBL was 19.39 and 22.64 ml in TAT and TOT respectively. Tables 2 and 4
3) Recurrent laryngeal nerve injury was reported in 10 studies with 1108 patients. There was no difference between TOT and TAT techniques (RD = −0.001 [-0.01; 0.01], P = 0.86). No heterogeneity among the included studies (I^2 = 0.0%).
4) Temporary hoarseness was reported in 13 studies, including 1968 patients and there was no difference between both groups (RD = −0.005 [-0.017; 0.007], P = 0.41). There was minimal heterogeneity (I^2 = 2.0%).
5) Any hoarseness (temporary or permanent) was reported in 14 studies with a total of 2093 patients and there was no difference between both groups (RD = −0.01 [-0.02; 0.01], P = 0.31). No heterogeneity among the included studies (I^2 = 0.0%).
6) Post-operative seroma was reported in 8 studies with 1530 patients. There was no difference between TOT and TAT (RD = −0.01 [-0.02; 0.004], P = 0.18). Heterogeneity was moderate with an I^2 of 33%.
7) Wound infection was reported in 14 studies with 2153 patients, and it was similar among TOT vs TAT (RD = −0.00 [-0.01; 0.01], P = 0.99). No heterogeneity among the included studies (I^2 = 0.0%).
8) Chyle leak was reported in 3 studies with 954 patients. It was similar among TOT vs TAT (RD = 0.002 [-0.007; 0.011], P = 0.67). No heterogeneity among the included studies (I^2 = 0.0%).
9) Hypocalcemia was reported in 12 studies with 1942 patients. It was similar among TOT vs TAT (RD = −0.01 [-0.04; 0.01], P = 0.33). Heterogeneity was high with I^2 of 72.1%.
10) Length of hospital stay was reported in 14 studies with 2011 patients, and there was no difference between both groups (SMD = −0.27 [-0.83; 0.29], P = 0.34). Heterogeneity was high with an I^2 of 96.6%. The weighted mean of hospital stay was 3.71 and 4.14 days in TAT and TOT respectively. Tables 2 and 4
11) Total hospital cost was reported in 3 studies with a total of 247 patients. *Trans*-oral group did not show difference from TAT (SMD = 0.19 [-0.18; 0.56], P = 0.32). Heterogeneity was moderate with I^2 of 42.0%. The weighted mean of hospital cost was 5919.05 and 6253.79 dollars in TAT and TOT respectively. Tables 2 and 4
12) Post-operative pain (assessed by VAS) was analyzed in 8 studies with a total of 1201 patients. No statistical significance was shown between TOT and TAT (SMD = −0.75 [-1.99; 0.49] P = 0.23). Heterogeneity was high with an I^2 of 95.5%. The weighted mean score of post-operative pain was 3.36 and 3.11 in TAT and TOT respectively. Tables 2 and 4

4.1. Threshold analysis based on the annual number of cases (learning curve)

1. Operative time:

TOT: Regarding total annual endoscopic cases, a statistically significant cutoff was detected at 7 annual cases. Mean OR time in studies with less than 7 annual cases was 299.6 vs 144.9 in studies with 7 or more annual cases (Interaction-P = 0.0001).

Regarding TOT-specific annual cases, a trend in significance was detected at 10 annual cases. Mean OR time in studies with less than 10 annual cases was 226.6 min vs 129.7 in studies with more than 10 annual cases (Interaction-P = 0.095).

TAT: Considering total annual endoscopic cases, there was statistical significance at a cutoff of 7 annual cases, where mean OR time was 221.6 and 147.9 in studies less than 7 and more than 7 annual cases respectively (Interaction-P = 0.019).

