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TECHNICAL REPORT

Central Lymph Node Dissection by Endoscopic Bilateral Areola Versus Open Thyroidectomy

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Background: Endoscopic thyroidectomy by bilateral areola approach (ETBAA) potentially expose a technical limitation for anatomize the central compartment lymph nodes located in its most caudal portion because of visual obstruction and instrument interference of clavicles and sternum. We provide a comparative analysis of ETBAA versus open thyroidectomy approach (OTA) for central compartment dissection (CND).

Methods: From October 2013 to August 2017, 400 patients with papillary thyroid cancer (PTC) underwent CND; 200 patients were enrolled in each group. For the endoscopic group, a 10-mm curved incision is made along the margin of the right areola at 2 to 4 o'clock for the 30 degrees endoscope. Bilaterally 5-mm incisions are on the edges of the areola at 11 to 12 o'clock as accessory operating ports. Supplementary video (Supplemental Digital Content 1, <http://links.lww.com/SLE/A180>) depicts steps of ETBAA with CND.

Results: In ETBAA group, a total of 1049 lymph nodes were removed, nodes excision ranged from 1 to 19 (mean, 5.25), the ratio positive/metastatic rate was 18.6%. In OTA group, 916 lymph nodes were excised, nodes removal amplitude was 1 to 20 (average, 4.58), 12.1% were metastatic. Compared with the open group, significantly more lymph nodes were extracted during ETBAA ($P < 0.05$). There was no significant difference between the 2 groups per resected side or surgical morbidity ($P > 0.05$). Periodic monitoring of PTC patients revealed no clinical or US recurrence, undetectable serum Tg in both groups.

Conclusions: Our results show the feasibility of CND in ETBAA.

Key Words: central node dissection, lymph node metastases, morbidity, neuromonitoring, recurrent laryngeal nerve, endoscopic thyroidectomy (*Surg Laparosc Endosc Percutan Tech* 2018;00:000–000)

Therapeutic (level VI) central lymph node dissection (CND) for papillary thyroid cancers (PTC) with clinically involved central nodes accompanies total thyroidectomy to provide

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clearance of disease.¹ Prophylactic CND (ipsilateral or bilateral) is considered in patients with PTC with clinically uninvolved central neck lymph nodes (cN0) who have advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes (cN1b), or if the information will be used to plan further steps in therapy.¹ In the People's Republic of China, endoscopic thyroidectomy by bilateral areola approach (ETBAA) is widely adopted because of national practice tradition, intrinsic advantages in dissecting the superior gland pole, and the external branch of superior laryngeal nerve (EBSLN), realizes clearance of level II lymph nodes and fine cosmetic results.^{2,3} Conversely, there is potential technical limit to anatomize the central compartment lymph nodes located in its most caudal portion because of the endoscopic visual obstruction and instrument interference of clavicles and sternum barbell (Fig. 1).⁴ The safety, completeness, and pathologic results of CND for PTC through the ETBAA and conventional open thyroidectomy approach (OTA) were compared.

METHODS

Patients, Informed Consent, Recruitment Strategy

The protocol was approved by the Institutional Review Board of the China-Japan Union Hospital of Jilin University, Division of Thyroid Surgery, Changchun, China (#AZ-pr-2016-87). On the day of the clinic visit, before grouping, we described the operative methods and relative complications of both endoscopic thyroidectomy and open thyroidectomy to the patients. All patients provided written informed consent before beginning the study. The patient selection criteria were as follows: all the patients consented to participate in this study, they were all pathologically diagnosed thyroid cancer preoperatively. All the patients had a definitive pathologic diagnosis and complete clinical data. In addition, the patients were suitable candidates for thyroid cancer resection. Open or endoscopic surgery was selected according to the wishes of the patients and the including criteria. The inclusion criteria for the study were as follows: according to patient's and thyroid gland features as medical history, signs and symptoms, imaging, laboratory results the Patients were stratified into two groups: (1) patients eligible for endoscopic treatment, who accepted ETBAA; (2) patients eligible for ETBAA, who opted for traditional open thyroidectomy approach (OTA). Eligible patients were assigned to either endoscopic resection or open resection. The exclusion criteria were patients with concomitant tumors that significantly affected survival. Patients with pT4 and pN2 were not included in the study, as such patients were only treated with open surgery in our hospital at that time. Finally, patient records/information were anonymized and deidentified before analysis. All patients

