

## Research

# Endoscopic thyroidectomy for central lymph node dissection—is there a difference in the number of lymph node dissections performed through different surgical approaches? A retrospective cohort study and pooled data research

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## Abstract

**Background** Endoscopic thyroidectomies are commonly performed for thyroid cancer. Previous studies indicated that trans-areola approach is inferior in central lymph node dissection (CLND) due to clavicle protruding. The present study aimed to compare different surgical approaches of endoscopic thyroidectomies regarding surgical outcomes.

**Methods** Retrospective analysis of 153 patients underwent endoscopic thyroidectomies through oral and areola approaches from Nov. 2019 to Dec. 2022 in our institution, baseline information, surgical outcomes and postoperative complications were recorded and analyzed. For pooled data analysis, comprehensive searching was done to identify studies concerning comparison of endoscopic thyroidectomies. Basic information and surgical outcomes were extracted. RevMan 5.4 was used to analyze the pooled data.  $p < 0.05$  was considered statistically different.

**Results** A total of 153 patients were included with 75 in oral, 78 in areola. The operative time was longer in oral compared with other two groups. Number of lymph nodes, positive lymph nodes, hospital stay, postoperative drainage and complications were not different between the two groups. For the systematic review, five studies of oral and areola comparisons containing 568 patients was finally included in the meta-analysis. The operative time was slightly longer in oral group. Number of positive lymph nodes were slightly larger in areola. The blood loss, lymph nodes, hospital stay and transient hoarseness were not different between oral and areola.

**Conclusions** Oral demanded more operative time than other approaches. Lymph nodes, positive lymph nodes and hospital stay were similar between different groups. Areola was comparable with oral in lymph nodes and positive lymph nodes.

**Keywords** Transoral trans-axillary trans-areolar approaches · Endoscopic thyroidectomy · Central lymph nodes dissection · Thyroid cancer · Surgical outcomes

Zheng Wang, Han Yan and Jun Yu These three authors provided equal contributions.

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## 1 Introduction

Thyroid carcinoma (TC) is estimated as the seventh most prevalent malignancy worldwide. The incidence of thyroid cancer in female is growing rapidly in the last decade [1, 2]. Surgery is the mainstream treatment for TC. Conventional open thyroidectomy leaves the patients with an obvious scar in the neck. Despite the advantages of suture techniques to minimize the appearance of the scar and various extra ways of eliminating the scar, many young patients diagnosed with TC are reluctant to choose open thyroidectomy [3, 4].

Remote-access thyroidectomy (RAT) means endoscopic thyroidectomy with remote access from the neck, thus leaving no scar in the sensitive cosmetic-wise neck [5, 6]. In 1997, the first endoscopic thyroidectomy was reported by Germany researcher Huscher [7]. After that, various methods of RATs were reported worldwide. Transoral endoscopic thyroidectomy vestibular approach (oral); total endoscopic thyroidectomy via areola approach (areola), retro-auricular endoscopic thyroidectomy (RA-ET) and bilateral axillo-breast approach (BABA) were brought up with different advantages and weaknesses. However, existing studies have point out that RATs could cause extra damage in the soft tissues and nerve structures, demand longer operative time and pose difficulties during lymph node dissections [8]. BABA is commonly performed for selected patients that wish no scarring in the neck. Areola approach is commonly performed in China with promising results, yet researchers demonstrated that areola approach is less convenient in dissecting the central lymph nodes (CLND) due to protruding of the clavicles [9], although a comprehensive CLND is a key factor which influences the prognosis of TC. However, these conclusions were made from single center studies or retrospective studies. Oral approach is a hot topic in minimal invasive thyroidectomy as it offers a truly scarless cosmetic outcome. Some scholars believed that oral was more efficient in dissecting the central lymph nodes due to the top down view of the procedure [10]. However, few studies have reported CLND of different endoscopic approach with concise results. To investigate whether there are differences in the total number of CLND and the number of metastatic lymph nodes between different endoscopic approaches. In the present study, we retrospectively analyzed patients who underwent endoscopic thyroidectomies performed by the same surgical team in our institution for central lymph node dissection and performed a systematic review and meta-analysis to compare the surgical outcomes, especially in central lymph nodes dissections of endoscopic thyroidectomies from published studies.

## 2 Methods

### 2.1 Patients and surgical techniques

Clinical data for 153 patients who were diagnosed with thyroid cancer at the (Yijishan Hospital) First Affiliated Hospital of Wannan Medical College. suitable of endoscopic thyroidectomies from November, 2019 to December, 2022 were retrospectively analyzed. The selection of surgical procedure was mainly based on the consultation of patients and doctors. advises were made by the surgeon and the case will be ruled out of the study: (1) History of neck radiotherapy; (2) hyperthyroidism; (3) Hyperparathyroidism; (4) medullary carcinoma of the thyroid, undifferentiated carcinoma; (5) thyroid tumor invading muscle; (6) thyroid tumor recurrence; (7) abnormal coagulation function; (8) liver and kidney dysfunction leading to inability to tolerate surgery. Baseline information, surgical procedures, surgical outcomes, number of central lymph node dissection, pathological diagnosis and postoperative outcomes were collected. Laryngoscope was performed in every patient preoperatively to rule out tumor invasion of the recurrent laryngeal nerve (RLN) before the surgery. The diagnosis of postoperative RLN injury is based on patients symptoms and result of the laryngoscope. If the vocal symptoms last for more than a year, it is considered permanent injury. Postoperative neuromuscular symptoms are defined as muscle cramping, numbness in the jaw or arms and legs.

