Single-center, Retrospective Study of Retro - Auricular Single - Site Endoscopic, Transoral Endoscopic Thyroidectomy Vestibular Approach and Transareola Endoscopic Thyroidectomy in Patients With Early Stage Papillary Thyroid Carcinoma

Study Protocol

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Official Title	Single-center, Retrospective Study of Retro‐Auricular Single‐Site Endoscopic, Transoral Endoscopic Thyroidectomy Vestibular Approach and Transareola Endoscopic Thyroidectomy in Patients With Early Stage Papillary Thyroid Carcinoma
Brief Summary	The goal of this retrospective study is to compare the safety and efficiacy of endoscopic thyroidectomy via retro‐auricular single‐site approach, transoral endoscopic thyroidectomy vestibular approach and transareola approach.
Conditions	Age: 18 ~ 70 years.Patients with early stage papillary thyroid carcinoma.
Sample Size	160
Inclusion Criteria	● Age 18-70 years old, no gender restrictions. ● Fine-needle aspiration cytology(FNA) confirmed papillary thyroid carcinoma(PTC). ● Early stage PTC (stage T1N0M0). ● Preoperative ultrasonography showed unilateral glandular lobe malignant tumor and the largest diameter was not more than 2cm, without cervical lymph node metastasis and extensive metastasis. ● Patients undergoing thyroid lobectomy and central lymph node dissection. ● Patients who have signed an approved Informed Consent.
Exclusion Criteria	● Patients who do not accept case data collection for various reasons. ● The clinical data unfit this study （at the discretion of the investigator）. ● Patients who have undergone neck surgery or radiotherapy before this trail. ● Patients who have uncontrolled hyperthyroidism.
Elimination Criteria	● Patients who violated the requirements of the research protocol. ● The quality of data records is incomplete and inaccurate. ● Lost cases.
Study Completion	2023-02-28
Locations	1
Statistical Analysis Plan	All analyses were performed using SPSS 26.0, and a *P* value less than 0.05 was considered significant. Normally distributed quantitative data are represented by mean (SD) [range]. Non-normally distributed quantitative data are represented by M（Q_R）. Comparison between groups was performed using the Mann-Whitney U test. Categorical data are expressed as frequencies and percentages. Comparisons between groups were performed using theχ^2 test or Fisher's exact test.

Study Protocol

1.Background

Thyroid cancer is one of the most common malignant tumors in the head and neck. Among it, papillary thyroid carcinoma accounts for about 70% of thyroid cancer. The degree of malignancy is low, but there is a tendency for multicentricity, and cervical lymph node metastasis occurs early. Due to the development of diagnosis technology, the amount of papillary microcarcinoma is getting higher and higher. At the same time, the change of aesthetic makes young women pursue a scarless neck[1, 2].

Surgery is the first choice of treatments for early-stage thyroid cancer.[3, 4] Traditional open surgery tended to leave a long scar on the neck, which affects the cosmetic outcome. At present, many reported approaches, such as trans-areola approach[5], trans-axillary approach[6], trans-oral approach [7, 8]or some combined approaches[9], all have wider flap dissection or greater body trauma, and at the same time, these above approaches are difficult to achieve complete dissection of central lymph nodes[10].

Therefore, based on the experience of transauricular hairline endoscopic thyroidectomy[11-13], we established a new operative method-the Retro-auricular single-site endoscopic thyroidectomy (RASSET). The incision is only 3cm and located at the posterior sulcus of the auricle, which can meet the cosmetic needs. Compared with other endoscopic approaches, the dissection area is small and the flap dissection is small, which may reduce the surgical trauma. The RASSET is easy to resect the upper pole of the thyroid gland, and can achieve complete dissection of the central lymph nodes.

The article titled " A comparative study between retro‐auricular single‐site endoscopic thyroidectomy and transoral endoscopic thyroidectomy vestibular approach: a single‐center retrospective analysis " has been published in " Chin J Surg "[14]. Guangdong Medical Information Research Institute recognized that there was no report of endoscopic thyroid surgery for this approach at home and abroad, and it also passed the new technology evaluation in the Sun Yat-sen University Cancer Center, and was recognized as an international leader.