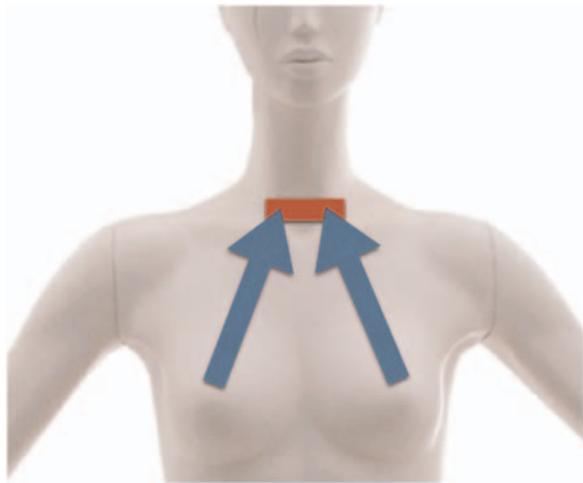


FIGURE 1. Endoscopic thyroidectomy by bilateral areola approach has potential technical limit to anatomize the central compartment lymph nodes located in its most caudal portion because of the endoscopic visual obstruction and instrument interference of clavicles and sternum barbell.

were explained about the possibility of conversion from endoscopic to open thyroidectomy. All patients were opted for endoscopic thyroid surgery. The sole prospect difference was not only the cosmetic result, here also, patient was informed of the time of the operations, cost and given instructions about when to take medications and what to wear. No randomization was performed, the choice for the two different surgical techniques was dictated by patients voluntarily to choose endoscopic thyroidectomy by areola approach or conventional low-collar incision approach according to their cosmetic request. The groups were constructed in the same study period, that is, from October 2013 to August 2017 and by the same surgeon (DZ), in a single-institutional, tertiary referral center (Thyroid Surgery Division, China-Japan Union Hospital of Jilin University). The surgical team had performed 100 endoscopic procedure to assess safety of surgical technique before starting the trial (before October 2013). Furthermore, patients in the endoscopic group could be converted preoperatively to an open resection if there was malfunctioning equipment or if no surgeon with endoscopic skills was available. All converted patients, that is, preoperative and intraoperative, remained in the endoscopic group for analysis based on intention-to-treat principle.

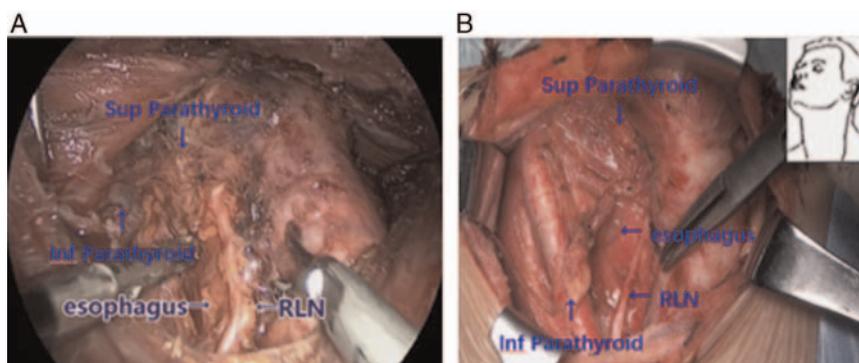


FIGURE 2. Right central lymph node dissection in endoscopic (A) and open (B) procedures.

Investigations

Routine preoperative examinations included for all groups cervical ultrasound (US), pre- and postoperative laryngoscopy, thyroid function, neck computer tomography (CT) and fine needle aspiration (FNA). Preoperative diagnoses of thyroid nodules were made by ultrasonography and ultrasonography-guided fine needle aspiration cytology (FNAC). If FNAC identified malignancy or atypical cells that were suspicious for malignancy, computed tomography was performed to identify the tumor location, invasion, and central lymph node metastasis.

