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ORIGINAL SCIENTIFIC REPORT WITH VIDEO

Recurrent Laryngeal Nerve Morbidity: Lessons from Endoscopic via Bilateral Areola and Open Thyroidectomy Technique

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Abstract

Background and aim Elucidating the mechanism of recurrent laryngeal nerve (RLN) injuries through intraoperative electromyographic (EMG) and laryngeal examination approaches may deepen our knowledge regarding its prevention strategies. To date, no studies have been reported on the mechanism of RLN injury caused by endoscopic thyroidectomy via bilateral areola approach (ETBAA).

Methods Both intraoperative EMG profiles and postoperative laryngeal examination were used to investigate the mechanisms of RLN injury and compare the safety aspects between ETBAA and open thyroidectomy approach (OTA).

Results This study examined 1420 nerves at risk. The mean follow-up period was 17 ± 4 (range 6–48) months. The incidence of vocal cord paralysis was 4.1% (59/1420). The number of cases with decreased EMG signals and vocal cord palsy was higher in ETBAA group than in OTA group ($P < 0.05$). The left RLNs in ETBAA group were at higher risk compared to the right nerves.

Conclusions The results of the current study indicate that ETBAA exhibits higher risk of RLN injury. The topic includes a video.

Nan Liang and Hui Sun have equal contributors.

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Introduction

An alternative endoscopic approach to the thyroid gland has emerged for the treatment of both benign and malignant lesions [1–7]. Since 2000, a breast incision approach has been developed for performing endoscopic thyroidectomy, in order to avoid an operative scar on the neck [8]. Endoscopic thyroidectomy via bilateral areola approach (ETBAA) is a common surgical procedure, especially for young patients in Asian countries [4–9]. The major advantages include better cosmetic outcome, improved visualization of superior laryngeal nerves and level II lymph nodes [1–15].

To date, no studies have been reported on the mechanism of recurrent laryngeal nerve (RLN) injury during endoscopic thyroidectomy via ETBAA. Comparing remote access approaches to the traditional one, findings may help future surgeons.

This study aimed to assess the incidence of RLN injury among patients underwent ETBAA and open thyroidectomy approach (OTA), with special emphasis given on intraoperative electromyographic (EMG) RLN profiles and laryngeal examination.

Materials and methods

Patients' selection

This study prospectively recruited patients who underwent surgery at a tertiary referral center (Thyroid Surgery Division, China-Japan Union Hospital, Jilin University) from October 2013 to December 2017. All patients were treated by an experienced surgeon (DZ). Detailed inclusion and exclusion criteria for ETBAA are summarized in Table 1. All patients were stratified into three groups: (a) patients who were eligible for endoscopic treatment and received ETBAA; (b) patients who were candidates for ETBAA, but opted for traditional intervention (OTA-L); (c) patients who were noncandidates for endoscopic intervention and underwent open thyroidectomy (OTA-H). The flowchart of the grouping process is depicted in Fig. 1. All patients were analyzed for clinical, pathological, operative features and followed up. This study was approved by the medical ethical committee board (Protocol No. 2012-wjw001) and conducted in accordance with the Declaration of Helsinki.

Surgical methods

Patients were offered endoscopic thyroidectomy with ETBAA or OTA [16]. ETBAA surgery consisted of a 10-mm curved incision which was made along the margin of the right areola at 2–4 clock, for 10-mm trocar and 30-degree endoscope usage (Fig. 2). Bilateral 5-mm incisions were made on the areola at 11–12 clock and were then used for operating 5-mm trocars [16, 17]. Dissection and hemostasis were achieved with an ultrasonic scalpel (Johnson and Johnson Company, Cincinnati, Ohio, USA).

Table 1 Detailed inclusion and exclusion criteria for ETBAA

Selection and exclusion criteria
Selection criteria
Papillary thyroid cancer with low-risk factors[a]
Dominant benign nodule with a diameter <5 cm, whereas cystic nodule could be 6 cm or greater
The patients needed a cosmetic requirement
Exclusion criteria
General factors
Obesity
Clinical history of radiation or surgery on the neck or chest
Preoperative dysfunction of voice cord
Thyroid-related factors
Advanced cancer
Local invasion
Posteriorly located lesions
Diffuse or adhesion or fixation enlargement of lymph node
Evidence available of local or distant metastases
Graves' disease
Severe thyroiditis
Associated parathyroid disease

[a]Low risk factors including lesion size <4 cm, age <55 years, no prior radiation, no distant metastases, no lymph node metastases, no extrathyroidal extension, no aggressive variant, and no first-degree family history of thyroid carcinoma

RLN management

Vocal cord movement was evaluated by video-laryngofiberoscopy before surgery (*L*1) and on the first postoperative day (*L*2). IONM was provided via an intermitted mode of application in accordance with international standards [18]. RLNs were stimulated for both OTA and ETBAA groups using a single-use, sterile, incrementing Prass stimulating probe, monopolar, standard flexible and ball tip (Medtronic, Jacksonville, Florida, USA) In each group, vagus nerve (VN) was stimulated before surgical dissection (*V*1), while RLN was stimulated at first identification (*R*1) and after the completion of thyroid dissection (*R*2) [18]. Subsequently, VN was re-stimulated following thyroidectomy and hemostasis (*V*2) (Supplementary Video) [18]. For ETBAA group, the stimulating probe was percutaneously inserted [17] (Fig. 3).