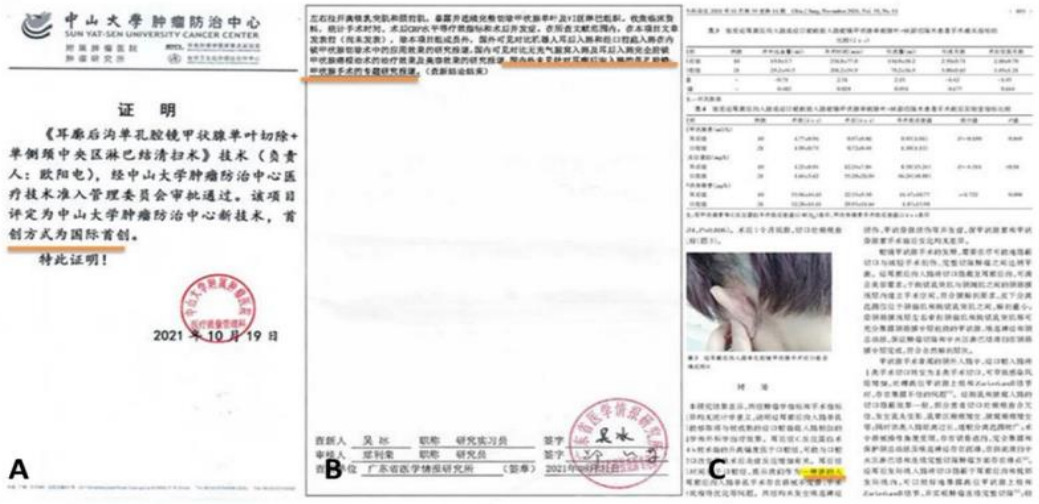


Figure 1. **A:**Sun Yat-sen University Cancer Center Certificates(international innovation). **B:**Guangdong Medical Information Research Institute Certificates(no report of this approach).**C:**Zhonghua Wai Ke Za Zhi(a new approach).

2. Study purpose

2.1 Primary purpose:

Compare the traumatic differences between the three groups by comparing the preoperative and postoperative CRP levels of the three groups.

2.2 Secondary purpose:

Compare the degree of surgical trauma between the three groups by comparing the level of SAA, blood loss, VAS pain score, and postoperative drainage.

Compare the clinicopathologic characteristics between the three groups by comparing the number of resected lymph nodes, and the positive rate of lymph nodes.

Compare the safety between the three groups by comparing the types and rate of complications.

2.3 Primary Outcome Measure:

CRP level

2.4 Secondary Outcome Measures:

- Cosmetic outcome: postoperative cosmetic outcomes
- Surgical outcomes: SAA level, blood loss, VAS pain score, postoperative drainage volume, Operative time.
- Clinicopathologic characteristics: tumor size, number of lymph nodes, the positive rate of lymph nodes.
- Complication: complication rates and types.

3. Study Eligibility

3.1 Inclusion Criteria:

- Age 18-70 years old, no gender restrictions;
- Patient must be suitable candidates for surgery;
- Be able to understand the purpose of the test;
- Preoperative ultrasound showed unilateral glandular lobe malignant tumor and the largest diameter was not more than 2cm, and preoperative imaging examination showed that the largest diameter of central lymph node was not more than 2cm without lateral cervical lymph node metastasis and extensive metastasis;
- Patients who have cosmetic requirements;
- Patients who have signed an approved Informed Consent

3.2 Exclusion Criteria:

- Patients who do not accept case data collection for various reasons.
- The clinical data unfit this study （at the discretion of the investigator）.
- Patients who have undergone neck surgery or radiotherapy before this trail.
- Patients who have uncontrolled hyperthyroidism.

3.3 Withdrawal criteria:

(A withdrawal case refers to a patient who withdraws from treatment for various reasons in study. Patients with the following conditions will be withdrawn from investigational treatment.)

