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Clinical significance of retrograde inferior parathyroid protection technique based on thymus preservation in thyroid surgery

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Abstract

Background The importance of parathyroid gland preservation in thyroid surgery has been well recognized; however, the rapid identification of the parathyroid gland, particularly the inferior parathyroid gland (IPG), remains challenging. This study aimed to evaluate the effectiveness of retrograde inferior parathyroid protection technique (RIPPT) based on thymus preservation.

Methods A total of 236 patients were enrolled in this study between August 2019 and December 2020. RIPPT was employed to identify and protect the inferior parathyroid gland (IPG), and its identification rate and the anatomical variations were analyzed. The parathyroid hormone (PTH) and serum calcium levels were compared between patients who underwent IPG orthotopic retention and those who received IPG auto-transplantation, stratified by the anatomical type of the IPG.

Results In total, the IPG identification rate was 97.88% (231/236), and the auto-transplantation rate was 74.46% (172/231). The anatomical relationship between IPG and thymus was observed in 77.97% of patients (184/236). Additionally, PTH levels were higher in patients with IPG orthotopic retention compared to those with IPG auto-transplantation both on postoperative day 1 (POD1) and at 6 months. PTH levels were also higher in patients with superior parathyroid gland (SPG) and IPG orthotopic retention compared to those who underwent both auto-transplantation procedures.

Conclusion Retrograde inferior parathyroid protection technique (RIPPT) underscores the importance of protecting inferior parathyroid gland (IPG) in thyroid surgery and has been demonstrated to be effective in the rapid identification and functional preservation of IPG, based on short-term outcomes.

Clinical trial number Not applicable.

Keywords Inferior parathyroid gland, Papillary thyroid cancer, Thymus-related inferior parathyroid gland, Thyroid surgery, Retrograde inferior parathyroid protection technique, Thymus preservation

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Introduction

Papillary thyroid cancer (PTC) is the most common type of endocrine malignancy, with a steadily increasing incidence rate over the past three decades [1, 2]. Surgical resection aims to remove the tumor while preserving vital structures such as recurrent laryngeal nerve (RLN) and parathyroid glands (PGs). The RLN, when damaged, can cause vocal cord paralysis, while damage to the PGs can lead to hypoparathyroidism, which in turn can cause complications such as osteoporosis, numbness in the extremities, and other debilitating symptoms [3–6].

Intraoperative neuromonitoring (IONM) has become an essential tool in the identification and preservation of RLN [7, 8]. However, despite progress in this area, the protection and identification of PGs, particularly IPGs, remains a significant challenge. The anatomical location of superior parathyroid gland (SPG) is relatively fixed, located on the dorsal side of the upper pole of the thyroid lobe, at the inferior border of the cricoid cartilage [9]. On the contrary, the position of IPG can vary due to its embryologic relationship with thymus, making its identification more difficult during surgery.

The Chinese guideline had reported correlations between PG and thyroid gland [10]. Most surgeons rely on certain anatomical landmarks and characteristics of PG, such as its light brown color, texture, and the presence of micro vessels on its surface, to aid in its identification [11]. Some surgeons also use advanced technology like Nano carbon to assist with locating PG, especially when IPG is obscured by thymus or other anatomical variations. Additionally, lacking experience, patient obesity, PG fatty degeneration, and intraoperative bleeding can all hinder IPG locating [12–14].

In some cases, PG fluorescence technology has been employed to improve PG detection, but it has limitations to popularize in primary hospitals, including defective recognition effects, restriction of obesity and extended procedure time [15]. Furthermore, IPG and thymus share a close developmental relationship during embryogenesis, which suggests that understanding this relationship could potentially enhance the identification and retention of IPG during thyroid surgery [16].

Given these considerations, we hypothesize that incorporating a refined approach to IPG identification—referred to as RIPPT—can improve the accuracy of IPG localization and retention rates in thyroid surgery.