Regarding group-specific annual cases, a trend in significance was

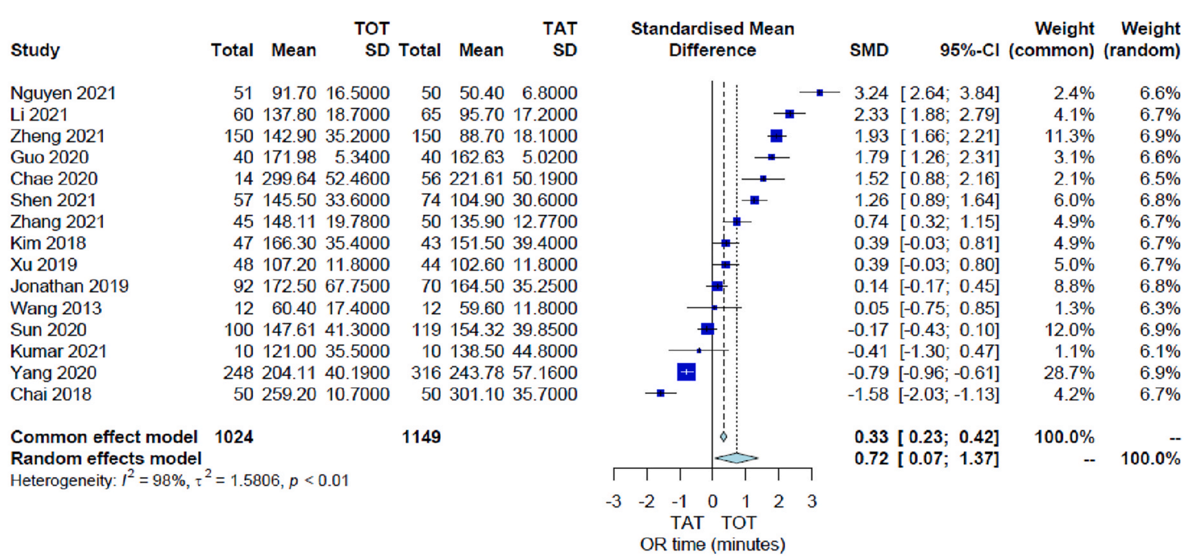
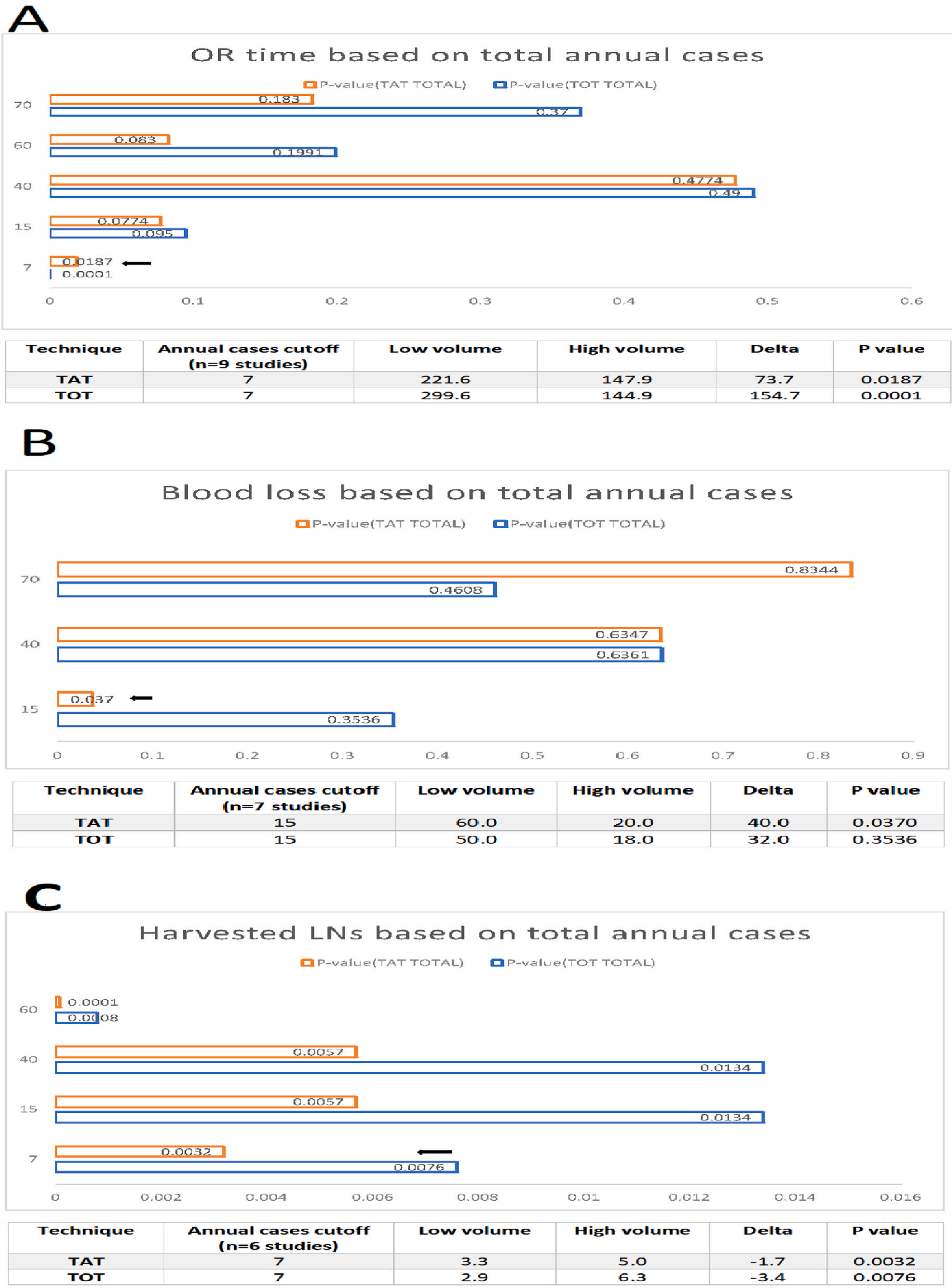