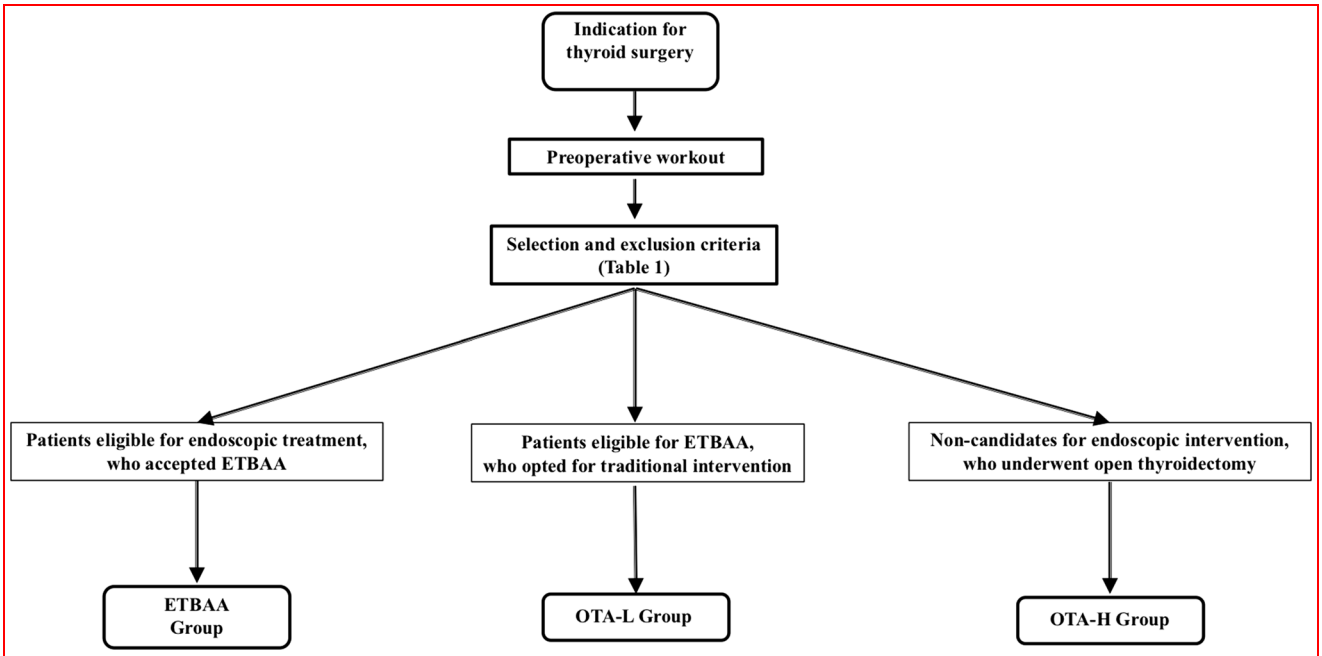

Fig. 1 Flowchart for the indications of surgical treatment

Definitions

The definition of decreased EMG amplitude or loss of signal (LOS), types of RLN injury (type 1 segmental and type 2 global), mechanism of injury and troubleshooting algorithm was referred to the published guidelines [18]. Briefly, *compression injury* was defined as the compression from peripheral tissues to RLN, mainly from inferior thyroid artery (ITA), Berry's ligament (BL) connective tissue or lymph nodes [18]. *Traction* was the injury caused by direct traction to the RLN during surgical operation, whereas *contusion* was the injury on the surface of RLN caused by blunt surgical instruments, including aspirator, etc. [18]. Moreover, *maximal EMG decrease* is defined as $R1 - \mathrm{Rm}/R1 \times 100\%$, where $R1$ is the initial EMG signal value of RLN and Rm indicates minimum EMG signal value during the entire operation. Meanwhile, *final EMG decrease* is defined as $R1 - R2/R1 \times 100\%$, where $R2$ represents EMG signal value after surgery. The mechanism of RLN injury was recorded and documented by a surgeon in both operative notes and resultant EMG profile.

Primary and secondary outcomes

Patients' clinicopathological characteristics and complications were analyzed among the 3 groups. The primary outcome measure was RLN injury. Parameters recorded on each RLN injury were stratified either unilateral or bilateral, which counted on each nerve at risk (NAR). Vocal cord dysfunction included two forms of weakened and fixed at postoperative laryngeal examination. RLN injury was considered permanent if it persists for 6 months [19]. The secondary outcome measures were the EMG signal profile of laryngeal nerve during different operational times, mechanism of determined nerve injury and location of injury. Patients with abnormal vocal cord movement were routinely followed up at the first week and 1, 2, 3 and 6 months after surgery.

Statistical analysis

All statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, USA) and SAS 9.4 (SAS Inc., North Carolina, USA). The data were presented as mean ± standard deviation, with fitted normal distribution, and expressed as n/N, where N is the total number of samples and n is the number of positive cases. The differences in EMG loss or vocal cord dysfunction, RLN injury causes and recovery conditions after various injuries among ETBAA, OTA-L and OTA-H groups were analyzed by Cochran's and Mantel–Haenszel Chi-square test, Fisher's exact test and Kruskal–Wallis H test, respectively. The level of statistical significance was set at 0.05.

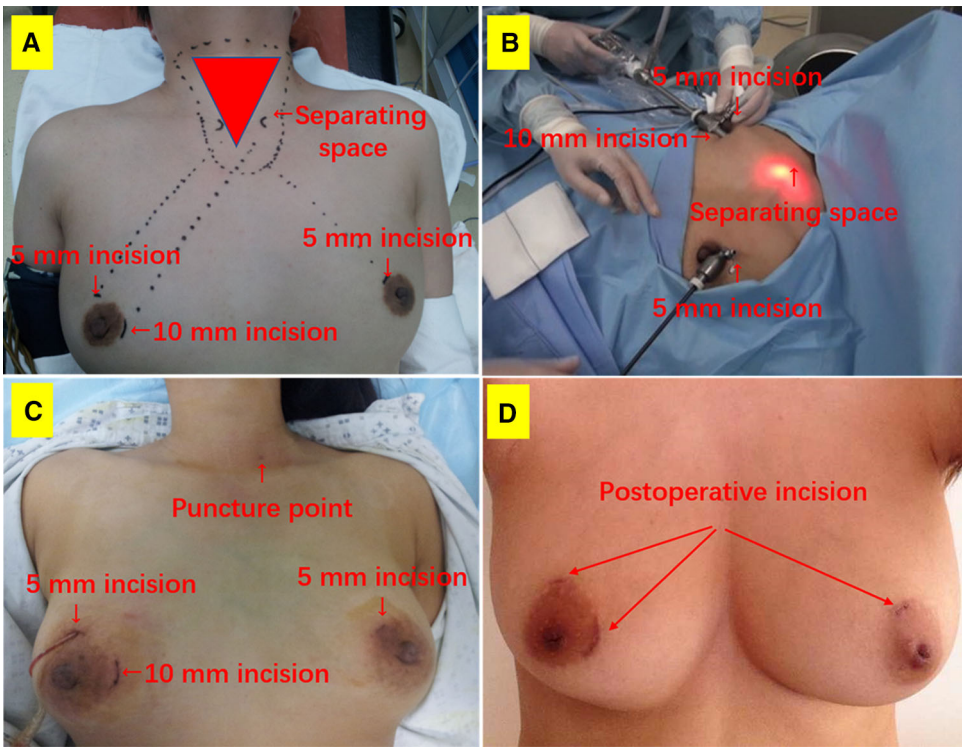

Fig. 2 Endoscopic thyroidectomy. **a** Incision and operative separation range; **b** intraoperative view; **c** 1-day postoperative outcome; **d** 1-month postoperative outcome