Informed consents were obtained from every patients and the study was approved by the First Affiliated Hospital of Wannan Medical College Ethical Committee. That the study involving human participants was performed in accordance with the Declaration of Helsinki.

There were two endoscopic thyroidectomy procedures performed during the study. The brief introduction of the procedures were as following: Endoscopic transoral thyroidectomy (oral), After placed in a supine position with nasotracheal intubation, three laparoscopic instruments were inserted at the oral vestibula area in the lower lip. The working space was established through the two 5mm ports. The target thyroid lobe was dissected and removed while the parathyroid glands were identified and preserved. The surgeons identified RLN as well. Trans-areola approach (areola), the procedure

was similar to oral approach except the patients shoulders were slightly elevated. The observational port was inserted in the intersection of the connection of two nipples and the sternum. The two auxiliary ports were inserted around the two areola edges with about 5mm length. The thyroid glands and the lymph nodes were carefully dissected and removed, all incisions were carefully sutured and a drainage tube was routinely placed after the operation.

## 2.2 Searching and identification of studies

The present review is conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA). Comprehensive searching of Medline, Embase, Cochrane library and Clinical Trials for studies comparing TOETVA and AREOLA was conducted in December 12th, 2022. The searching terms includes: Thyroidectomy; Thyroid cancer; Endoscopic thyroidectomy; Transoral; Trans-areola; TOETVA; AREOLA. Each searching element are searched by both subject terms and entry words. For terms without corresponding subject terms, alternative words from published studies are used as many as we could identified. Relative references from the studies were manually searched. The detailed searching terms were summarized in Supplementary Materials.

## 2.3 Screening of studies

The titles and abstracts were reviewed by two authors independently. Full texts were reviewed for further screening. Studies with surgical outcomes including operative time, blood loss, CLND, hospital stay and postoperative complications were enrolled. If disagreement occurred, a group meeting was hold to discuss the enrollment of the debatable study.

## 2.4 Quality evaluation and data extraction

Observational studies were evaluated by the Newcastle–Ottawa Scale. For clinical trials, the Cochrane risk of bias tool was used. Data from the enrolled studies were extracted by two independent reviewers. The following data was extracted: titles, authors, published year, study design, number of patients, age of patients, gender, ways of endoscopic thyroidectomy, operative time, blood loss, number of CLND, hospital stay, postoperative complications.

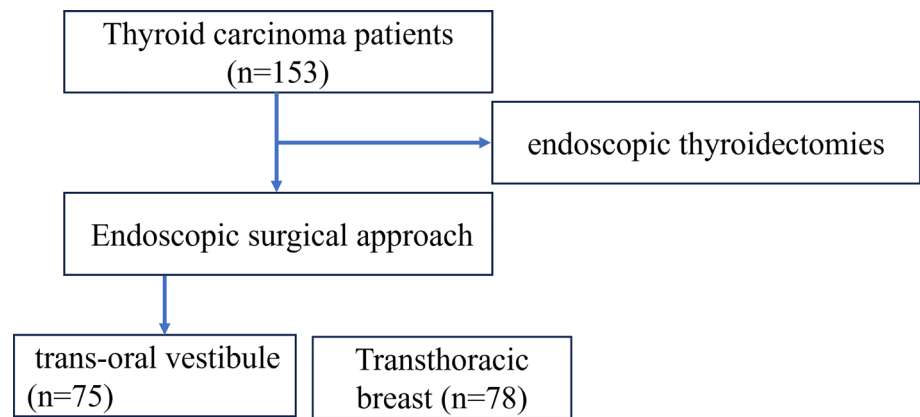
## 2.5 Statistical analysis

The extracted data was analyzed by Review Manager Software Version 5.4 (Cochrane Collaboration, Oxford, UK) and GraphPad Prism 7 (San Diego, USA). For continues variables, we used standardized mean difference (SMD) for pooled calculation, for dichotomous variables, odds ratio (OR) was used. Heterogeneity was reflected by  $I^2$  ( $I^2 > 50\%$  considered substantial heterogeneity). Statistically significance is considered if  $p < 0.05$ .