Methods

Patients characteristics

A total of 236 patients were enrolled in this prospective, single-arm observational study from August 2019 to December 2020. The inclusion criteria were as follows: all patients were diagnosed with unilateral PTC through preoperative fine needle aspiration, with the longest PTC diameter measuring less than 4 cm. Patients were excluded if they met any of the following criteria: tumor invasion of IPG or surrounding tissues, history of thyroid surgery, age under 16 years, inability to comply with follow-up protocols, presence of metastatic LNs detected during preoperative evaluation. General characteristics, intraoperative factors, pathological findings, total number of LNs and metastatic LNs in the resected specimens, and postoperative complications were retrospectively collected. The primary outcomes included SPG and IPG recognition rates, orthotopic retention, auto-transplantation, serum calcium levels, and PTH levels in both hands. All patients underwent thyroid lobectomy with central LN dissection, performed by the same surgeon.

This is a single-center observational study, and clinical trial registration will be applied for in the subsequent phase.

IPG types

IPG was classified into five types based on the relationship with its location and thymus (Fig. 1). Type A: within thymus (Fig. 1A); Type B: at the superior aspect of thymus (Fig. 1B); Type C: very close to the superior aspect of thymus, with a distance of 5 mm or less (Fig. 1C); Type D: near the superior aspect of thymus, with a distance greater than 5 mm (Fig. 1D); Type E: anatomically unrelated to thymus, or IPG was attached to thyroid gland (Fig. 1E).

Surgical procedure of IPG identification by RIPPT

Initially, the lateral side of thyroid gland was carefully separated to expose the common carotid sheath, extending from the upper pole of thyroid down to thymus. Thyroid gland was then gently pulled to the contralateral side to provide a clear view and better access for the observation of IPG. After retraction, the IPG in the lower part of thyroid was examined (Fig. 2). If IPG was closely adhered to thyroid gland or was at risk of being dislodged and not remaining in situ, immediate auto-transplantation was performed.

Following the previous method [17], we quickly exposed RLN and identified the thymus, which was then separated from its lower (caudal) to upper (cephalic) aspect (Fig. 3). During this process, we either encountered IPG within thymus or located at the top of thymus (Fig. 4). IPG and thymus were preserved together in situ as a whole unit (Fig. 5). However, in certain patients, IPG was wrapped within thymus tissue, making its identification more challenging (Fig. 6). In such cases, we proceeded by continuing the dissection of the thyroid-thymus ligament along thyroid gland to facilitate the exposure of IPG. Generally, IPG was located within 10 mm of the top of thymus. If IPG was found to be more than 10 mm away from the top of thymus, or if