Results

Patients and surgical parameters

A total of 900 patients were enrolled in this study, providing 1420 RLN for the analysis. No cases were excluded due to instrument failure. The mean follow-up period was 17 ± 4 (range 6–48) months. Among the 300 patients underwent ETBAA, 369 RLN data were obtained and divided into 173 (46.9%) left and 196 (53.1%) right lobectomies. Meanwhile, 459 RLNs were found in OTA-L group (n = 300), involving 219 (47.7%) occurred at the left side, while 240 (52.3%) were at the right side. Besides, 592 RLNs were observed in OTA-H group (n = 300), including 288 (48.6%) left and 304 (51.4%) right sides.

Comparison of clinical characteristics among patients in the three groups

Detailed clinical data are shown in Table 2. Compared to traditional open surgery groups, patients who underwent ETBAA were younger, with more lobectomies and longer operative time. Additionally, the number of central lymph node dissection and malignancy for ETBAA was lower.

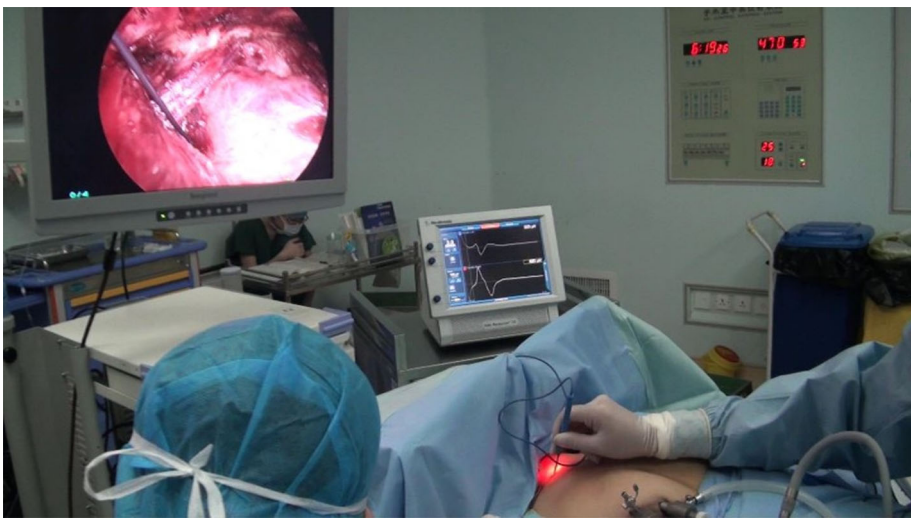

Fig. 3 Neural monitoring during endoscopic thyroidectomy

Table 2 Basic characteristics

	ETBAA (n = 300)	OTA-L (n = 300)	OTA-H (n = 300)	*P	&P	^P
Age (years)	32.8 ± 9.19	37.2 ± 10.3	45.9 ± 18.7	0.00	0.00	0.00
Gender						
M	31	45	51	0.06	0.06	0.29
F	269	255	249	–	–	–
Nerve at risk	369	459	592	0.87	0.32	0.42
Left	173	219	288	–	–	–
Right	196	240	304	–	–	–
Mean operating time (min)	103.6 ± 21.2	35.3 ± 9.38	58.2 ± 19.26	0.00	0.00	0.00
Intraoperative blood loss (ml)	6.83 ± 3.12	6.12 ± 2.98	8.53 ± 3.42	0.00	0.02	0.00
Postoperative hospital stay time (D)	3.62 ± 0.61	3.02 ± 0.73	4.21 ± 0.99	0.00	0.00	0.00
Postoperative bleeding (number)	0	0	3	–	–	–
Total drain volumes (ml)	57.35 ± 20.3	21.13 ± 15.2	50.31 ± 16.7	0.00	0.00	0.00
Mean draining days	1.83 ± 0.45	1.33 ± 0.41	1.92 ± 0.68	0.00	0.00	0.00
Parathyroid dysfunction (number)	7	6	15	0.63	0.46	0.68
Transient	7	5	12	–	–	–
Persistent	0	1	3	–	–	–
Hypocalcemia (number)	9	11	18	0.80	0.55	0.51
Transient	9	10	15	–	–	–
Persistent	0	1	3	–	–	–
Type of thyroidectomy				0.00	0.00	0.00
Total/near-total thyroidectomy	69	118	281	–	–	–
Lobectomy	164	142	8	–	–	–
Subtotal thyroidectomy	67	40	11	–	–	–
Central lymph node dissection	214	245	289	–	–	–
Type of histopathology				0.00	0.00	0.00
Benign	86	55	11	–	–	–
Malignant	214	245	289	–	–	–
Mean diameter of tumor (cm)	1.47 ± 1.33	1.58 ± 1.86	2.87 ± 1.93	0.00	0.72	0.00
Extracapsular invasion	0	0	121	–	–	–
Central LN meta	88	71	141	–	–	–

N is the number of patients in the different groups. Data, which fitted the normal distribution, were presented as mean ± SD

*$P < 0.05$, **$P < 0.01$; analysis of the total three groups with Cochran's and Mantel–Haenszel Chi-square (χ^2_{CMH}) test, while the variable of side was controlled

&$P < \alpha'$, analysis of group ETBAA and group OTA-L with χ^2_{CMH} test

^$P < \alpha'$, analysis of group OTA-L and group OTA-H with χ^2_{CMH} test

Interestingly, the numbers of NAR were significantly different between ETBAA group and OTA-H group ($P < 0.05$). However, there was no significant difference between the left and the right sides per group ($P > 0.05$).