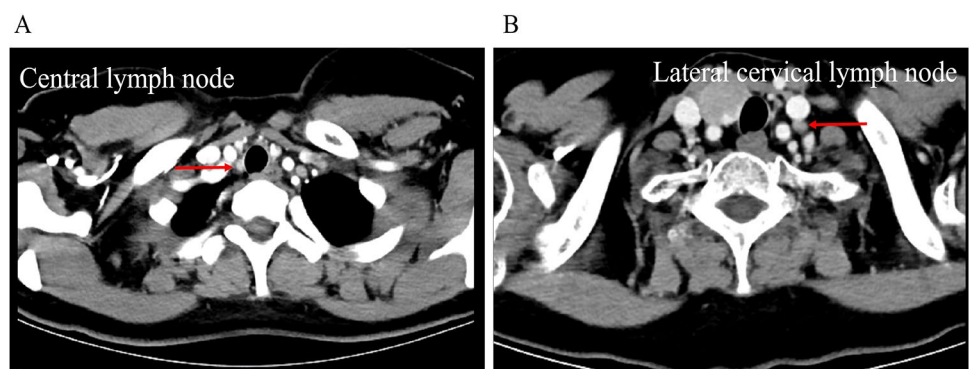
# 3 Results

## 3.1 Retrospective cohort study

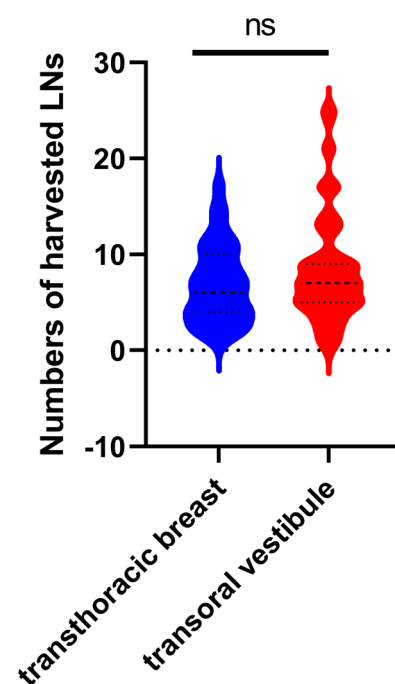
There were totally 153 patients concluded in the study, 78 in areola, 75 in oral group respectively (Fig. 1). All procedures were completed successfully without conversion to open procedures. Summarized information of the patients was in Table 1. The age of the two groups were similar. The vast majority of the patients were female (95.6% in Transthoracic breast and 88% Transoral vestibule). The operative time is longer in oral groups longer than that of in areola ( $190.44 \pm 49.05\text{min}$ ,  $159.15 \pm 45.55\text{min}$ ,  $p=0.001$ ). The average sides of the nodule are not different between the three groups. showed the computerized tomography (CT) scan of positive lymph nodes pre-operatively (Fig. 2). The number of CLND in each group was  $6.84 \pm 3.1$  and  $8.28 \pm 3.5$  respectively with no significant differences between the groups ( $p=0.06$ ) (Fig. 3). Positive CLND was similar between the three groups ( $2.36 \pm 1.71$  and  $2.75 \pm 2.05$  respectively,  $p=0.38$ ) (Fig. 4). One patient in areola and two patients in oral group developed transient RLN injury. One patient suffered from permanent RLN injury. Two patients in areola and two patients in oral group reported neuromuscular symptoms. All patients were pathologically diagnosed with papillary TC. Postoperative drainage volume of transthoracic approach was more than that of transoral approach but Postoperative drainage time and hospital stay were not different between the groups ( $p=0.63$ ,  $p=0.62$ ). The exposition of prelaryngeal, pretracheal and around RLN lymph nodes in areola approach was shown in (Figs. 5) and 6.

**Fig. 1** Study population**Table 1** Characteristics of the patients

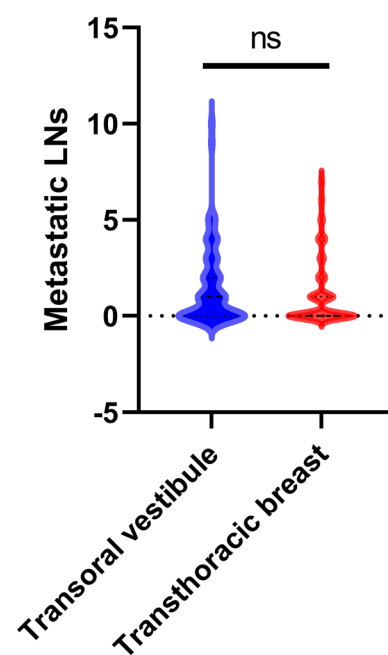
	Transthoracic breast (n = 78)	Transoral vestibule(n = 75)	<i>p</i>
Age	31.19 ± 6.87	32.22 ± 7.09	0.84
Gender	78	75	> 0.05
Female	73(95.6)	66(88%)	
Male	5(6.4%)	9(12%)	
Operative timing(min)	159.15 ± 45.55	190.44 ± 49.05	0.001
Size of the nodule(cm)	0.89 ± 0.70	0.73 ± 0.4	0.06
Number of CLND	6.84 ± 3.1	8.28 ± 3.5	0.06
Positive CLND	2.36 ± 1.71	2.75 ± 2.05	0.38
Postoperative RLN injury	1/78	2/75	0.27
Transient	1	2	
Permanent	0	0	
Neuromuscular symptoms	2/78	2/75	0.64
Transient	2	2	
Permanent	0	0	
Pathology			
Papillary	78	75	N/A
Follicular	0	0	
Medullary	0	0	
Anaplastic	0	0	
Postoperative drainage (ml, mean ± SD)	157.41 ± 62.03	132.77 ± 46.93	0.0084
Postoperative drainage time (day, mean ± SD)	3.60 ± 0.76	3.60 ± 0.73	0.63
Postoperative hospital stay (day, mean ± SD)	3.60 ± 0.75	3.61 ± 0.73	0.62