- The patient himself or his legal representative requests to withdraw;
- In the opinion of the investigator, the patient's continued participation in the study will

be detrimental to his health.

3.4 Elimination Criteria:

- Patients who violated the requirements of the research protocol;
- The quality of data records is incomplete and inaccurate.
- Lost cases.

4. Case Screening

4.1 examination items

All cases must complete the following examination items before being considered for entry into this study. It is generally required to be completed within 7 days before treatment.

- Complete medical history and comprehensive physical examination, including symptoms, signs and specialist examination.
- Check items that must be done before routine treatment, including:

Blood routine: neutrophil/lymphocyte ratio,
Coagulation function: d-dimer,
Serological tests: CRP, SAA, procalcitonin, calcium level,
Thyroid function: TSH level, parathyroid hormone level,
Thyroid ultrasonography and FNA, thyroid Computed tomography scan if necessary,
Chest X-ray, abdominal ultrasonography, electrocardiogram.

The above examinations are all routine preoperative examinations, which do not cause additional financial burden on patients.

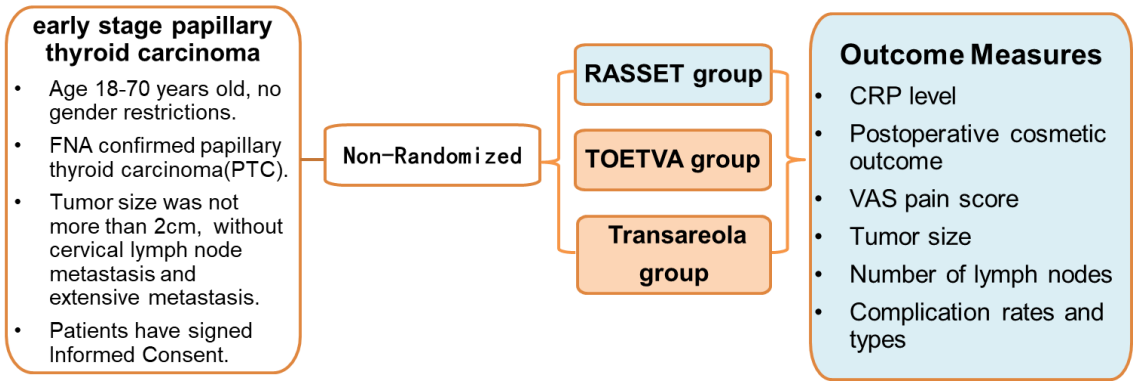
4.2 Case screening

According to various examinations, those who meet the inclusion criterias are screened out.

The patients entered the study after completing the required examinations and being evaluated according to the inclusion criterias. Then sign the informed consent form and get treatment.

5. Study Process

Figure 2. flowchart



6. Surgical Technique

6.1 Retro-auricular single-site endoscopic thyroidectomy (RASSET)

For the RASSET technique, in the beginnig, patient was placed in a supine position with slight neck bending. When the lower pole of the thyroid gland was going to be dissected, the patient was placed in a supine position with slight neck extension. Mark the operation path on the surface. Slit the skin, subcutaneous tissue and superficial cervical fascia in turn. Expose the middle branch of the great auricular nerve and the sternocleidomastoid muscle under direct vision. The working space was created in the superficial layer of deep cervical fascia between the sternocleidomastoid muscle and the platysma muscle, which meets the principle of membrane anatomy. The area of flap dissection just includes the anterior cervical muscle and the anterior edge of the sternocleidomastoid muscle, which is so narrow to minimize the traumatic dissection. Pulling apart the anterior cervical muscle and the sternocleidomastoid muscle along the deep cervical fascia can fully expose the thyroid gland, the recurrent laryngeal nerve (RLN) and common carotid artery that are surrounded by the middle layer of deep cervical fascia and ensure that tumor and central lymph nodes en‐bloc resection can be operated in the middle layer of deep cervical fascia to conform the natural anatomical region. For details, please refer to "Retroauricular Single-Site Endoscopic Thyroidectomy—A Balanced Endoscopic Approach for Thyroid Excision".