EMG profiles

Overall, EMG signals were decreased by >50% among 75 cases (5.3%). After 30 min of standby operation, the recovery performances of EMG signals were relatively different among the three groups and remained stable (>50%) in 54 cases (3.8%), as presented in Table 3 and Fig. 4. In ETBAA group, EMG signals were reduced by >50% in 33 (8.9%) cases, including 23 (13.3%) left and 10 (5.1%) right RLNs. After 30 min of surgical standby, there were 23 (6.2%) cases with EMG signals <50%, including 19 (11%) left and 4 (2%) right RLNs. In OTA-L group, there were 12 (2.6%) patients who experienced a reduction of >50% EMG signals, including 5 (2.3%) left and 7 (2.9%) right RLNs. Of them, 9 (2%) patients experienced >50% of EMG signal loss after 30 min of surgical standby, including 4 (1.8%) left and 5 (2.1%) right RLNs.

Table 3 EMG changes of RLN and vocal cord dysfunction in RLN

	ETBAA	OTA-L	OTA-H	*P	&P	^P
Total RLN						
EMG loss maximal >50%	33/369**	12/459#	30/592	<0.001	<0.001	0.044
EMG loss final >50%	23/369**	9/459#	22/592	0.006	0.002	0.095
Vocal cord dysfunction	26/369**	9/459#	24/592	0.001	<0.001	0.054
EMG loss	23	9	22			
EMG normal	3	0	2			
Left RLN						
EMG loss maximal >50%	23/173**	5/219#	13/288	<0.001	<0.001	0.179
EMG loss final >50%	19/173**	4/219#	10/288	<0.001	<0.001	0.263
Vocal cord dysfunction	20/173**	4/219#	11/288	<0.001	<0.001	0.190
EMG loss	19	4	10			
EMG normal	1	0	1			
Right RLN						
EMG loss maximal >50%	10/196	7/240	17/304	0.293	0.198	0.131
EMG loss final >50%	4/196	5/240	12/304	0.316	0.975	0.215
Vocal cord dysfunction	6/196	5/240	13/304	0.353	0.517	0.156
EMG loss	4	5	12			
EMG normal	2	0	1			

*$P < 0.05$, **$P < 0.01$; analysis of the total three groups with Cochran's and Mantel–Haenszel Chi-square (χ^2_{CMH}) test, while the variable of side was controlled

&$P < \alpha'$, analysis of group ETBAA and group OTA-L with χ^2_{CMH} test, $\alpha' = \alpha/4 = 0.0125$

^$P < \alpha'$, analysis of group OTA-L and group OTA-H with χ^2_{CMH} test, $\alpha' = \alpha/4 = 0.0125$

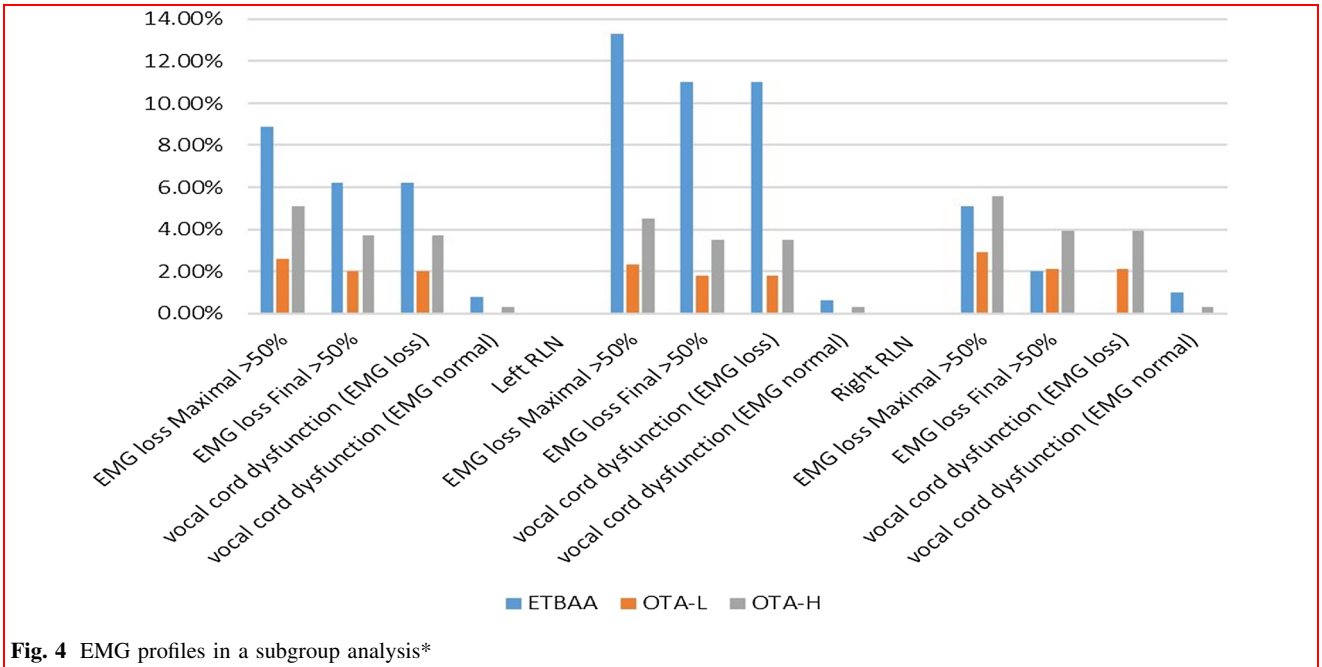

Fig. 4 EMG profiles in a subgroup analysis*

In OTA-H group, there were 30 (5.1%) cases with EMG signals <50%, including 13 (4.5%) left and 17 (5.6%) right RLNs. After 30 min of paused operation, 22 (3.7%) cases demonstrated a final EMG signal loss of >50%, including 10 (3.5%) left and 12 (3.9%) right RLNs. Notably, there was a significant difference between ETBAA group and