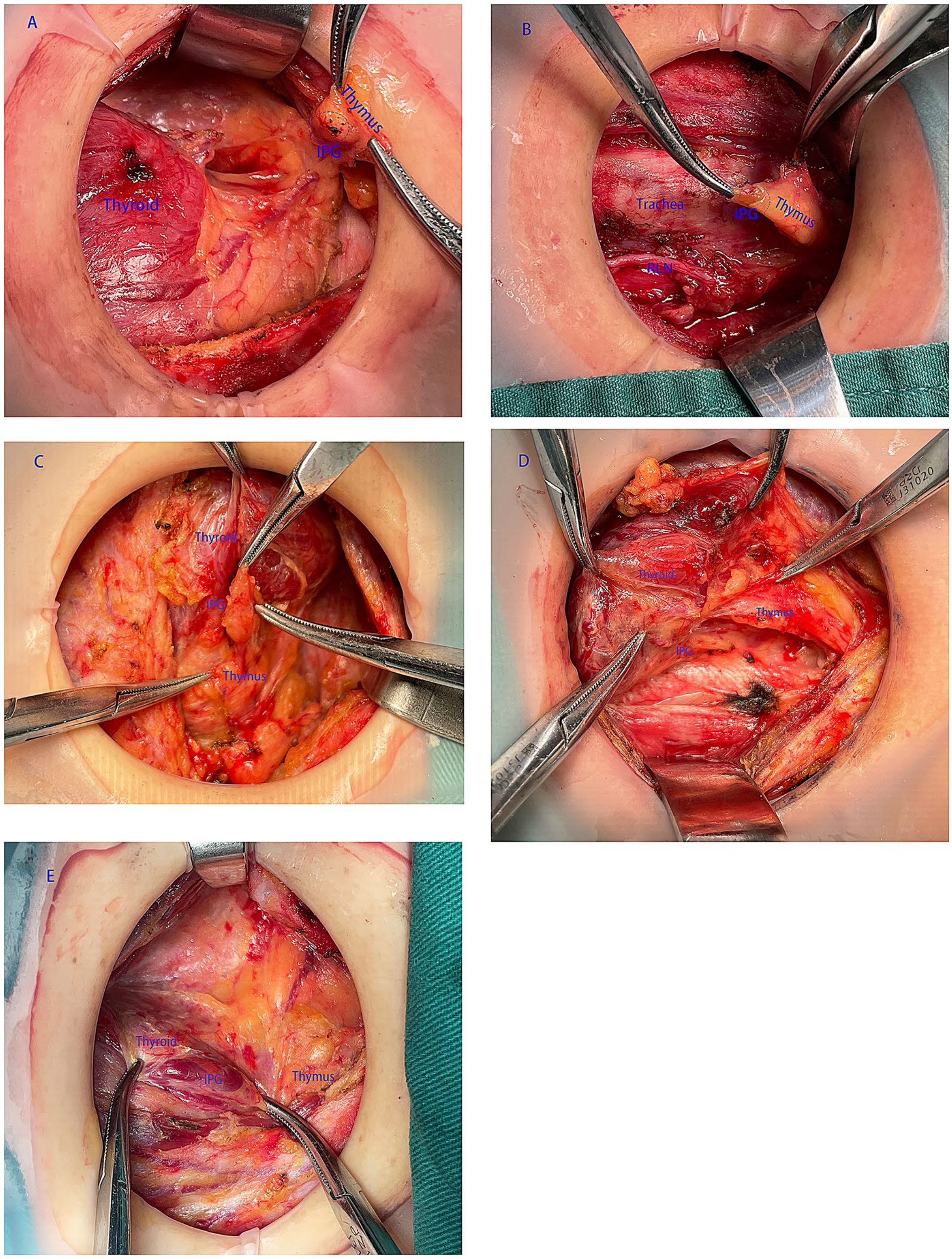

Fig. 1 IPG classifications from Type **A** to Type **E**

it appeared to be devoid of a blood supply, we promptly performed auto-transplantation of IPG into the brachioradialis muscle of the left forearm. This step was critical, as studies have shown that PG auto-transplantation can help preserve its function [18].

For all patients, suspected parathyroid tissue was punctured 3 to 5 times with a 1 mL needle (Fig. 7), and the needle was then thoroughly rinsed in 1mL saline. Subsequently, a rapid PTH test was performed by applying 100 μL of the eluent to the test paper. The result was read 5 min later, with a color change indicating a positive result, and no color change indicating a negative result (Fig. 8).

Subsequently, thyroidectomy and central lymph node dissection were performed following the guidelines outlined in China's thyroid protocols [19, 20]. If IPG was not identified during the steps we have outlined earlier, it became essential to search for IPG in the excised specimen.

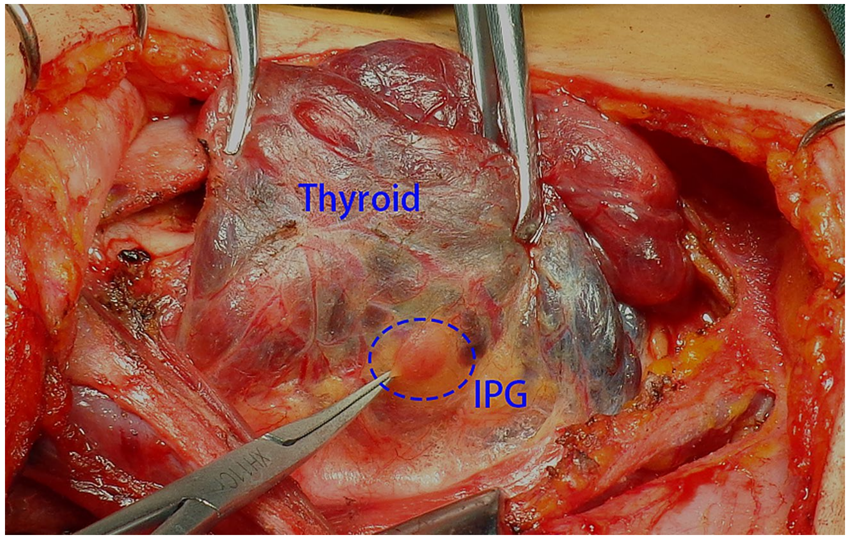

Fig. 2 Thyroid gland was retracted to the contralateral side, and IPG was observed in the lower portion of the gland