Fig. 1. Forest plot of operative time (minutes).



Technique	Annual cases cutoff (n=9 studies)	Low volume	High volume	Delta	P value
TAT	7	221.6	147.9	73.7	0.0187
TOT	7	299.6	144.9	154.7	0.0001

Technique	Annual cases cutoff (n=7 studies)	Low volume	High volume	Delta	P value
TAT	15	60.0	20.0	40.0	0.0370
TOT	15	50.0	18.0	32.0	0.3536

Technique	Annual cases cutoff (n=6 studies)	Low volume	High volume	Delta	P value
TAT	7	3.3	5.0	-1.7	0.0032
TOT	7	2.9	6.3	-3.4	0.0076

Fig. 2. Threshold analysis for cutoff determination based on annual total thyroidectomy for A) OR time, B) Blood loss and C) Harvested lymph nodes (LNs). P value was obtained from subgroup analysis (P-interaction).

found in 10 annual cases. Mean OR time was 221.126 and 123.917 min for studies with less than and more than 10 annual cases respectively (Interaction-P = 0.0774).

We ran subgroup analysis for the 1ry outcome (OR time) based on type of procedure (bilateral/unilateral) and it revealed: SMD = 1.9186 [1.4440; 2.3931] vs 0.3072 [−0.4177; 1.0321], in bilateral and unilateral respectively (P-interaction= <0.001).

2. Blood Loss:

Table 2
Outcomes summary. RD: risk difference, SMD: standard mean difference, TOT: trans-oral thyroidectomy.