Prophylactic CNDs constituted this investigation. No therapeutic CNDs. Patients with prior neck, mediastinum or breast radiation, distant metastases, gross extrathyroidal extension, aggressive variant, associated Graves' disease, recurrent laryngeal nerve palsy were excluded from the study. Thyroidectomy without CND, "berry picking" dissection, redo central neck dissections, lateral neck dissections were removed from this analysis. Obesity (body mass index, $> 30 \text{ kg/m}^2$), enlarged thyroid gland detected by ultrasound examination (one thyroid lobe volume, $> 40 \text{ mL}$), and a possible extrathyroidal extension or abutment on the thyroid capsule, especially when occurrence was near the tracheoesophageal groove detected by preoperative sonography or CT were criteria of exclusion. We evaluated the vocal cord mobility with laryngoscope before the surgery routinely.

Definitions and Surgical Technique

The surgical treatment was performed by dedicated surgeons who belong to the same thyroid cancer high-volume surgical Unit with extensive experience in endocrine surgery. The technique for ETBAA has been previously reported by this group.⁵ Standardized neural monitoring was implemented in both groups.^{5,6} The ATA consensus statement regarding the terminology and classification of the central neck defines the CND as all perithyroidal and paratracheal soft tissue and lymph nodes with borders extending superiorly to the hyoid bone, inferiorly to the innominate artery, and laterally to the common carotid arteries.⁷ The surgical technique for prophylactic nodal dissection adopted includes ipsilateral CND. Boundaries delimited by the ATA guidelines are the same, but there are peculiarities for the approaches between the two techniques (Figs. 2, 3).

Supplementary video (Supplemental Digital Content 1, <http://links.lww.com/SLE/A180>) depicts steps of ETBAA and CND. In ETBAA Dissection is performed under HD endoscopic vision. CND is accomplished from medial to

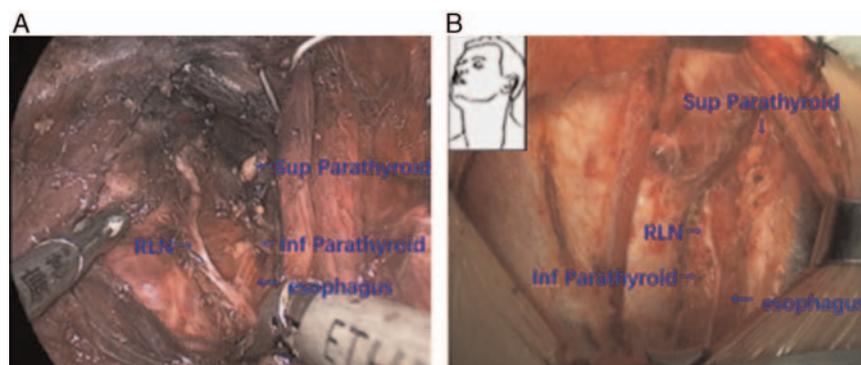


FIGURE 3. Left central lymph node dissection in endoscopic (A) and open (B) surgery.

lateral, starting from the anterior trachea surface. And then dissected the pretracheal, paratracheal, and delphian/prelaryngeal lymph nodes. The caudal part of the lymph nodes is grabbed and lift upwards to the neck region by endoscopic forceps, while using the energy-based device to dissect the lymphatic tissues off below to the clavicle. During ipsilateral or bilateral CND, the lymph nodes of the central compartment are carefully dissected to avoid injuries to the RLN and parathyroids. Dissection of the thyroid and central lymph nodes is performed with harmonic Focus (Ethicon Endo-Surgery Inc., Cincinnati, OH). The resected specimen is extracted through the sterile specimen bag. Vacuum-assisted draining system should be placed in the operative area though the areola tunnel. The wounds were closed with 5-0 absorbable monofilament sutures using an atraumatic needle, followed by placement of Steri-Strips.

In open surgery, CND is accomplished cranial to caudal, and lateral to medial.

