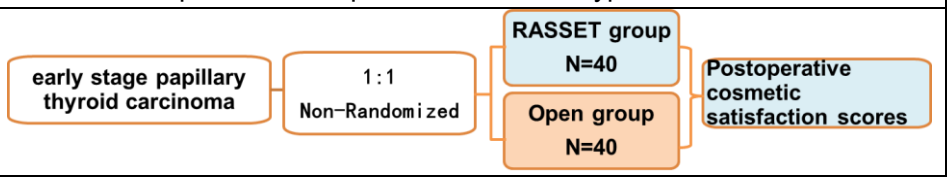
Single-center, Prospective, Non-Randomized Control Clinical Trial of Retro‐auricular Single‐site Endoscopic Versus Open Surgery in Patients with Early Stage Papillary Thyroid Carcinoma

Study Protocol

Version date: January, 19, 2022

Official Title	Single-center, Prospective, Non-Randomized Control Clinical Trial of Retro‐auricular Single‐site Endoscopic Versus Open Surgery in Patients with Early Stage Papillary Thyroid Carcinoma
Brief Summary	The goal of this non randomized control clinical research study is to compare the cosmetic outcomes and efficiacy of retro‐auricular single‐site endoscopic thyroid lobectomy and central lymph node dissection against conventional resection.
Conditions	Age: 18～70 years.Patients with early stage papillary thyroid carcinoma.
Outcome Measures	● Primary Outcome Measure: postoperative cosmetic satisfaction scores ● Secondary Outcome Measures: ➢ Cosmetic outcome: postoperative Vancouver Scar Scale ➢ Surgical outcomes: CRP level, SAA level, intraoperative blood loss, VAS pain score, Operative time. ➢ Clinicopathologic characteristics: tumor size, number of lymph nodes, the positive rate of lymph nodes. ➢ Complication: complication rates and types
Study Process	
Sample Size	80(40 VS 40)
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	2023-06-30
Locations	1

Groups	RASSET group VS traditional open thyroid lobectomy group
Masking and Allocation	None (Open Label). Non-Randomized(patient decided his surgery approach).
Statistical Analysis Plan	In this clinical study, the test level α was set to be 0.05 on both sides; the test efficiency Power (ie, 1-β) was selected as 0.8 (ie, type II error β=0.2); The sum standard deviation is 5.54±1.75, and the mean and standard deviation of the score of the cosmetic effect evaluation scale of the experimental group is expected to be 3.92±1.4 1. The 1:1 parallel control method is used, and the sample size calculation formula is based on the mean comparison of the two samples. According to the calculation of PASS software, this study requires a sample size of about 72 people (36 cases in each group). Considering the 10% dropout rate, the required sample size for each group is 40 cases, and a total of 80 cases in the two groups are required. 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.