Outcomes	Studies	Patients	Estimate (95%CI), P value	Heterogeneity (I^2, P)	Interpretation
OR time (minutes)	15	2173	SMD = 0.7225 [0.0734; 1.3716], P = 0.0291	97.7%, P < 0.0001	Higher in TOT
Harvested LN	9	1610	SMD = 0.3212 [0.0200; 0.6223], P = 0.0366	84.9%, P < 0.0001	Higher in TOT
Blood loss (ml)	7	567	SMD = −0.2645 [-0.4307; −0.0984], P = 0.0018	0.0%, p = 0.6497	Less in TOT
RLN injury ¶	10	1108	RD = −0.00094 [-0.01146; 0.00957], P = 0.8605	0%, P = 1	No difference
Temporary hoarseness	13	1968	RD = −0.00503 [-0.017; 0.00694], P = 0.4104	2.0%, P = 0.42	No difference
Any hoarseness	14	2093	RD = −0.00593 [-0.01745; 0.00559], P = 0.31	0.0%, P = 0.4594	No difference
• Any Hoarseness in Benign	6	563	RD = 0.0052 [-0.0159; 0.0263], P = 0.63	0.0%, P = 0.4356	No difference
• Any Hoarseness in malignant	4	476	RD = −0.0201 [-0.0691; 0.0289], P = 0.42	36.4%, P = 0.1936	No difference
Seroma	8	1530	RD = −0.00775 [-0.01919; 0.00369], P = 0.18	33%, P = 0.16	No difference
Infection	14	2153	RD = −0.0000 [-0.0055; 0.0055], P = 0.99	0.0%, P = 0.9987	No difference
Chyle leak	3	954	RD = 0.002 [-0.00732; 0.01133], P = 0.67	0.0%, P = 0.6975	No difference
Hypocalcemia	12	1942	RD = −0.01336 [-0.04034; 0.01362], P = 0.33	72.1%, P < 0.0001	No difference
Hospital stays (days)	14	2011	SMD = −0.2695 [-0.8278; 0.2888], P = 0.34	96.6%, P < 0.0001	No difference
Post-operative pain	8	1201	SMD = −0.7518 [-1.9909; 0.4873], P = 0.23	95.5%, P=<0.0001	No difference
Cost	3	247	SMD = 0.1899 [-0.1820; 0.5617], P = 0.32	42.0%, P = 0.1783	No difference

Table 3
Meta-regression of different variables on the different selected outcomes.

	OR time (n = 15)	Harvested LN (n = 9)	Blood loss (n = 7)
Variables	Beta ±SE, P-value	Beta ±SE, P-value	Beta ±SE, P-value
Mean age	−0.0253 ± 0.0631, P = 0.6887	−0.0467 ± 0.0421, P = 0.2674	0.021 ± 0.0147, P = 0.1523
Female percent	0.0012 ± 0.0425, P = 0.9784	−0.0251 ± 0.0319, P = 0.4321	−0.0018 ± 0.0065, P = 0.7755
Nodule size	0.2372 ± 0.375, P = 0.527	−0.6072 ± 1.0471, P = 0.562	−0.1249 ± 0.0826, P = 0.1306
Publication year	0.2634 ± 0.1535, P = 0.0861	0.1724 ± 0.1256, P = 0.1698	−0.0081 ± 0.0501, P = 0.8713
Study period (months)	−0.0119 ± 0.007, P = 0.0865	−0.0031 ± 0.0033, P = 0.3553	−0.026 ± 0.0172, P = 0.1302
Annual endoscopic thyroidectomy	0.0102 ± 0.0071, P = 0.1486	0.002 ± 0.0034, P = 0.5602	0.0016 ± 0.0027, P = 0.5581
Annual TOT thyroidectomy	0.0225 ± 0.0144, P = 0.1175	0.0042 ± 0.0068, P = 0.5346	0.0047 ± 0.0067, P = 0.4788
Annual TAT thyroidectomy	0.018 ± 0.0136, P = 0.1857	0.0036 ± 0.0066, P = 0.5898	0.0023 ± 0.0046, P = 0.622
No. of Institutions (Single (vs multiple))	−0.3661 ± 0.9511, P = 0.7003	−0.6018 ± 0.3615, P = 0.096	NA
No. of surgeons (Single (vs multiple))	−0.7242 ± 0.8261, P = 0.3807	−0.5221 ± 0.4097, P = 0.2025	0.1102 ± 0.2207, P = 0.6175

TOT: There was no statistically significant cutoff value for the number of cases in either total endoscopic or TOT-specific annual thyroidectomies.

TAT: Considering total annual endoscopic cases, there was statistical significance at a cutoff of 6 annual cases, where mean blood loss was 60 ml and 20 ml in studies less than 6 and more than 6 annual cases respectively (Interaction-P = 0.037).

Regarding group-specific annual cases, the same results were obtained.

3. Harvested LNs:

TOT: Considering total annual endoscopic cases, there was statistical significance at a cutoff of 7 annual cases, where mean number of lymph nodes was 2.9 and 6.3 nodes in studies less than 7 and more than 7 annual cases respectively (Interaction-P = 0.008).

Table 4
Single arm meta-analysis of continuous outcome.