Table 4 Reasons of RLN injury

Reasons	ETBAA** (n = 36)	OTA-L (n = 12)	OTA-H (n = 32)
Traction	8	2	7
Compression	20	6	6
Inferior thyroid artery	11	3	3
Berry ligament	6	3	2
Fibrous tissue	3	0	1
Clamping	1	1	2
Contusion	3	2	3
Ultrasonic scalpel	1	1	0
Tumor invasion	0	0	12
Delayed neuropraxia	3	0	2

16 cells with $T < 5$

**P = 0.0004, analysis of the total three groups with Fisher's exact test (*$P < 0.05$, **$P < 0.01$)

&P = 0.5954, analysis of group ETBAA and group OTA-L with Fisher's exact test, $\alpha' = \alpha/4 = 0.0125$

^P = 0.0311, analysis of group OTA-L and group OTA-H with Fisher's exact test, $\alpha' = \alpha/4 = 0.0125$

OTA-L group ($P < 0.0125$), which was predominantly found in the left RLN (Table 3).

Postoperative laryngeal examination outcomes

The overall incidence of vocal cord paralysis was 4.1% (59/1420). In ETBAA group, there were 26 (7%) patients with abnormal vocal cord movement on the first postoperative day, including 11.6% (20/173) left and 3% (6/196) right RLNs (Table 3 and Fig. 4). A lower number of cases with abnormal vocal cord movement (n = 9, 2%) was found in OTA-L group, including 1.8% (4/219) left and 2.1% (5/240) right RLNs. Moreover, the prevalence of abnormal vocal cord movement was increased in OTA-H group (n = 24, 4%), involving 11 (3.8%, 11/288) left and 13 (4.2%, 13/304) right RLNs. Besides, the incidence of postoperative vocal cord palsy was significantly higher in ETBAA group compared to OTA-L and OTA-H groups. There was a significant difference between ETBAA group and OTA-L group ($P < 0.0125$), especially on the left-side RLNs (Table 3). When EMG signal decreased by more than 50%, the accuracy of predicting vocal cord paralysis was 88.5% (23/26) in ETBAA group, 100% (9/9) in OTA-L group and 91.7% (22/24) in OTA-H group.

The mechanisms of RLN injury

The elucidated mechanisms among 80 RLN lesions were included tissue compression (n = 32, 40%), traction (n = 17, 21.2%), contusion (n = 8, 10%), clamp (n = 4, 5%) and thermal injury (n = 2, 2.5%), as shown in Tables 4, 5 and Fig. 5. In ETBAA group, 20 cases (55.6%) were tissue compression, 8 (22.2%) traction, 1 (2.8%) clamp, 3 (8.3%) contusion and 1 (2.8%) thermal injury. In OTA-L group, the main causes of RLN injury were tissue compression (n = 6, 50%), followed by traction (n = 2, 16.7%), clamp (n = 1, 8.3%), contusion (n = 2, 16.7%) and thermal injury (n = 1, 8.3%). The RLN lesions in OTA-H group were caused by tumor invasion (n = 12, 37.5%), traction (n = 7, 21.9%), tissue compression (n = 6, 18.7%), clamp (n = 2, 6.2%) and contusion (n = 3, 9.4%). Additionally, there were 3 cases with vocal cord paralysis in ETBAA group and 2 in OTA-H group, in which their EMG signals were normal during surgical operation. As shown in Table 4, statistically significant differences were found in the total three groups ($P < 0.0125$).

Follow-up results

All patients with vocal cord paralysis caused by traction, compression and contusion were recovered within 90 postoperative days. Of the 4 cases injured by clamping, 1 case in ETBAA group was returned to normal, 1 case in OTA-H group was weakened and 2 cases were fixed (1 from each OTA-L group and OTA-H group) during the 6-month follow-up. Of the 2 cases injured by energy-based devices, 1 case in ETBAA group remained weakened, whereas 1 case in OTA-L group was fixed. Of the 12 cases in OTA-H group with tumor invasion, 4 cases returned to normal and 3 cases had weakened vocal cords and 5 cases had vocal cord fixation. Taken together, there were 46 (3.2%) transient and 13 (0.91%) permanent RLN lesions. Of the patients with permanent injuries, 8 (61.5%) of them were fixed and 5 (48.5%) had weakened vocal cords (Table 5 and Fig. 6).

Table 5 Different causes of RLN injury and vocal cord dysfunction recovery (6 months after operation)

Causes	Normal	Weakened	Fixed	$^{\#}P$	$^{£}P$	$^{\$}P$
Traction**$^{\#\$\$}$	17	0	0	0.025–0.05	0.05–0.10	<0.005
Compression$^{\#£\$\$}$	32	0	0	0.01–0.025	0.025–0.05	<0.005
Inferior thyroid artery	17	0	0			
Berry ligament	11	0	0			
Fibrous tissue	4	0	0			
Contusion$^{\$}$	8	0	0	0.05–0.10	0.05–0.10	0.01–0.025
Delayed neuropraxia	5	0	0	0.10–0.25	0.10–0.25	0.05–0.10
Clamping	1	1	2			
Ultrasonic scalpel	0	1	1			
Tumor invasion	4	3	5			

*$P < 0.05$, **$P < 0.01$; analysis of the total causes with Kruskal–Wallis H test. P value of all is <0.005

$^{\#}P < 0.05$, $^{\#\#}P < 0.01$; contrast with clamping group by adjusted Kruskal–Wallis H test

$^{£}P < 0.05$, $^{££}P < 0.01$; contrast with ultrasonic scalpel by adjusted Kruskal–Wallis H test

$^{\$}P < 0.05$, $^{\$\$}P < 0.01$; contrast with tumor invasion by adjusted Kruskal–Wallis H test