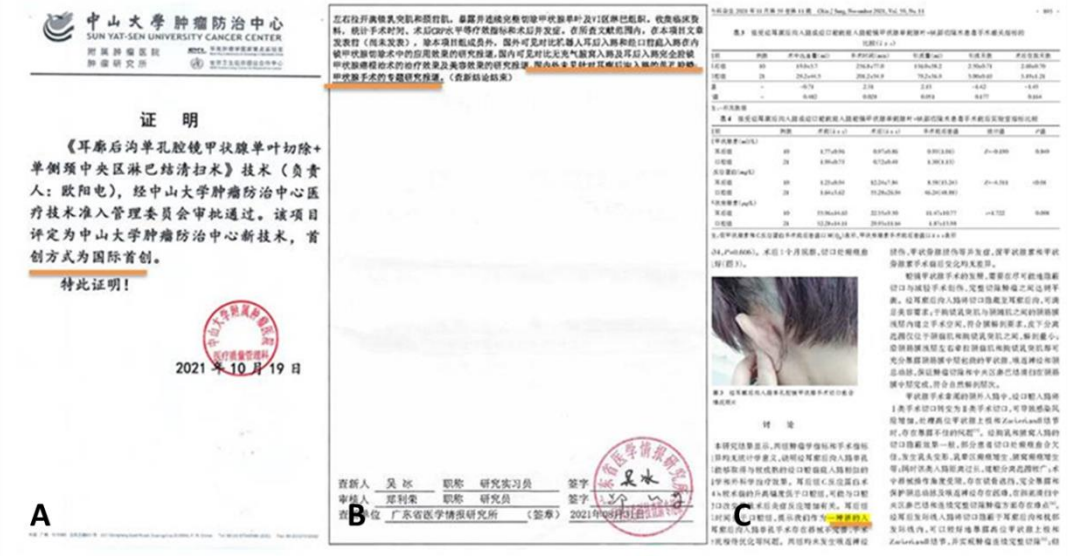


Figure 1. **A:**Sun Yat-sen University Cancer Center Certificates(international innovation). **B:**Guangdong Medical Information Research Institute Certificates(no report of this approach).**C:**Zhonghua Wai Ke Za Zhi(a new approach).

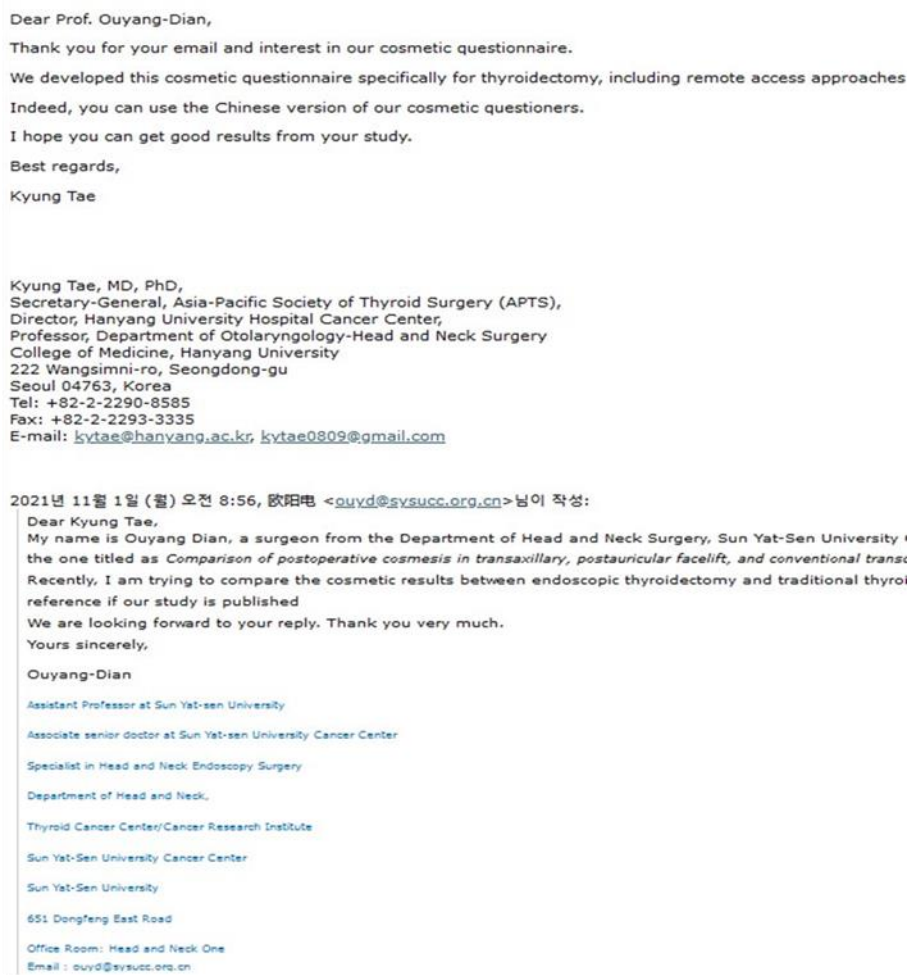
2. Study purpose

- Primary purpose:

Comparing the cosmetic outcomes of the retroauricular approach and the open group by comparing postoperative cosmetic satisfaction scores. (Appendix 1)

- Secondary purpose:
  - Comparing the degree of surgical trauma between the retroauricular group and the open group by comparing the level of CRP and SAA, blood loss, VAS pain score, and postoperative drainage.
  - Comparing the clinicopathologic characteristics between the retroauricular group and the open group by comparing the number of resected lymph nodes, and the positive rate of lymph nodes.
  - Comparing the safety between the retroauricular group and the open group by comparing the types and rate of complications between the two groups.
- Primary Outcome Measure: postoperative cosmetic satisfaction scores
- Secondary Outcome Measures:
  - Cosmetic outcome：postoperative Vancouver Scar Scale

- Surgical outcomes: CRP level, 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.



Dear Prof. Ouyang-Dian,

Thank you for your email and interest in our cosmetic questionnaire.

We developed this cosmetic questionnaire specifically for thyroidectomy, including remote access approaches

Indeed, you can use the Chinese version of our cosmetic questioners.

I hope you can get good results from your study.

Best regards,

Kyung Tae

Kyung Tae, MD, PhD,
Secretary-General, Asia-Pacific Society of Thyroid Surgery (APTS),
Director, Hanyang University Hospital Cancer Center,
Professor, Department of Otolaryngology-Head and Neck Surgery
College of Medicine, Hanyang University
222 Wangsimni-ro, Seongdong-gu
Seoul 04763, Korea
Tel: +82-2-2290-8585
Fax: +82-2-2293-3335
E-mail: kytae@hanyang.ac.kr, kytae0809@gmail.com

2021년 11월 1일 (월) 오전 8:56, 欧阳电 <ouyd@sysucc.org.cn>님이 작성:

Dear Kyung Tae,
My name is Ouyang Dian, a surgeon from the Department of Head and Neck Surgery, Sun Yat-Sen University
the one titled as *Comparison of postoperative cosmesis in transaxillary, postauricular facelift, and conventional transo*
Recently, I am trying to compare the cosmetic results between endoscopic thyroidectomy and traditional thyroi
reference if our study is published
We are looking forward to your reply. Thank you very much.
Yours sincerely,

Ouyang-Dian

Assistant Professor at Sun Yat-sen University

Associate senior doctor at Sun Yat-sen University Cancer Center

Specialist in Head and Neck Endoscopy Surgery

Department of Head and Neck,

Thyroid Cancer Center/Cancer Research Institute

Sun Yat-Sen University Cancer Center

Sun Yat-Sen University

651 Dongfeng East Road

Office Room: Head and Neck One
Email : ouyd@sysucc.org.cn

Figure 2. Kyung Tae's authorization

3. Study Eligibility

- 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.

- 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.

- 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

- 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, thyroid Computed tomography scan if necessary,Chest X-ray, abdominal ultrasonography, electrocardiogram.

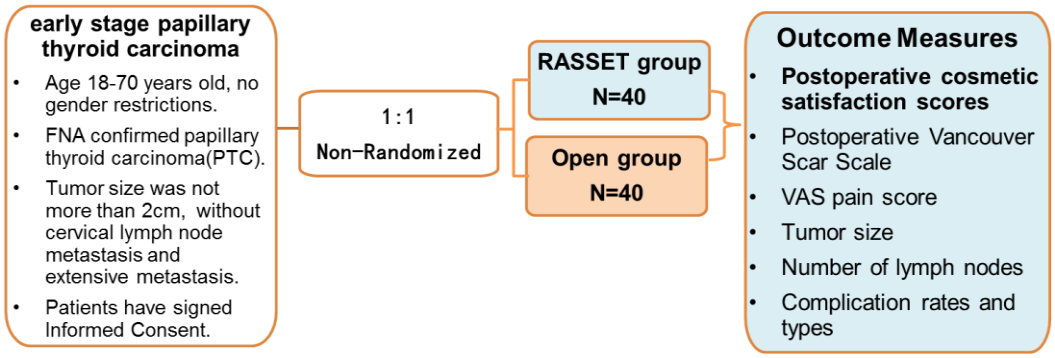
The above examinations are all routine preoperative examinations, which do not cause additional financial burden on patients.