Postoperative Care

There was no difference between the 2 groups as for the postoperative care. Patients with no complications were usually discharged on day 3 to day 5 after the surgery. All the patients received thyroid hormone replacement therapy for life-long time. All complications were recorded.

Pathologic Examination

The method of pathologic analysis is the same in both groups. The specimen is described as a total thyroidectomy, left lobectomy, or right lobectomy (\pm isthmus). The specimen should be weighed and measured. Where possible, the thyroid gland is sectioned horizontally. The site of the tumor should be noted, along with the distance to the nearest excision margin. The size of the thyroid lesion is noted for the pT aspect of pathologic staging, taking the size of the largest lesion if >1 is identified. Extension of the tumor beyond the thyroid gland is reported. Representative blocks are selected based and it is well recognized that PTC can be multifocal and, therefore, if this diagnosis is suspected, the adjacent and opposite lobe are sampled, and any pale areas processed. Any lymph nodes submitted with the specimen is dissected, noting whether they are ipsilateral or contralateral to the tumor, or in the midline. The diagnosis of PTC is based on the identification of papillary architecture, in addition to several well recognized nuclear features with hematoxylin and eosin stain. The routine lymph node sectioning of the central compartment by paraffin pathology comprehended the number of lymph node dissected, number of positive metastatic nodes and the lymph node ratio,

defined as the ratio of lymph nodes with tumor metastasis to the total lymph nodes dissected. PTC were described using tumor-node-metastasis (TNM) staging on the basis of the latest edition of the recommendations of the American Joint Committee on Cancer (AJCC).

Outcomes Measured

A comparison was made between groups according to the clinical, pathologic data. Primary outcome measured was the number of lymph nodes resected, the number of positive/metastatic lymph nodes, lymph node ratio, therapeutic dissection versus prophylactic dissection, the side of resection, follow-up, nodal diseases free, local recurrences, distant metastases. Other parameters recorded were transient or permanent laryngeal nerve injury either unilateral or bilateral, hypocalcemia and/or parathyroid glands in specimen. All patients were treated with levothyroxine to suppress thyroid-stimulating hormone, and all patients were regularly followed at 6-month intervals. In detail, patients underwent serial physical examination, neck US, blood test for T4 level, TSH, thyroglobulin, thyroglobulin antibody, postoperative laryngoscopy, radioactive iodine whole body scanning. CT scanning of the neck and or chest is obtained for operated PTC patients when there have been clinical, US or pathology findings which suggest a recurrence in locations that ultrasound has limitations. Follow-up may include PET/CT scanning when there is: (1) an “angry appearing” PTC; (2) significant elevation of thyroglobulin levels above what would be anticipated for the known disease; (3) when there is known recurrent cancer but no detectable thyroglobulin. Vocal cord dysfunction or hypocalcemia were considered permanent if they persisted for 12 months.

Sample Size Calculation and Statistical Analysis

All patients' data were collected in a prospective manner with a dedicated electronic Microsoft Office Access Data Base (Microsoft Corp, Redmond, Wash). The database was continuously updated with the follow-up data from our clinic, endocrinologist, and general practitioners. To ensure sufficiently large numbers of patients and events in each group, the required sample size was determined according to a difference of number of lymph nodes dissected between different approaches considered in the study, a power of 90 ($\beta=0.9$), a -10 SD in the mean, and a 90% probability at $P<0.05$ (using power curve and sample size tools for one-way analysis of variance); that is, a sample size approximating 100 subjects should provide 90% power to detect differences. Statistical analysis was computed with

SPSS, release 15.0 for Windows (SPSS Inc, Chicago, IL). The level of significance was set at $P < 0.05$. All efforts were made to avoid sources of bias such as the loss of individuals to follow up during the study.

RESULTS

Patients

From October 2013 to August 2017, 400 patients with PTC documented by fine needle aspiration cytology underwent CND. There were 47 men and 353 women; ages ranged from 17 to 53 years (mean age, 34 y). In all, 100 bilateral CND and 300 ipsilateral CND (150 right, 150 left) were performed, covering 376 “nerve at risk” (NAR). 200 patients were enrolled in each group. The clinicopathologic characteristics of 400 patients with PTC are summarized in Table 1. The open surgery cases equally distributed during the study period than the endoscopic surgery cases.