**Fig. 2** Computerized tomography(CT) scan of pre-operative lymph nodes(**A**: central, **B**:lateral). The arrow indicated positive lymph nodes

**Fig. 3** The number of harvested central lymph nodes in each group. *ns* no significant differences



**Fig. 4** The number of positive central lymph nodes in each group. *ns* no significant differences



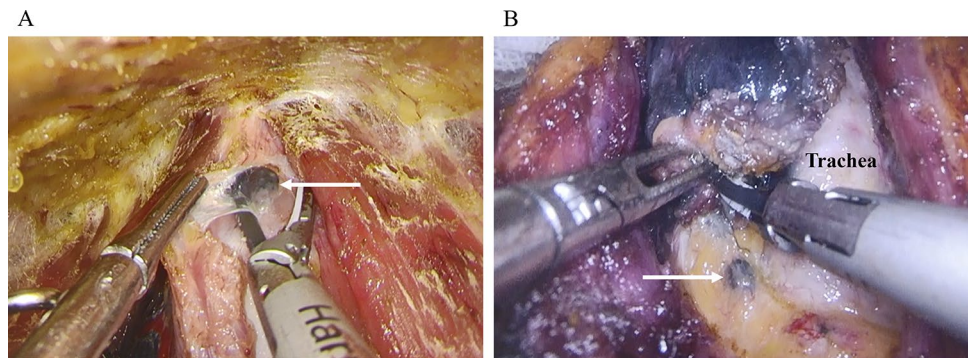
## 3.2 Pooled data research

### 3.2.1 Included studies

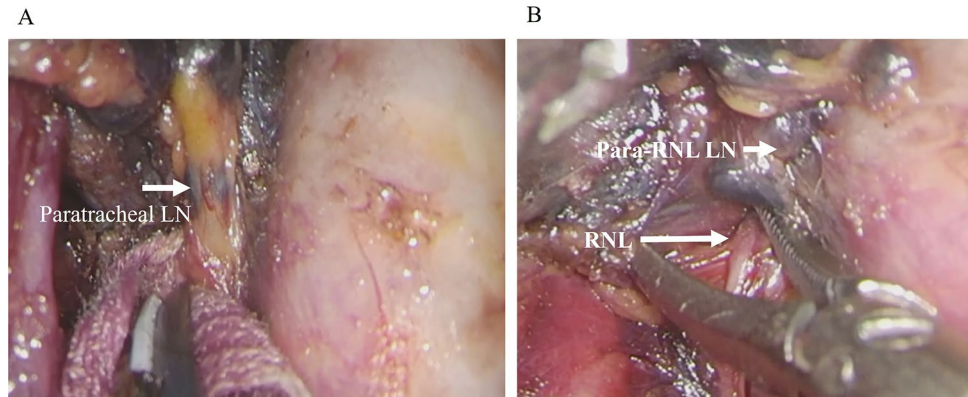
The searching flowchart was shown in (Fig. 7). Basic characteristics were summarized in Tables 2, 3. Due to the lack of studies focusing on pure axillary, unfortunately, we only got enough studies compared Oral and Areola, thus only comparisons of oral and areola were available in further analysis. Five studies containing 568 patients were finally enrolled in the review [11–18]. Three studies were retrospective studies and two were clinical trials (One RCT and One NRCT). All studies were conducted in Asia. For quality evaluation, all retrospective studies were of high quality according to Newcastle–Ottawa



**Fig. 5** Exposition of prelaryngeal(A) and pretracheal(B) lymph nodes in areola approach. The white arrow indicates the position of the dissected lymph nodes. ACM anterior cervical muscle, TG thyroid gland



**Fig. 6** Exposition of paratracheal lymph node(A) and para-recurrent laryngeal nerve (B) lymph nodes in Areola approach. The white arrow indicates the position of the dissected lymph nodes. LN lymph node, RNL recurrent laryngeal nerve



Scale (Supplementary material). Randomized trials were evaluated by Risk of Bias tool in RevMan Software(Supplementary Materials).

### 3.3 Operative time

Five studies with 568 patients compared in operative time between Oral and Areola (Fig. 8A). The pooled results showed that operative time was longer in Oral group than that in Areola group (SMD=6.46 95% CI 1.99 to 10.94  $p < 0.05$ ). Moderate heterogeneity ( $I^2=67\%$ ,  $p=0.02$ ) was found so the random effect model was used in the analysis.