- 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 3. flowchart



6. Surgical Technique

- 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 "A comparative study between retro‐auricular single‐site endoscopic thyroidectomy and transoral endoscopic thyroidectomy vestibular approach: a single‐center retrospective analysis".

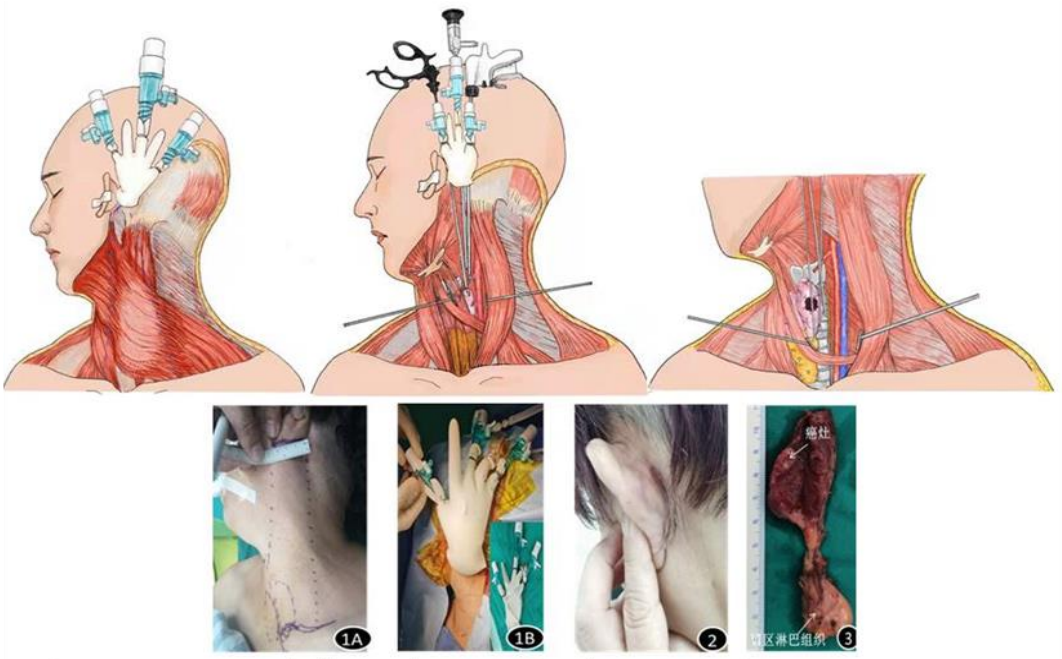


Figure 4. model and practical operation

- traditional open surgery

For traditional open surgery, the patient was placed in a supine position. A 4-6cm transverse incision was made. Subplatysmal flaps were dissected up to the thyroid cartilage and down to the sternal notch.The strap muscles were separated in the midline to expose the thyroid gland. Lateral dissection of the thyroid gland was performed. The middle thyroid vein was ligated. Superior thyroid vessels were individually ligated close to the thyroid gland. The RLN was identified and dissected near the inferior thyroid artery. Branches of the inferior thyroid vessels were ligated, preserving the lower parathyroid gland. Berry ligament was then dissected, and finally the isthmus was transected. The thyroid and central lymph nodes were resected. For details, please see "Clinical Practice and Skills in Head and Neck Oncology Surgery".