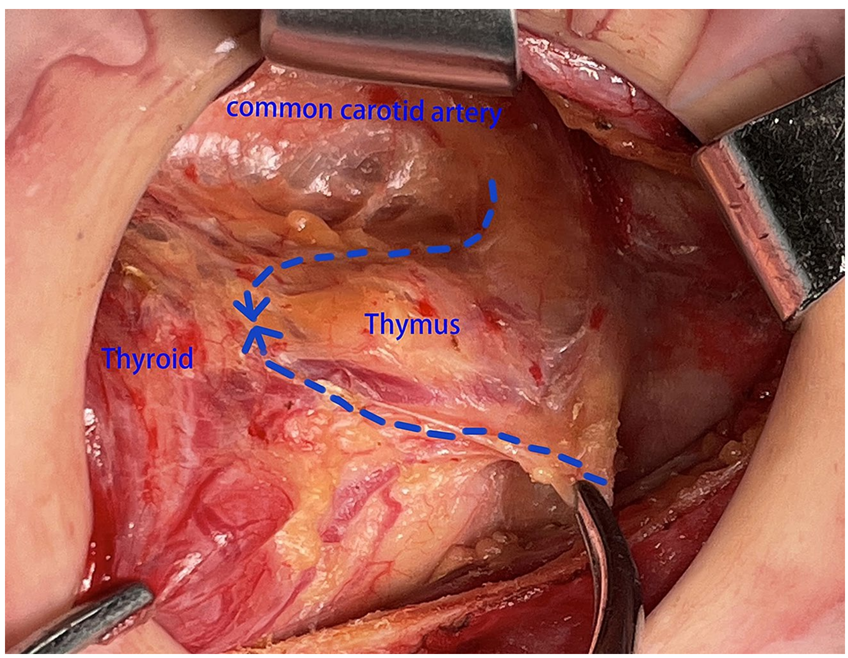

Fig. 3 Thymus was identified and separated from the tail to the head side

Follow-up and postoperative treatment of hypoparathyroidism

All patients underwent follow-up for 12 to 20 months. PTH level and serum calcium level were measured on postoperative day 1, 2 months, and 6 months. Postoperative hypoparathyroidism was diagnosed when PTH level was below 1.3 pmol/L six months after surgery, as per hospital protocol. Levothyroxine therapy was administered to all patients. Calcium supplementation and Vitamin D were prescribed until PTH level normalized in patients with symptomatic hypoparathyroidism. Intravenous calcium substitution was administered for severe symptomatic hypocalcemia, if necessary.

Statistical analysis

Statistical analysis was conducted using SPSS version 26.0 (IBM Corp., Chicago, IL, USA). Data were presented as the mean ± standard deviation. Comparisons between the two groups were made using the independent samples t-test or Chi-square test, with $P < 0.05$ considered statistically significant. P-values were considered significant if $P < 0.05$, and non-significant if $P \geq 0.05$.