### 3.4 Blood loss

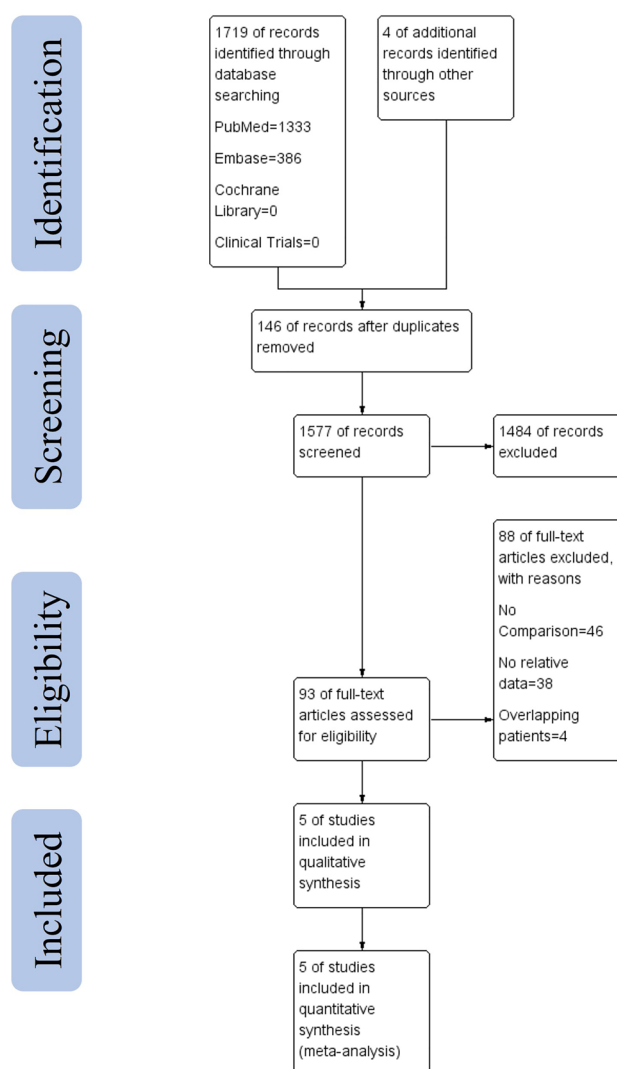
Four studies with 349 patients were analyzed in blood loss (Fig. 8B). The difference between oral and areola was not significantly different (SMD=−0.82 95%CI −2.32 to 0.68  $p=0.29$ ). No heterogeneity between the studies were found ( $I^2=0$ ).

### 3.5 CLND

Five studies with 568 patients compare number of CLND in the results (Fig. 9A). The pooled results showed no significant difference in number of CLND (SMD=0.24 95%CI −0.31 to 0.79  $p=0.39$ ). High level of heterogeneity was found ( $I^2=90\%$   $p < 0.0001$ ).

### 3.6 Number of positive lymph nodes

Three studies reported results of number of positive lymph nodes from prophylactic CLND (Fig. 9B), the pooled results showed that number of positive lymph node was slightly larger in Areola group (SMD=0.42 95%CI 0.05 to 0.78  $P=0.02$ ). The heterogeneity between the studies were moderate ( $I^2=65\%$   $p=0.06$ ).

**Fig. 7** Study searching flow**Table 2** Basic characteristics of included studies

Author	Year	Region	Study design	Group	Number of patients
Guo	2019	Asia	Retrospective	Transoral/Areola	40/40
Sun	2019	Asia	Retrospective	Transoral/Areola	100/119
Xu	2019	Asia	Retrospective	Transoral/Areola	48/44
Zhang	2021	Asia	NRCT	Transoral/Areola	50/45
Yang	2015	Asia	RCT	Transoral/Areola	41/41

### 3.7 Hospital stay

The length of hospital stay was not statistically different between the two groups (Fig. 10A) (SMD=0.28 95%CI – 0.28 to 0.23  $p=0.32$ ). High heterogeneity was found in the pooled result ( $I^2=90\%$   $p<0.0001$ ).

**Table 3** Newcastle–Ottawa Scale for observational studies

Study	Selection				Comparability	Outcome Assessment			Score
	1	2	3	4		7	8	9	
Guo 2019	*	*	*	*	**	*	*	*	9
Sun 2019	*	*	*	*	**	*	*	*	9
Xu 2019	*	*	*	*	**	*	*	*	9

**Explanation**

1, Adequate definition of the cases, study enrolled cases with independent validation. (Yes, \*; No or Not reported,0)

2, Representative of the cases, consecutive or obviously representative cases. (Yes, \*; No or Not reported,0)

3, Selection of controls, community controls. (Yes, \*; No or Not reported,0)

4, Clear definition of the controls, no previous history of the same procedure. (Yes, \*; No or Not reported,0)