Surgical Outcomes and Morbidity

The endoscopic thyroidectomy with CND was completed successfully in all patients. There was no conversion from the endoscopic surgeries to open surgeries. In the ETBAA group, mean operating time was 84.8 ± 19.4 min, whereas the mean total of conventional OTA group was 43.8 ± 9.29 minute ($P < 0.05$). The differences of the 2 groups in the estimated intraoperative blood loss, postoperative hospital stay time, primary tumor sizes, total drain volumes, mean draining days, follow-up period and number of patients whose tumors showed multicentricity or multifocality were not statistically significant ($P > 0.05$) (Table 1). The overall incidence of vocal fold dysfunction was 5.5%

TABLE 1. Clinicopathologic Characteristics of Patients

Characteristics	ETBAA	OTA	P
Patients (N)	200	200	–
L	75	75	–
R	75	75	–
B	50	50	–
Age \pm SD (y)	31.46 ± 7.75	37.28 ± 6.22	–
Sex (M/F)	17/183	30/170	–
BMI	19.7 ± 6.58	22.9 ± 6.13	–
CND (N)			
Prophylactic	200	200	–
Therapeutic	0	0	–
Mean operating time (min)	84.8 ± 19.4	43.8 ± 9.29	+
Intraoperative blood loss	8.72 ± 3.44	6.56 ± 3.24	–
Postoperative hospital stay time (d)	3.47 ± 0.51	3.17 ± 0.73	–
Primary tumor sizes (mm)	5.2 ± 0.31	4.8 ± 0.22	–
Total drain volumes (mL)	62.22 ± 20.1	48.28 ± 13.9	+
Mean draining days	1.83 ± 0.38	1.5 ± 0.51	–
Nerve at risk (NAR, L/R)	250 (125/125)	126 (60/66)	+
EMG signals changed (nerve) [n (%)]	15 (6)	12 (4.8)	+
Vocal cord palsy (nerve) [n (%)]			
Temporary/permanent	13/0	9/0	+
Hypocalcemia in bilateral CND [n (%)]	5 (10)	7 (14)	–
Temporary/permanent	5/0	7/0	–

BMI indicates body mass index; CND, central compartment dissection; ETBAA, endoscopic thyroidectomy by bilateral areola approach; L/R/B indicates left/right/ bilateral; M/F, male/female; OTA, open thyroidectomy approach.
+ $P < 0.05$; – $P > 0.05$.

TABLE 2. TNM Classification in ETBAA and OTA Groups

TNM Classification	ETBAA	OTA
T1aN0	125	147
T1aN1a	51	40
T1b N0	13	6
T1b N1a	11	7

ETBAA indicates endoscopic thyroidectomy by bilateral areola approach; OTA, open thyroidectomy approach.

($n = 22$). Of injured nerves during CND 15 (6%) versus 12 (4.8%) were temporary, none were permanent in group ETBAA and OTA, respectively ($P > 0.05$). The rate of temporary and permanent hypocalcemia in bilateral CND was 10% versus 14% in group ETBAA and OTA, respectively ($P > 0.05$). As for parathyroid gland auto-transplantation: 5 occurred in endoscopic group versus 7 in conventional open approach group ($P > 0.05$).