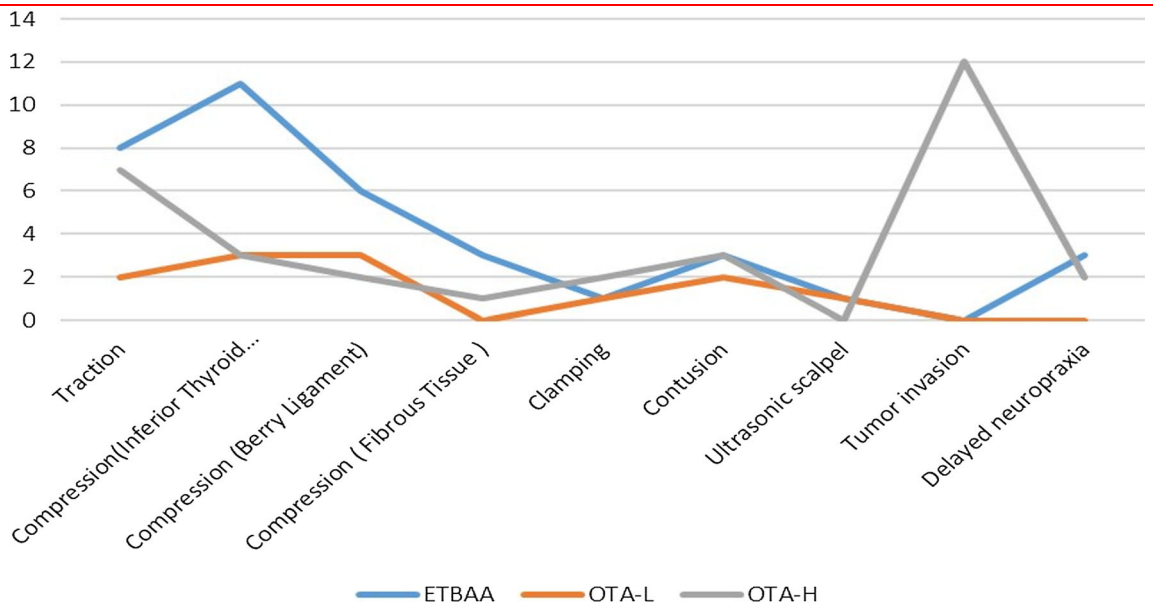

Fig. 5 Mechanism of nerve injury in subgroup analysis*

Discussion

OTA is preferred by most surgeons due to its greater working space, familiar landmarks of the neck, shorter operative time, lower cost, safer and minimal incision. Advances in technology have made it possible to offer patients the standardized open surgical approaches and/or combined with endoscopic or robotic procedures.

ETBAA allows endocrine surgeons to remove the thyroid gland from a remote site, while providing a scarless cosmetic appearance on the neck [4–9]. ETBAA has been commonly used in Asian countries [4–9]. China has the largest number of ETBAA usage worldwide, and this procedure is more preferable in our clinic [4–9]. However, none of the nationwide, population-based, non-claim-based studies have yet to evaluate the differences in outcomes between ETBAA and OTA [4–9]. Hence, additional

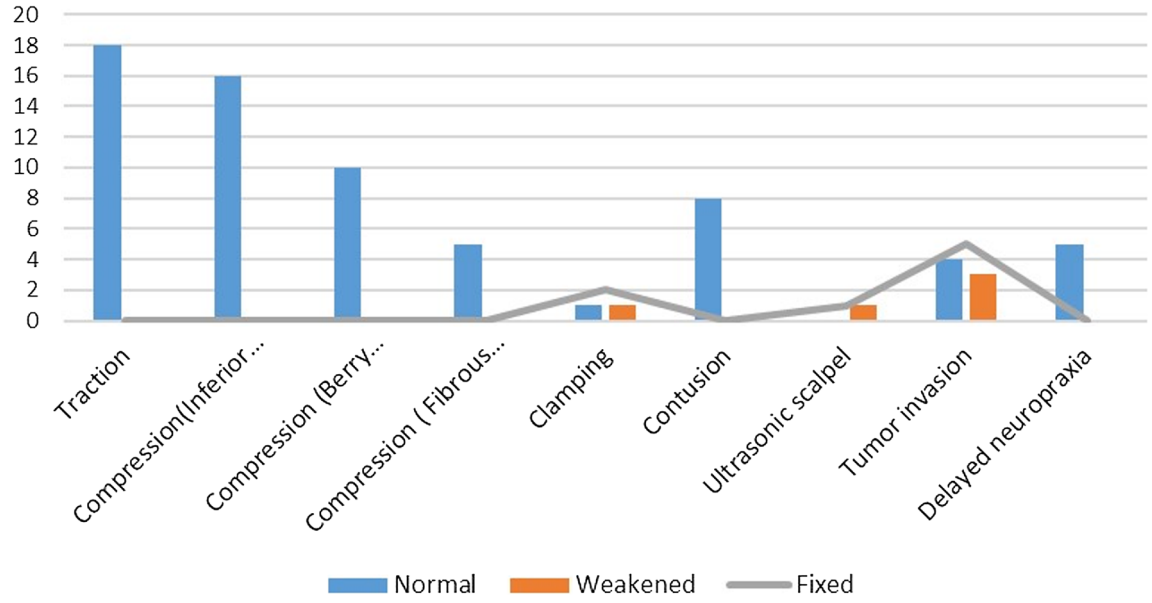

Fig. 6 Severity of nerve injury in subgroup analysis*

population-based clinical outcome studies involving larger sample size are needed to verify the safety and feasibility of ETBAA compared to other conventional approaches. Furthermore, the debate on RLN morbidity caused by surgical endoscopic approaches during thyroid surgery still remains controversial.

To the best of our knowledge, this study is the first to compare the incidence of RLN following ETBAA versus conventional open thyroidectomy. Noticeably, no detailed investigation has been conducted on the morbidity of RLN among patients underwent ETBAA [1–15, 17]. In the present study, a total of 900 patients were enrolled, providing 1420 NAR for the analysis. We divided the patients into three groups: ETBAA and open thyroidectomy [two groups (OTA-H and OTA-L)], and compared RLN injuries between the groups including a potential mechanism of RLN damage. Both intraoperative EMG parameters and postoperative laryngeal examination were used to determine the prevalence, underlying mechanism and severity of intra- and postoperative RLN disorders [20, 21].