6.2 Transoral Endoscopic Thyroidectomy Vestibular Approach(TOETVA)

For the TOETVA technique, the patient was placed in a supine position with slight neck extension under nasotracheal intubation. Amoxicillin–clavulanic acid, 1.2 g, was administered 30 minutes before incision.Three laparoscopic ports (a 10-mm port at midline and two 5-mm ports at the lateral junction between the canine and first premolar teeth) were inserted under the lower lip at the oral vestibular area. A standard 10-mm 30° laparoscope was used, allowing top-down visualization. The working space was created down to the sternal notch with the lateral border at the sternocleidomastoid muscles. The strap muscles were separated in the midline and retracted laterally by a transcutaneous 2/0 silk suture to expose the thyroid and trachea. The thyroid isthmus was divided first. Next, the superior pole was dissected, and the branches of the upper pole vessels were divided using ultrasonic shears (Harmonic Scalpel) on the surface of the thyroid gland. Upper parathyroid and lower parathyroid glands were identified and preserved. The recurrent laryngeal nerve (RLN) was identified at the insertion to the larynx, then followed downandparallel tothe trachea inferiorly. A thyroid lobe specimen was placed in a specimen pouch and retrieved through the 10- to 15-mm central incision.

6.3 Transareola Endoscopic Thyroidectomy

After endotracheal intubation and general anesthesia, the patient was placed in supine position. Incision was made inside the right areola and a 10-mm port was placed, subcutaneous tunnel separation rod was used to separate the space, and a 30° laparoscope was introduced, a 5-mm port was placed in the 5mm incision in the left areola, free flap with ultrasonic shears, and subcutaneous separation space in the upper sternal segment. A 5-mm port was placed on the lateral side of the right areola, and the anterior cervical flap was further dissociated to establish space. Above the flap was the thyroid cartilage and behind the sternocleidomastoid muscle on both sides, the median cervical line was cut, the isthmus of the thyroid was cut off, and the tracheal fascia ligament of the thyroid was separated on both sides, and the lower pole blood vessel and the lateral middle vein were treated close to the gland, and the inferior parathyroid gland was exposed. The

recurrent laryngeal nerve was exposed in the parathyroid groove at the lower pole of the gland, the space along the nerve was separated to protect the nerve and protect the superior parathyroid gland, the suspensory ligament was cut off, the upper pole blood vessels were treated close to the upper pole glands, and the affected lobe glands were excised.

7. Outcome Measures

7.1 Baseline Characteristics of Patients

Gender, Age, BMI, Tumor size, Pathological type, Tumor location, ASA grade.

7.2 Postoperative Outcomes

- Surgical outcomes: CRP level, SAA level, Drainage volume, intraoperative blood loss, VAS pain score, Operative time.
- Clinicopathologic characteristics: tumor size, number of lymph nodes, the positive rate of lymph nodes.
- Complications: complication rates and types.

7.3 Primary Outcome Measure: CRP level

8. Code of Ethics

8.1 Informed consent

Before each patient was enrolled in this study, the research investigators are responsible for a complete and comprehensive introduction to the surgical method of this study, its possible side effects and possible risks, and let patients know their rights, risks and benefits to be assumed. Patients should have signed informed consent before enrollment.

8.2 Ethical norms and policies and regulations

This clinical trial must comply with the Declaration of Helsinki (2000 Edition), the Good Clinical Practice (GCP) promulgated by the SFDA, and related regulations. Before the start of the trial, the study could be started only after the protocol was approved by the ethics committee of the lead unit. Any modification of the trial protocol during clinical research should be reported to the ethics committee and filed.

8.3 Obtaining ethics approval

Ethical approval has been obtained.