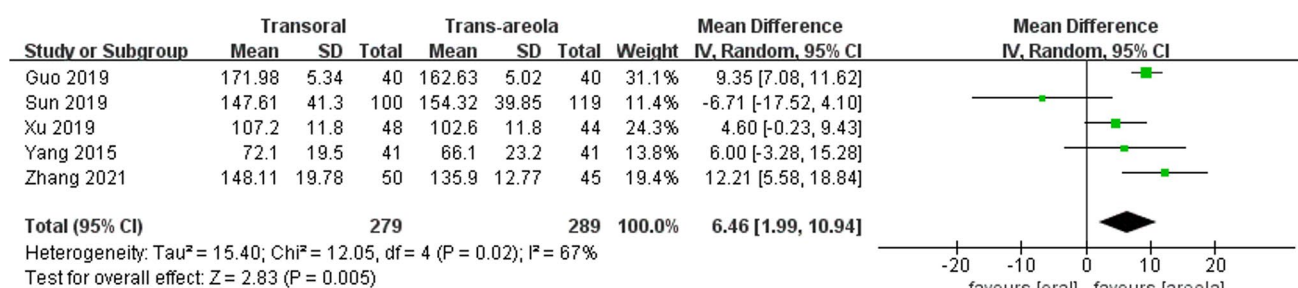
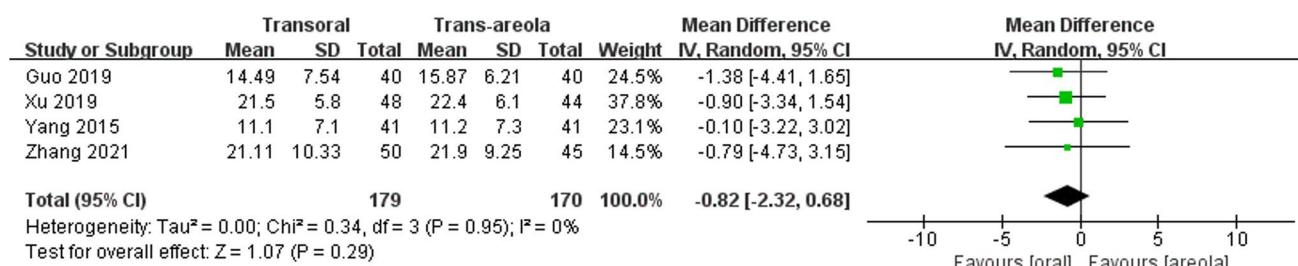
5, Comparability of cases and controls on the basis of the design or analysis, the patients baseline characteristics were similar between different groups. (Yes, \*; No or Not reported,0)

6, Comparability of cases and controls for other factors, the same type of procedure, the same surgical team to perform the procedure. (Yes, \*; No or Not reported,0)

7, Ascertainment of exposure, complete surgical records. (Yes, \*; No or Not reported,0)

8, Same method of ascertainment for cases and controls. (Yes, \*; No or Not reported,0)

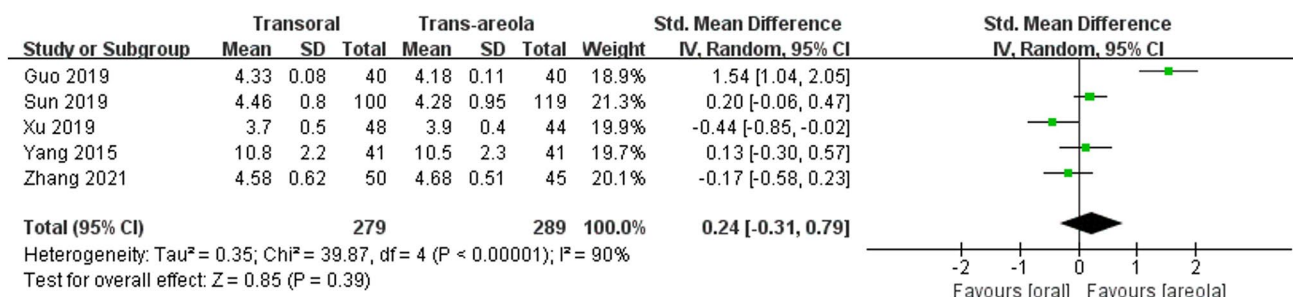
9, Adequacy of follow up of cohorts (Yes, \*; No or Not reported,0)

**A****B****Fig. 8** Forest plots of comparison of operative time(A) and blood loss(B) of oral and areola approach**3.8 Transient hoarseness**

Three studies with a total of 406 patients were analyzed for this outcome (Fig. 10B). The analysis showed that no differences of transient hoarseness was found between the two groups (OR = 0.69 95%CI 0.23 to 2.10  $p = 0.51$ ). No heterogeneity was found between the two groups ( $I^2 = 0$ ,  $p = 0.46$ ).