Histology

Permanent pathologic diagnosis showed that all 400 patients had PTC. Based on TNM classification of AJCC (American Joint Commission for Cancer, 2017), there were 363 T1a cases, 37 T1b; 291 cases with N0 and 109 cases with N1a. Table 2 defines TNM classification by groups. In ETBAA group, lymph nodes excision ranged from 1-19 (average, 5.25). A total of 1049 lymph nodes were removed, the overall positive/metastatic ratio was 18.6%. In OTA group, lymph nodes removal amplitude was 1 to 20 (mean, 4.58). In OTA group, 916 lymph nodes were excised, 12.1% were metastatic. Compared with the open group, the endoscopic group significantly more lymph nodes were extracted ($P < 0.05$) (Table 3) (Figs. 4–7). In the subgroup analysis for left central group dissection, lymph nodes ranged from 1-15 in ETBAA group (mean, 4.46). A total of 335 lymph nodes were removed, 14.3% were metastatic. Lymph nodes isolated ranged from 1 to 19 in OTA group (average, 3.32). A total of 242 lymph nodes were removed, 9.5% positive for thyroid cancer. There was no significant difference between the 2 groups ($P > 0.05$) (Table 3) (Figs. 4–7). In the subgroup analysis for right central group, lymph nodes excised ranged from 1 to 14 in ETBAA group (mean, 4.34). 325 lymph nodes were separated with a 14.8% metastatic rate. Lymph nodes cover from 1 to 10 in OTA group (average, 3.32); 249 nodes were removed, 8.4% metastatic. There was no significant difference between the two groups ($P > 0.05$) (Table 3) (Figs. 4–7). In bilateral CND, 4 to 19 lymph nodes were excised in ETBAA group, with an average of 7.78, total 389 (25.7% metastatic). Lymph nodes ranged from 2 to 20 in OTA group, average

TABLE 3. Lymph Node Dissection and Pathology

	n (%)	
	ETBAA	OTA
Total lymph node	1049	916
Total metastatic	195 (18.6)	111 (12.1)
Left lymph node	335	242
Left metastatic	48 (14.3)	23 (9.5)
Right lymph node	325	249
Right metastatic	48 (14.8)	21 (8.4)
Bilateral lymph node	389	425
Bilateral metastatic	100 (25.7)	68 (16)

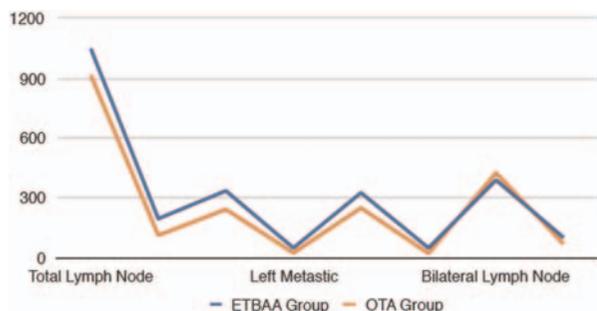


FIGURE 4. Comparative analysis of central lymph node dissection in ETBAA and OTA groups. ETBAA indicates endoscopic thyroidectomy by bilateral areola approach; OTA, open thyroidectomy approach.

8.5, overall 425, positive 16.0%. There was no significant difference between the 2 groups ($P > 0.05$) (Table 3) (Figs. 4–7).

Follow-up

Complete follow-up was available for all patients. Mean overall length of follow-up was 54 ± 3.4 months. Periodic monitoring of PTC patients revealed no clinical or US recurrence, undetectable serum Tg during TSH suppressive therapy with L-T4 and serum Tg after TSH stimulation in both groups.

DISCUSSION

The cervical approach is currently the “gold standard” procedure for thyroidectomy and CND in PTC treatment. The conventional surgical approach requires to extend the incision up to a 5 cm to complete the CND. Because the anterior neck is prominent and constantly exposed part of the body, an unsightly neck scars can be distressing for the patients. Furthermore, a majority of patients with PTC are young women, who prefer no scar in the neck. Therefore, surgeons have made every effort to resolve the scar problem. Endoscopic thyroidectomy was first described in 1997.⁸ A variety of access have been explored such as the areola, breast, infraclavicular, transoral, submental, video-assisted, transaxillary, and hybrid axillary-breast approaches.^{9–13} The obvious advantage of the extracervical approach is the absence of visible scar in the neck or upper chest. All of the approaches have their own merits and drawbacks, such as the transaxillary approach is limited in arriving at the lymph nodes of the contralateral central compartment.