9. Quality Assurance

In order to ensure that this trial can be carried out in strict accordance with the clinical research protocol, during the entire process of the clinical trial, clinical investigators and clinical sponsors should behave in strict accordance with the requirements of the Good Clinical Practice for Drugs (GCP), and be sure to follow the trial procedures. Standardized, accurate test data, and reliable research conclusions. Specific requirements are as follows:

1. Requirements for collaborators:

- Lectures on clinical programs, CRF filling, etc. are given to the researchers before the clinical start.
- Send clinical monitors to conduct on-site inspections.
- Ensure that the researchers can keep in touch with the researchers at any time by telephone or email.

2. Requirements for researchers:

- Responsible for obtaining the "Informed Consent" signed by each subject or his agent.
- Complete the case report form (CRF) carefully as required.
- Regular visits.
- Completely maintain records of clinical records, and original medical records of subjects.

10. Data Processing and Preservation

10.1 Case report form (CRF)

The case report form should be filled out by investigators, and the CRF form should be filled out in time to ensure accurate content and timely summary. Generally, the CRF form should not be altered. If there is an error that needs to be revised, it should be signed at the revised place. The CRF form is in triplicate, and after the trial is over, it will be handed over to the clinical team leader hospital, the sponsor and the trial hospital for preservation. Data entry was performed after the completed case report was reviewed by the clinical monitor. The contents of the case report form are no longer modified.

10.2 Create a database

After receiving the CRF form, the statistician will verify the question by the researcher, and the researcher should answer and return as soon as possible. Statisticians will establish a database at the same time. After the database is reviewed, the data will be locked by the principal investigators, sponsors, statistician and clinical monitors. To ensure data security, irrelevant personnel cannot access and modify the data, and the data must be backed up.

10.3 Storage of data

The researcher should keep the data intact. According to the principle of GCP in China, for the investigators or hostipals, the data storage should be more than 5 years.

11. Statistical analysis

Professional statisticians undertake statistical analysis tasks and participate in the whole process from experimental design, implementation to analysis and summary. After the study protocol and case report form are completed, a statistical analysis plan shall be formulated. After some necessary modifications shall be made during the study process as required, and a statistical analysis report shall be provided after the data analysis is completed.

All analyses were performed using SPSS 26.0, and a P value less than 0.05 was considered significant. Normally distributed quantitative data are represented by mean (SD) [range]. Non-normally distributed quantitative data are represented by M（QR）. Comparison between groups was performed using the Mann-Whitney U test. Categorical data are expressed as frequencies and percentages. Comparisons between groups were performed using theχ2 test or Fisher's exact test.

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Appendix

Appendix AJCC 8th Edition/TNM Classification System for Differentiated Thyroid Carcinoma

Staging flowchart for differentiated thyroid cancer (AJCC 8e)

Age at diagnosis	M category	Gross ETE	Structures involved	Tumor size	N category	Stage
<55 years	M0	yes or no		any	any	I
	M1	yes or no		any	any	II
≥ 55 years	M0	no		≤ 4 cm (T1-2)	N0/Nx	I
					N1a/N1b	II
				> 4 cm (T3a)	any	II
		yes	only strap muscle (T3b)	any	any	II
			s/cutaneous, larynx, trachea, esophagus, RL nerve (T4a)	any	any	III
			prevertebral fascia, encasing major vessels (T4b)	any	any	IVA
	M1	yes or no	any or none	any	any	IVB

TNM definitions (AJCC 8e)

for papillary, follicular, poorly differentiated, Hürthle cell, medullary, and anaplastic thyroid carcinomas

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3*	Tumor > 4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles
T3a*	Tumor > 4 cm limited to the thyroid
T3b*	Gross extrathyroidal extension invading only strap muscles (sternohyoid) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size
NX	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph nodes metastasis
N0a*	One or more cytologic or histologically confirmed benign lymph node
N0b*	No radiologic or clinical evidence of locoregional lymph node metastasis
N1*	Metastasis to regional nodes
N1a*	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
N1b*	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
M0	No distant metastasis
M1	Distant metastasis

*all categories may be subdivided as solitary tumor (s) and multifocal tumor (m) – the largest tumor determines the classification