7. Outcome Measures

- Baseline Characteristics of Patients

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

- Postoperative Outcomes
  - Cosmetic outcome: postoperative Vancouver Scar Scale 1 and 3 months from surgery, postoperative cosmetic satisfaction scores 1 month from surgery.
  - Surgical outcomes: CRP level, SAA level, Drainage volume (ml), 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.
- Primary Outcome Measure: postoperative cosmetic satisfaction scores 3months from surgery.

8. Code of Ethics

- 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.

- 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.

- 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:

- 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.
- 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

- 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.

- 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.

- 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.

- Sample size

In this clinical study, the test level α was set to be 0.05 on both sides. the test efficiency Power (ie, 1-β) was selected as 0.8 (ie, type II error β=0.2). The sum standard deviation is 5.54±1.75, and the mean and standard deviation of the score of the cosmetic effect evaluation scale of the experimental group is expected to be 3.92±1.41. The 1:1 parallel control method is used, and the sample size calculation formula is based on the mean comparison of the two samples. According to the calculation of PASS software, this study requires a sample size of about 72 people (36 cases in each group). Considering the 10% dropout rate, the required sample size for each group is 40 cases, and a total of 80 cases in the two groups are required.

- Statistical Analysis

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 the$\chi 2$ test or Fisher's exact test.

12. Follow-up

During the study period, each enrolled case was independently archived and registered for evaluation (CRF), and a resident physician was to be hired to be responsible for follow-up, registration, filling, and storage. After the end of treatment, the enrolled patients will be reviewed in the outpatient clinic in the first month after surgery, and then will be followed up regularly for 3-6 months until the death of the patient or the end of the study. The content of each review must include: thyroid function, parathyroid hormone level, thyroid ultrasonography. Questionnaires were conducted in the first and third months after surgery, and the scores of the Beauty Evaluation Scale and the Postoperative Scar Scale

were recorded and counted.

13. Study Start and Completion

Study Start: March 1, 2022
Anticipated Study Completion: June 30, 2023
A total of 40 patients in the RASSET group and 40 patients in the open group will be Enrolled, follow up 1 and 3 months after the operation, and the clinical data will be collected and analyzed statistically.

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Appendix

Appendix 1 Cosmetic satisfaction questionnaire

Q1. How satisfied are you with your neck scar or a scarless neck?
Very satisfied(1) Satisfied(2) Average(3) Dissatisfied(4) Verydissatisfied(5)
Q2. How satisfied are you with the contour of your neck?
Very satisfied(1) Satisfied(2) Average(3) Dissatisfied(4) Verydissatisfied(5)
Q3. Do you think others look at your neck scar?
Absent (0) Sometimes (1) Frequent (2) Always (3)
Q4. Do you try to conceal your scar?
Absent (0) Sometimes (1) Frequent (2) Always (3)
Q5. Does your neck scar influence your choice of clothes?
Absent (0) Sometimes (1) Frequent (2) Always (3)
Q6. How often do you think about your scar?
Absent (0) Sometimes (1) Frequent (2) Always (3)

Appendix 2 Vancouver scar scale score

	Feature	Score
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pigmentation	Normal	0
	Hypo-pigmentation	1
	Mixed-pigmentation	2
	Hyper-pigmentation	3
Pliability (Elasticity)	Normal	0
	Supple (flexible with minimal resistance)	1
	Yielding (giving way to pressure)	2
	Firm (inflexible, not easily moved, resistant to manual pressure)	3
	Banding (rope-like tissue that blanches with extension of the scar)	4
	Contracture (permanent shortening of scar, producing deformity or distortion)	5
Height	Flat	0
	< 2 mm	1
	2-5 mm	2
	> 5 mm	3
Pain	None	0
	Occasional	1
	Requires medication	2
Itchiness	None	0
	Occasional	1
	Requires medication	2

Appendix 3 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