Outcomes	Number of Studies	Number of patients	Mean of TOT	Mean of TAT
OR Time	15	2173	158.03 [127.68; 188.38]	144.9678 [110.1119; 179.82]
Estimated blood loss (ml)	7	567	19.39 [14.10; 24.68]	22.64 [17.31; 27.98]
Hospital Stay (days)	14	2011	3.71 [3.19; 4.24]	4.14 [3.74; 4.54]
Harvested LN	9	1610	6.33 [5.21; 7.45]	5.16 [4.21; 6.10]
Cost ($)	3	247	5919.05 [501.61; 11336.48]	6253.79 [217.04; 12290.54]
Post-op Pain	8	1201	3.36 [2.47; 4.25]	3.11 [2.54; 3.68]

Regarding group-specific annual cases, the same results were obtained.

TAT: Considering total annual cases of endoscopic thyroidectomy, there was statistical significance at 7 annual cases with a mean number of lymph nodes of 3.3 nodes in studies with less than 7 annual cases and 5.0 nodes in those with >7 cases (Interaction-P = 0.003).

When considering techniques specific annual cases, statistical significance was found in 6 annual cases. Mean number of lymph nodes in studies with less than 6 annual cases was 3.3, and in studies with more than 6 annual cases it was 5 (Interaction-P = 0.003).

5. Discussion

In an era of rapidly evolving minimally invasive surgery, endoscopic and robotic surgical approaches have progressed significantly over the recent years and widely replaced conventional open techniques in many fields of surgery [29–31]. Thyroid surgery is not an exception, with the development of a number of endoscopic thyroidectomy techniques aiming at reaching efficacy and safety with fewer perioperative adverse events and better cosmetic outcomes [32].

Trans-oral endoscopic thyroidectomy is a promising endoscopic technique in terms of cosmesis, along with enhanced accessibility to the central compartment [33]. In this meta-analysis, we analyzed surgical outcomes and overall patient satisfaction from studies comparing *trans*-oral thyroidectomy with other endoscopic thyroidectomy techniques. We also investigated the impact of surgeons learning curves on intra and post-operative outcomes.

The results of our meta-analysis showed that *trans*-oral thyroidectomy had a significantly longer operative time. Even though flap raising is supposed to be shorter and more feasible in TOT, yet the developing learning curves for this new technique can be the reason for the longer operative time [33,34]. In addition, the narrow working space and the limited number of working arms further affect retraction and dissection [35]. Our results are corresponding to results published in a previous meta-analysis [36].

In our meta-analysis, TOT was superior regarding the number of harvested lymph nodes. In general, this was already one of the proposed advantages of the *trans*-oral approach due to better visual access to the central compartment in addition to the more feasible top to down approach for lymph node dissection [26]. In contrast to our results, data from another meta-analysis did not show a difference in the number of lymph nodes between the 2 groups, this discrepancy can be due to limited number of studies in previous meta-analyses [36].

Intra-operative blood loss was less in the *trans*-oral technique compared to other endoscopic thyroidectomy techniques. This can be due to the shorter distance of flap dissection and more direct access to the thyroid gland and its blood supply [18]. Data from the previous meta-analysis didn't find a difference in the amount of blood loss between *trans*-oral and non-trans-oral techniques, which again can be explained by the lower number of included studies [36].

There was no significant difference between the 2 groups regarding, hospital stay, RLN injury, transient or permanent hoarseness (TOT: 21 cases (2.05%), TAT: 34 cases (2.95%)), this is lower than the reported RLN injury in conventional thyroidectomy with incidence up to 14% [37], transient or permanent hypocalcemia(TOT: 15 cases(1.46%), TAT: 46 cases(4%)) this is much better than conventional open thyroidectomy where the incidence of hypocalcemia is reported to be between (15–30%) [38], the improvement in rates of RLN injuries and hypocalcemia compared to open group can be attributed to the magnification power of the endoscopy which allows better identification and preservation of RLN and parathyroid glands [39,40]. Wound infection (TOT: 5 cases (0.48%), TAT: 5 cases (0.43%)) and seroma collection (TOT: 7 cases (0.68%), TAT: 11 cases (0.95%)), showed no statistically significant difference between both groups. These results are similar to results from prior meta-analyses [36], This can be explained by the magnification power of endoscopic and robotic techniques which allows better visualization of RLN and parathyroids [39,40].