In this large single-institution cohort study, the findings revealed that ETBAA group had an increased risk of RLN injury. The incidence of temporary postoperative vocal cord palsy was significantly higher in ETBAA group (7%) compared to OTA-L group (2%) and OTA-H group (4%). Moreover, adverse EMG profiles were more frequently observed in ETBAA group (9%) than in OTA group (2–5%). The significant differences in NAR, malignancy rate and CND prevalence between the two groups (Table 2) indicated that the risk of RLN injury is lowest in ETBAA group, whereas OTA-H group might be at highest risk. Nevertheless, the unfavorable outcomes of intra- and postoperative RLNs were more common in ETBAA group. This confirms the consistency of our results. In addition, our analysis demonstrated that a higher injury rate of the left RLNs was observed in ETBAA group (11.6% left vs. 3% right). Similarly, a greater number of the left RLN with >50% drop in EMG amplitude were found in ETBAA group (13.3% left vs. 5% right).

The higher risk of RLN injury in ETBAA is multifactorial.

ETBAA approaches the neck structures from caudal to cranial. The endoscopic view and dissection are caudal to cranial.

The thyroid gland plane is below the endoscopic 30° camera visual field. The more the thyroid gland is tractioned upwards during the endoscopic operation, the clearer the view for RLN dissection is achieved. In this way, the RLN may be entangled at the intersection of inferior thyroid artery (Fig. 7a, b). Similarly, during Berry's ligament dissection (Fig. 7c), it might induce the compression injury of RLN. The course of the RLN might be too vertical to the trachea, which is beyond to be fixed to bands of connective tissue of the Berry's ligament or branches of the inferior thyroid artery.

The different view angles (caudal to cranial) during ETBAA sometimes do not let the surgeon to know what is behind the nerve (i.e., more cranially).

Furthermore, open surgery offers more modes for RLN dissection than ETBAA (Table 6). In open surgery, the surgeon can dissect the RLN concurrently from caudal to cranial, or cranial to caudal, or lateral to medial according

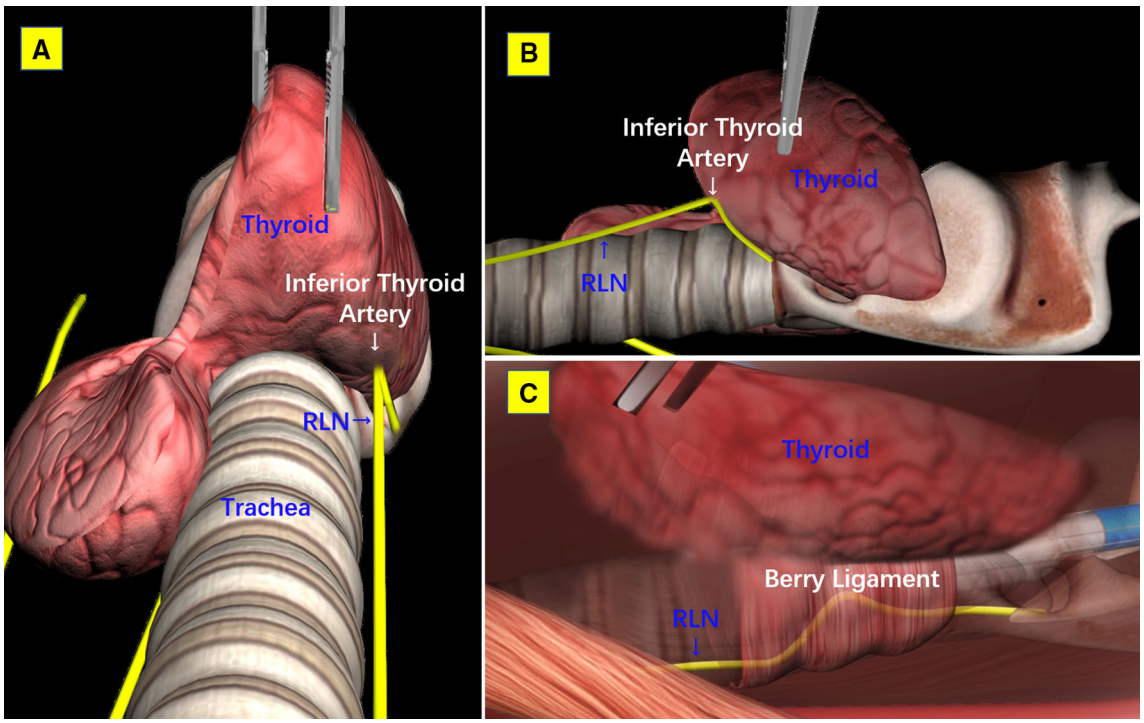

Fig. 7 ETBAA approaches neck structures from caudal to cranial. The thyroid gland plane is below the endoscopic 30° camera visual. RLN may be entangled at the intersection of inferior thyroid artery (**a**, **b**). Similarly, during Berry's ligament dissection (**c**), by compression injury. *Patients were stratified into three groups: **a** patients eligible for endoscopic treatment, who received ETBAA; **b** patients eligible for ETBAA, but opted for traditional intervention (OTA-L); **c** non-candidates for endoscopic intervention, who underwent open thyroidectomy (OTA-H)

Table 6 Surgeon approach to the RLN identification and dissection in ETBAA and open surgery

	Open surgery	ETBAA
Cranial to caudal*	+	–
Caudal to cranial§	+	+
Lateral to medial	+	±
Hybrid technique	+	–
Bilateral exposure	+	±

*Cranial to caudal: RLN is identified and dissected from the laryngeal entry point

§Caudal to cranial: RLN is identified and dissected from the thoracic outlet

to intrinsic anatomy and necessity. The surgeon who performs ETBAA surgery has fewer modes of dissecting the nerve (i.e., mostly only caudal to cranial).

Furthermore, we considered a more adverse postoperative influence on the left RLN due to unilateral access and different anatomical courses of the left RLN. The unilateral (i.e., right, non-median) access may hinder the complete evaluation of contralateral RLN. Thyroid tissues are comprised of two lobes. Bilaterally, the posterior plane of thyroid lobe communicates with RLN, and its plexuses may occur anywhere from the caudal section of the gland to the laryngeal entry point. Since the thyroid has abundant and variable amount of blood supply, complicated tracheal (Berry's ligament) and esophageal communications, the dissection of RLN remains difficult to be controlled during thyroidectomy. Because ETBAA approach is conducted on the right areola, the operator can have a clearer front view and observe the omolateral anatomical structures of the right thyroid lobe, right RLN and right parathyroid glands. However, the left RLN is limitedly visualized and exposed from the contralateral side of endoscopic camera. Additionally, the left RLN ascends more vertically, medially and deeply in the left tracheoesophageal groove [22–25], which hinder its complete exposure by the right endoscopic view.