A



B

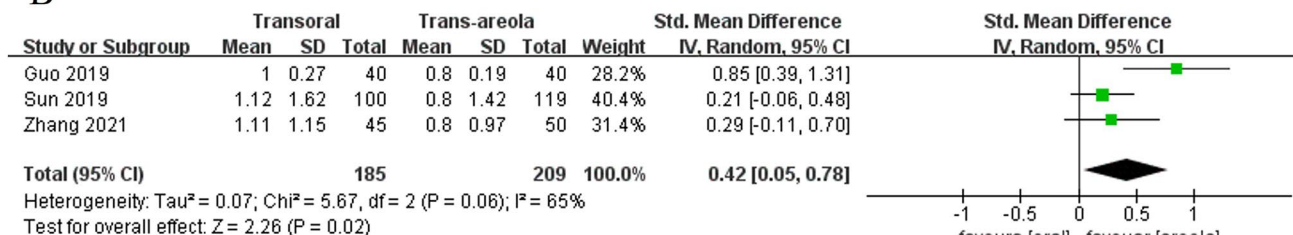
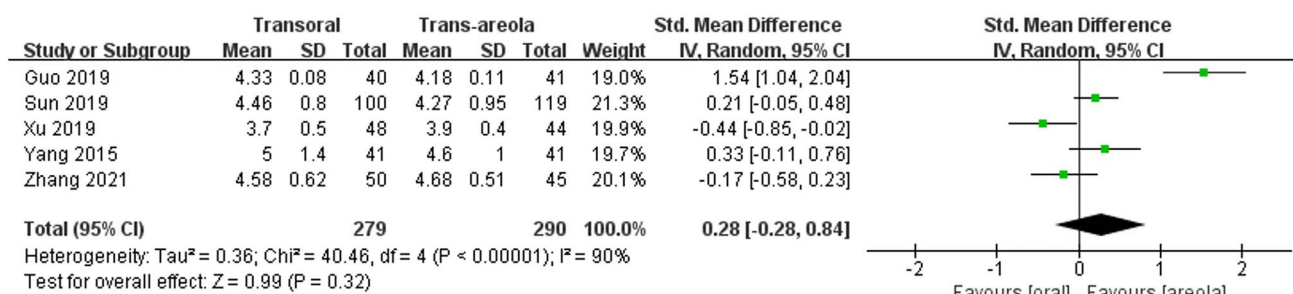


Fig. 9 Forest plots of comparison of CLND(A) and number of positive lymph nodes(B) of oral and areola approach

## 4 Discussion

The present study retrospectively analyzed patients underwent areola and oral approaches of thyroidectomy in our institution and found that number of CLND and positive lymph node were not different between these two groups. The operative time was longer in oral group compared with areola, postoperative RLN injury, neuromuscular symptoms and postoperative drainage time, hospital stay were not different between two groups, the amount of postoperative

A



B

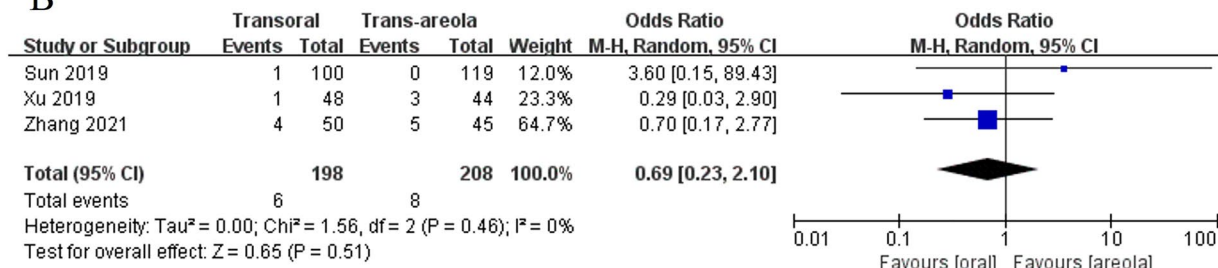


Fig. 10 Forest plots of comparison of hospital stay(A) and transient hoarseness(B) of oral and areola approach

drainage was larger in areola group than oral group. The meta-analysis compared two most commonly performed endoscopic thyroidectomy for surgical outcomes. The operative time was slightly longer in oral group, the number of positive lymph nodes were slightly larger in areola, the blood loss, number of CLND, length of hospital stay and risk of transient hoarseness were not different between oral and areola. Previous meta-analysis have focused on comparison between endoscopic thyroidectomy and conventional open procedure or endoscopy versus robotic thyroidectomy. To our knowledge, this is the first study comparing central lymph node and other surgical outcomes about oral and areola with institutional experience and meta-analysis.

Thyroidectomies through oral and areola approaches are considered RATs thus these procedures require longer operative time compare with open thyroidectomy [19, 20]. Setting up facilities and creating working space from access to thyroid require additional time. The additional operating time can be reduced when the working team gain more experiences [10, 21]. According to our results, the operative time is slightly longer in oral group than areola, the reasons may be the operating space through the oral route is narrower, and the interference of surgical instruments with each other, known as the “chopstick effect” is more pronounced. Blood loss was not different between oral and areola. Both these two approaches are equipped with endoscopy hence dissecting and cutting may be more clear with magnified visions. Previous studies reported that endoscopic thyroidectomy caused less bleeding compared with open procedure.