Threshold analysis, done for both groups regarding A) OR time, B) blood loss, and C) number of harvested LNs, demonstrated enhanced outcomes at cut-off points ranging between 6 and 15 annual cases. This reflects an improvement in the learning curve. Results were similar for both groups. For *trans*-oral thyroidectomy, our results regarding the learning curve cut-off point are concordant with other reports in the literature. Razavi et al. and Lira et al. both reported annual cases cut off point of 11 and 15 cases respectively, while Anuwong et al. reported annual cases cut off point ranging from Refs. [7–10] cases [9,40,41], yet Chai et al. found improvement in learning curve at 58 cases [42] For other endoscopic techniques, the learning curve reported in previous studies was higher than our results. Lia et al. and Li et al. reported a learning curve of 27 and 35 cases respectively [43,44], Cao et al. described learning curve improvement at 25 cases [45], while Kandil et al. reported a learning curve at 69 cases for *trans*-axillary and 21 for retro-auricular [46]. Learning curves for endoscopic surgeries generally differ from one procedure to another [47]. Multiple studies in the literature investigated the learning curve for endoscopic thyroidectomy, yet the data were inconsistent with variable cut-offs of the learning curve reported (Supplementary Table 3). This discrepancy can be attributed to the different methods of learning curve assessment (CUSUM, moving average method, and threshold analysis) and the outcome assessed, the volume of patients, the type of thyroidectomy procedure, the tool used (endoscopic vs robotic), and the surgical background of the performing surgeon. Kwak et al., reported an improvement in the learning curve from 60 cases in the early experience with lobectomy cases, to 38 cases in the later total thyroidectomy cases [48]. Also, Lee et al. found different learning curves between endoscopic (55–70 cases) and robotic thyroidectomies (35–45 cases) [49]. The shorter learning curve required for *trans*-oral thyroidectomy may reflect a feasible and easy to learn technique, alternatively, it may be due to a cumulative effect from previously gained experience with endoscopic thyroidectomy.

Strength and Limitations: To our knowledge, this is the first meta-analysis that compared *trans*-oral and other endoscopic thyroidectomy techniques in terms of chyle leak, post-operative pain, and total cost. We did not find a significant difference between both groups. Furthermore, and up to our knowledge, our meta-analysis is the first meta-analysis that investigated the learning curve in those two relatively novel techniques.

Our meta-analysis has many limitations. There were some heterogeneities of the technique as some of the studies included *trans*-axillary and some-trans areolar and some used a combined technique. Additionally, some of the included studies had both endoscopic and robotic techniques, without specifying, all of which can vary in various outcomes and learning curves. Furthermore, there were some heterogeneities in the procedure done (total thyroidectomy ± neck dissection versus thyroid lobectomy). For threshold analysis, in order to get a statistically significant difference, the number of studies included in some subgroups was sometimes small which may be a cause of type I error, however; our obtained cutoffs were comparable to prior publications related to learning curve [9,40,41]. All the included studies are retrospective studies with possible inherent observer bias, as well as bias from unmatched confounders. While we collected data for cosmetic outcomes, we couldn't conduct a meta-analysis on that due to a lack of a universal definition/assessment approach for that.

6. Conclusion

Trans-oral thyroidectomy is a reliable and safe approach for benign and malignant thyroid conditions with comparable outcomes to other endoscopic thyroidectomy techniques. Our study showed that it is superior in terms of operative time, central lymph node harvesting, and blood loss. Being a novel technique, it is expected to have even improved outcomes with technique mastery, this meta-analysis found the learning curve to be ranging between 6 and 15 annual cases.

Ethical approval

IRB approval was not needed as this is a meta-analysis of published data, however, PROSPERO registration was done.

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None.

Author contribution

Study design: Mohamed Rahouma. Data collections: Anas Dabsha, Ismael Elkharbotly, Islam Hossam. Data analysis: Mohamed Rahouma, Anas Dabsha. Writing: Mohamed Rahouma, Anas Dabsha, Sherif Khairallah, Review and editing and final approval: All authors.

Trail registry number

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Declaration of competing interest

No Conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2022.106739.

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