Should left endoscopic approaches be avoided based on these results? Maybe cosmetic results are more important than a functioning voice? In future clinical operation, these observations may provide a more careful approach to contralateral left thyroid lobe for optimizing RLN management during ETBAA. The possibility of repositioning devices for left lobectomy with the endoscopic breast approach would be interesting to note and verify. Furthermore, a technological improvement with articulated

endoscopes may be useful. The routine use of IONM in ETBAA should be justified to monitor the adverse EMG signals and rapidly restore them with paused operation, and/or reduce both tension and duration. This technique can be applied specifically for the treatment of Berry's ligament as well as the intersection of RLN with inferior thyroid artery of the left thyroid lobe.

The present study indicates that IONM is a useful device for elucidating the mechanism of RLN injury caused by ETBAA. Laryngeal nerve injury in OTA and ETBAA exhibited no significant difference with regard to the types of injury. RLN lesions were mainly attributed to traction, clamping injury, compression, contusion, pressure and thermal stress. Besides, Dionigi et al. [20] have described the mechanism of RLN injury using video-assisted thyroidectomy. Traction and thermal lesions are the most frequently reported complications without side preferences. Specifically, traction lesions occur during the extraction of thyroid lobe from mini-incision, whereas thermal injury is resulted from the use of energy-based device near a nerve [20]. Moreover, Chiang et al. [21] have elucidated an inferior laryngeal nerve lesion resulted from open procedures. Their findings demonstrate that an inadvertent transection approach can be used to determine permanent nerve palsy, in which 1 injury is induced by the constriction band of connective tissues, 2 RLN are inadvertent clamping and 12 RLN traction injuries are found at Berry's ligament [21].

IONM consistency

We have found that a standardized IONM procedure is reproducible in ETBAA and includes the potential advantages of elucidating the mechanism of RLN injury. Our findings confirm previous studies [20, 21] on open surgery and endoscopic procedures. When evaluating EMG parameters also from ETBAA, a significant decrease in amplitude combined with increased latency was noticed, which is the predictor of RLN stress.

In some cases, in ETBAA, we could not identify the reason of RLN EMG signal decreased. But, when reviewing the surgical video (all endoscopic surgeries were recorded), we could outline the mechanism of nerve injury. In open surgery, the cause of nerve injury was determined by auditing the surgical steps with the assistants.

In this study, there are no multiple causes of injury; all the cases were single-factor injury. But, a combination of mechanism of injury cannot be excluded in the routine practice [20, 21].

In Table 4, we outlined 3 cases of delayed neuropraxia in ETBAA group and 2 in OTA-H group. In detail, during surgery, the EMG signal of RLN was unchanged and the nerves were endoscopically or visually intact, while postoperative laryngeal examination depicts vocal cord paralysis.

Future studies with continuous monitoring of the RLN by vagal nerve stimulation may provide even more information regarding changes in the RLN EMG signal in ETBAA to enhance safety, optimize nerve dissection, prevent LOS before it occurs and understanding those injures with unknown cause.

Clinical implications

Should surgeons doing ETBAA while knowing that the RLN injury rates are significantly higher? Should surgeons abandon this technique? What is the lesson to be learned? Endoscopic or robotic surgical technology that offers the promise of improved patient care is attractive. Intrigued, surgeons may adopt these technologies, despite little evidence of either their efficacy or their superiority over existing procedures. Understanding how such procedures have confined the modes for RLN management and furthermore modify the surgeons' technique is foremost. It is necessary to maintain greater distances of safety when using EBD around the RLN to prevent thermal injuries. Surgeon should manipulate the lobe gradually, carefully. It is advisable to modify the direction, strength and time of traction. It might be practicable to release sometime the thyroid gland, by intermittent traction and to pull the gland not upwards, but medially. Continuous monitoring of the RLN by vagal nerve stimulation may provide more information regarding changes in the RLN EMG signal in ETBAA to optimize dissection and prevent LOS before it occurs in ETBAA. Additional ports or new flexible endoscope to provide better visualization of neck structures may be useful. We are currently exploring the transoral approach as well.

Limitations of the study

Nevertheless, no firm conclusion can be drawn from any single-surgeon series. Unavoidably, the present study has some limitations which have to be pointed out. First, the bias related to the observational nature of our data and factors that influence patients' choice of ETBAA could affect the obtained results. The stratification in these three groups exposes to biases. Patients were not randomly assigned to each thyroidectomy group, but instead depended on clinical practice and patient preference. There is not an objective demonstration that ETBAA achieved a more favorable outcome since all patients undergoing this procedure chose the procedure, and this is a bias. Therefore, a randomized trial is required to avoid potential confounding.

It is obvious that younger patients were more numerous in ETBAA group and had less malignancies. Furthermore,

patients with locally advanced cancer were included, which might influence the outcomes. In OTA-H group, some RLN lesions were caused by tumor invasion.

The analysis was based on intraoperative signal loss and laryngoscopy examination, in which there were no differences in long-term permanent RLN palsy.

Elucidating the mechanism of RLN injury using continuous intraoperative electromyographic neuromonitoring would be needed, although a special probe/sensor needs to be positioned on the vagal nerve which is challenging in ETBAA.

Despite these limitations, the present study provides up-to-date information regarding the safety aspect of ETBAA, which is worthwhile for other unilateral accesses to endoscopic thyroid surgeries.

Author's contributions HS, NL and GD were involved in conception and design; HS, NL and GD contributed to administrative support; and DZ performed collection and assembly of data.

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Compliance with ethical standards

Conflict of interest The authors Daqi Zhang, Jiao Zhang, Gianlorenzo Dionigi, Fang Li, Tie Wang, Hongbo Li, Nan Liang and Hui Sun declare no conflict of interest. The funders had no role in (1) the design of this study; (2) the collection, analysis and interpretation of data; (3) the writing of the manuscript; or (4) the decision to submit the manuscript for publication.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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