Our experience and meta-analysis showed that CLND was not statistically different between different endoscopic thyroidectomies, the number of positive lymph nodes were slightly larger in areola from the meta-analysis but not from institutional experience. Empirically, CLND is routinely performed in patients diagnosed with thyroid cancer preoperatively due to high lymph node metastasis [22, 23]. Wang et al. conducted a study in clinically N0 patients with PTC with 1–2 central lymph nodes metastasis, they found that in those patients, larger tumor, nodular goiter were associated with later lymph nodes metastasis, indicating the importance of CLND [24]. CLND can reduce the risk of tumor recurrence and improve patients survival [25, 26]. In areola approach, due to the nature of straight endoscopic equipment, it may be incapable of dissecting the lymph nodes near the caudal from a bottom to top view. Some surgeons believed this inconvenience can be overcome in oral approach. However, based on our results, the number of CLND was not different between these two approaches, suggesting that areola is feasible and effective in CLND compared with oral. Positive lymph nodes was slightly larger in areola from the meta-analysis, this result indicated that areola is feasible and convenient in dissecting lymph nodes. However, moderate heterogeneity was found in this pooled results, making this mild difference less convincing. Future studies focused on the positive lymph nodes ratio of CLND in oral and areola are needed to further conclude on this result. Moreover, if the patient was diagnosed or suspected with lower compartment of central lymph node metastasis, areola approach was usually not the recommendation for the patient, hence selection bias may exist under this circumstances.

Hospital stay was not different both from our data and meta-analysis. Both oral and areola are minimal invasive procedure combined with Enhanced recovery after surgery (ERAS) which means patients were usually encouraged to eat earlier, regain body movement earlier and discharged earlier [27, 28]. The result was consistent with previous studies reporting results of endoscopic thyroidectomies.

For postoperative complications, only three enrolled studies reported data with transient hoarseness. The result showed no differences between oral and areola in transient hoarseness. In our experience, postoperative RLN injury was found in one patient in areola and two patients in oral group respectively. Transient hoarseness was caused by transient RLN palsy. In open thyroidectomy, temporary or permanent RLN injury were about 2.11 to 11.8% and 0.2 to 5.9% respectively [29–31]. Previous trials or meta-analysis have compared the incidence of transient hoarseness between oral and areola [32]. Existing study suggested that oral should be more convenient in dissecting RLN for surgeons who are more familiar with the top down methods of identification of the RLN [33]. In areola, incidence of RLN injury was comparable with open thyroidectomy and other endoscopic thyroidectomy [34].

The reason of promotion of transoral thyroidectomy by surgeons worldwide is that this approach is believed to have better vision for central lymph nodes dissection. However, due to the nature of the oral cavity (colonized by more than 1000 bacteria species [35]), oral approach is considered clean-contaminated procedure different from areola approaches, which are clean procedures. The patients may suffer surgical site infections even with the use of antibiotics prophylaxis [36]. While operating through the oral incisions, the endoscopic instruments interfere with each other if the surgeon is not proficient enough. The learning curve of oral is longer than areola approaches [37]. Our experience is that surgeons can shorten the operation time and reduce the incidence of surgical complications through hard training, passing through the learning curve period and skilled operation. Areola is considered inferior in CLND due to the hindrance of the clavicle and sternum. It is still controversial about the superiority in CLND from oral and areola. Our results suggested that both oral and areola presented similar outcomes in CLND.

There are some limitations about the present study, the sample of the patients included in our study was relatively small. To address this question, we performed a meta-analysis aiming to bring more statistical credibility. Secondly, although all procedures were performed by the same surgical team, the surgical outcomes could be influenced by many factors like learning-curve of the new techniques. For the meta-analysis part, there were also some limitations. Firstly, due to the nature of the study, two clinical trials were included, the majority of included studies were single center retrospective studies which may bring selection biases. Secondly, in some pooled results, heterogeneities were moderate, after analysis of heterogeneities, we failed at eliminating heterogeneity by subgroup analysis due to the scarcity of the data. As a result, certain consideration must be taken when interpreting our results. Thirdly, all included studies were from Asia which may bring selection bias and limit the applicability of the results. Future randomized studies with larger sample size or multicenter studies with different regions worldwide are needed to conclude more precise conclusions regarding endoscopic thyroidectomies.

## 5 Conclusions

From our institutional experience, oral and areola approaches were comparable in CLND, positive lymph nodes, post-operative complications and hospital stay. Operative time was longer in oral compared with areola methods. From the meta-analysis, oral and areola were comparable in CLND, hospital stay and transient hoarseness, the operative time was longer in oral and positive lymph nodes were lower in oral. Areola approach is comparable in CLND with oral in both our experience and pooled meta-analysis. Future multicenter clinical randomized trials are needed to further confirm the inferiority of areola approach in CLND.

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**Author contributions** ZW wrote the paper, HY, JY provide methodology, RS, BC, ZCY and CSY collected the patients data. ZW, JY and HY analyzed the data. RS, CSY, BC and YBW acquire funding and instructed the whole study. All authors reviewed the manuscript.

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**Data Availability** Data is provided within the manuscript or supplementary information files.

## Declarations

**Ethics approval and consent to participate** The patients/ participants provided their written informed consent to participate in this study. The studies involving human participants were reviewed and approved by the Ethics Committee of the (Yijishan Hospital) First Affiliated Hospital of Wannan Medical College (Ethical approval number: 2023132).

**Consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.

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