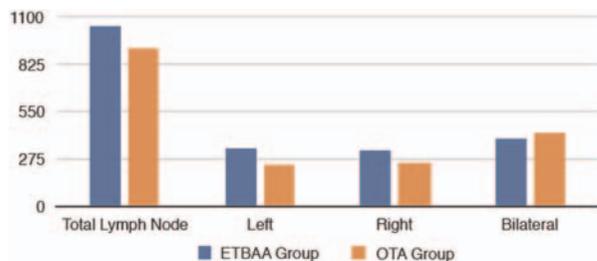


FIGURE 5. Comparative analysis of number of lymph node dissected in ETBAA and OTA groups. ETBAA indicates endoscopic thyroidectomy by bilateral areola approach; OTA, open thyroidectomy approach.

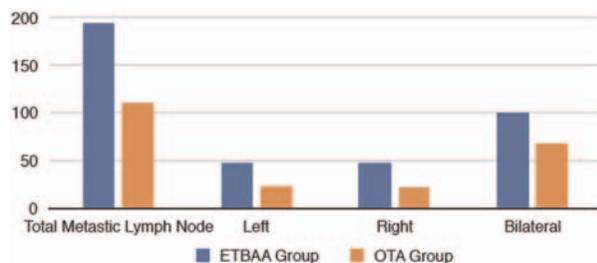


FIGURE 6. Comparative analysis of number of lymph node metastasis excised in ETBAA and OTA groups. ETBAA indicates endoscopic thyroidectomy by bilateral areola approach; OTA, open thyroidectomy approach.

ETBAA approach has advantages and potential technical limit particularly for anatomize the lymph nodes of the central compartment located in its most caudal portion because of the possible visual obstruction and instrument interference of the clavicles and the sternum barbell (Fig. 1).^{4–6} In the People’s Republic of China, ETBAA is widely adopted because of national practice tradition. Concerning the oncological safety and CND completeness, ETBAA procedures for thyroid cancers was evaluated in the current study. A supplementary video (Supplemental Digital Content 1, <http://links.lww.com/SLE/A180>) is provided to depict steps of ETBAA with CND. For any new emerging technique, careful patient selection is essential. PTC has a very good prognosis. Although tailoring the surgical approach to the patients’ concerns and desires is important, adhering to fundamental oncosurgical principles should always be a priority. The oncological safety is more important than the cosmetic demand. This comparative study suggested that there were no significant differences regarding the oncological and the technical safeties between two groups. Endoscopic procedure uniquely provided a perfect detailed endoscopic vision of the central compartment. These enabled surgeons to access deep, narrow spaces for a complete CND and to identify and preserve the RLN and parathyroid glands (parathyroid gland autotransplantation: 5 in endoscopic group vs. 7 in conventional open approach group, $P > 0.05$). In this study, the central lymph node metastasis rate was 18.6% for endoscopic and 12.1% for open procedures. The ratio of total lymph node dissection and lymph node metastasis was superior to that of conventional open surgery (Table 3) (Figs. 4–7). Endoscopic procedure is more invasive, more expensive, and more time-consuming than conventional open thyroidectomy. However, the use of HD endoscopic visual and neural monitoring set

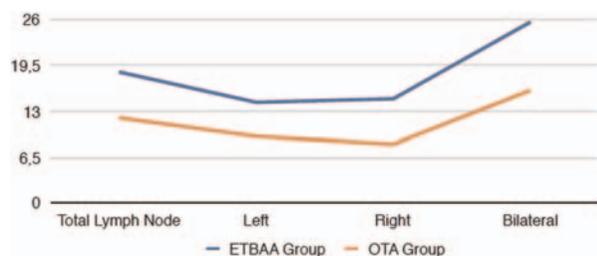


FIGURE 7. The ratio of lymph node metastasis in ETBAA and OTA groups. ETBAA indicates endoscopic thyroidectomy by bilateral areola approach; OTA, open thyroidectomy approach.

1 the procedure at the same level of safety of the conventional
 3 procedure. Endoscopic thyroidectomy with CND had similar
 5 complication rates as open procedure. In the future, we
 intend to compare longer-term follow-up results and onco-
 logic safety in a large sample size.

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