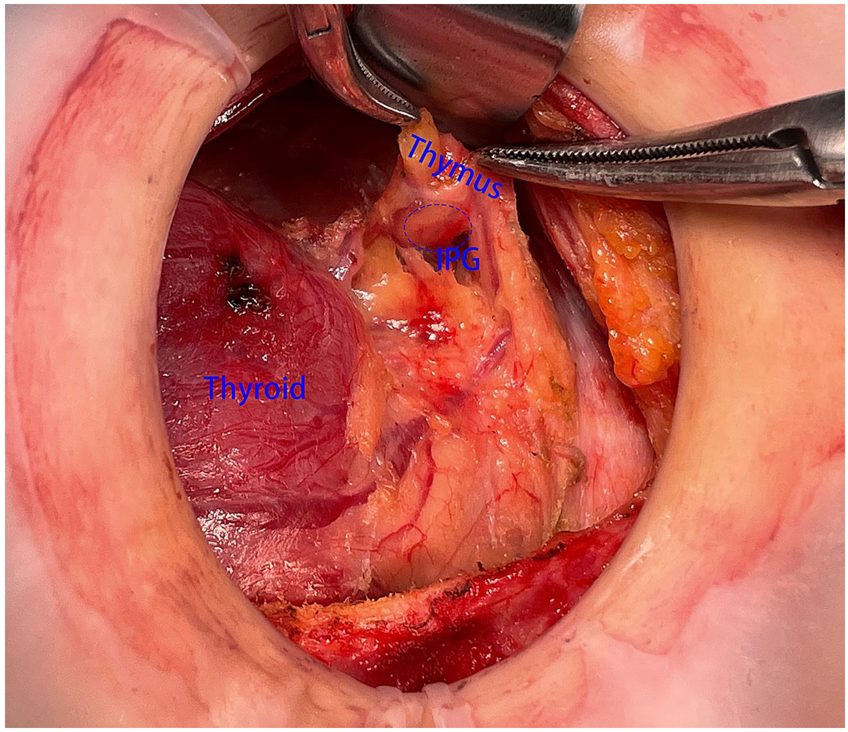

Fig. 4 IPG was located at the top of thymus

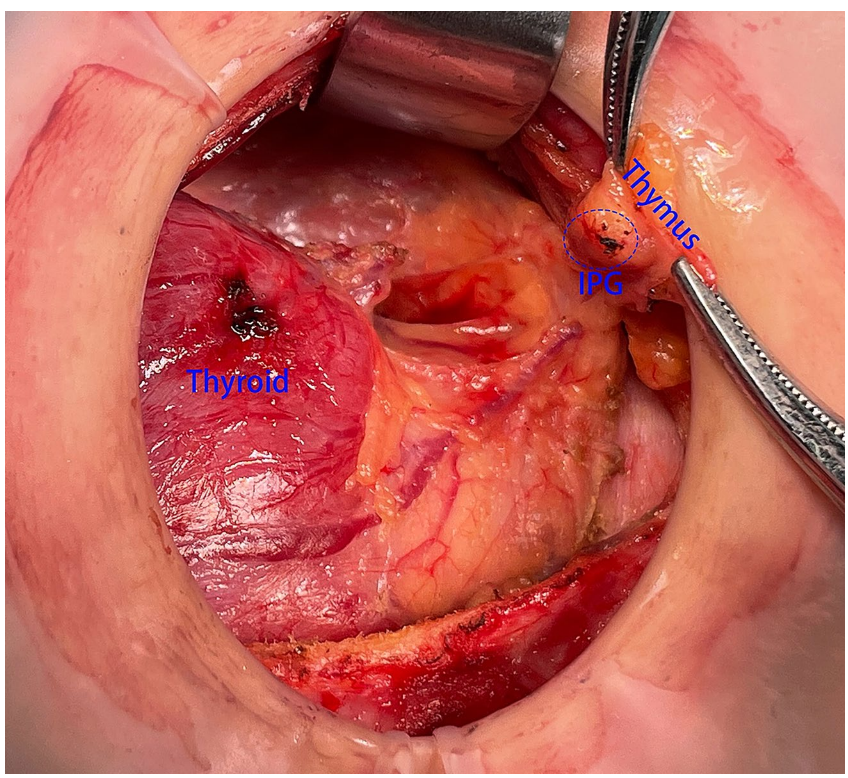

Fig. 5 IPG and thymus could be preserved in situ as an integration

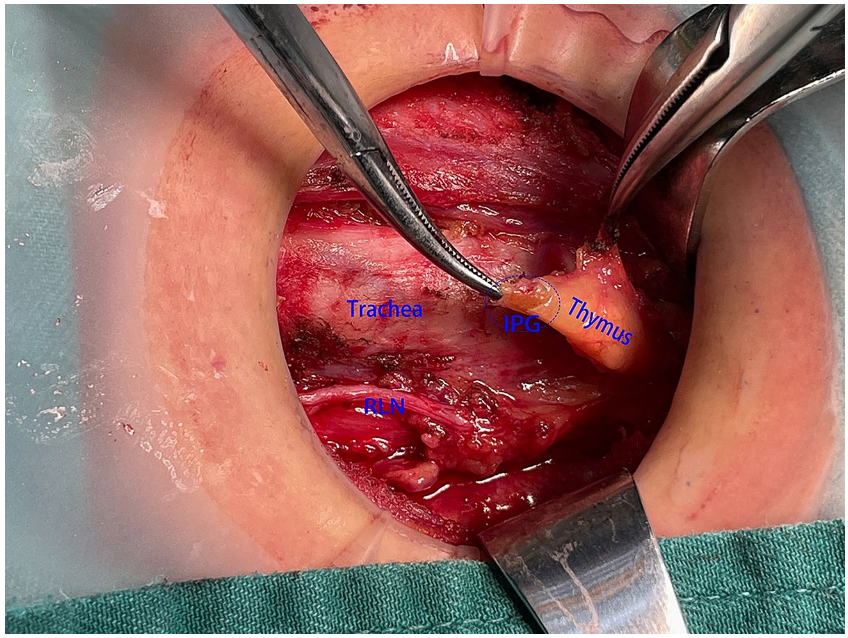

Fig. 6 IPG was enveloped by thymus, making it difficult to identify clearly with naked eye unless thymus capsule was opened

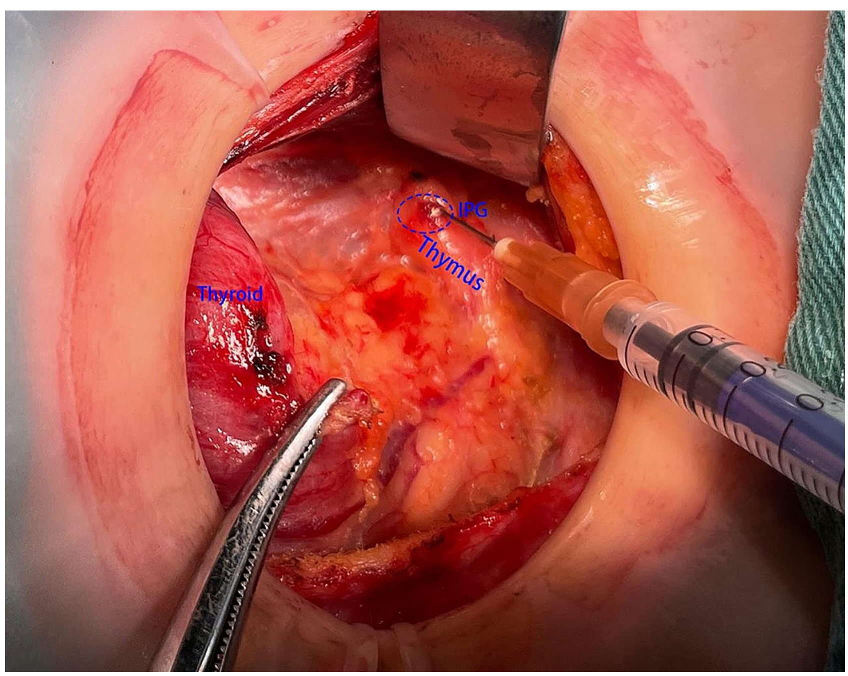

Fig. 7 Suspected parathyroid tissue was punctured 3 to 5 times with a 1 mL needle

Results

Patient characteristics: IPG anatomical types, SPG and IPG recognition, orthotopic retention, and auto-transplantation

The overall proportion of patients exhibiting a positive anatomical association between IPG and thymus was 79.65% (184/231). The distribution of IPG anatomical types was as follows: Type A 11.69% (27/231), Type B 11.69% (27/231), Type C 23.38% (54/231), Type D 32.90% (76/231), and Type E 20.35% (47/231). The corresponding IPG orthotopic retention rate for each anatomical type were as follows: Type A: 100% (27/27), Type B: 92.59% (25/27), Type C: 20.37% (11/54), Type D: 0% (0/76), Type E: 0% (0/47). Among the patients with IPG Type E, 35/47 (74.47%) had an IPG closely attached to the thyroid surface, while 12/47 (25.53%) required careful search of IPG in the resected specimens.

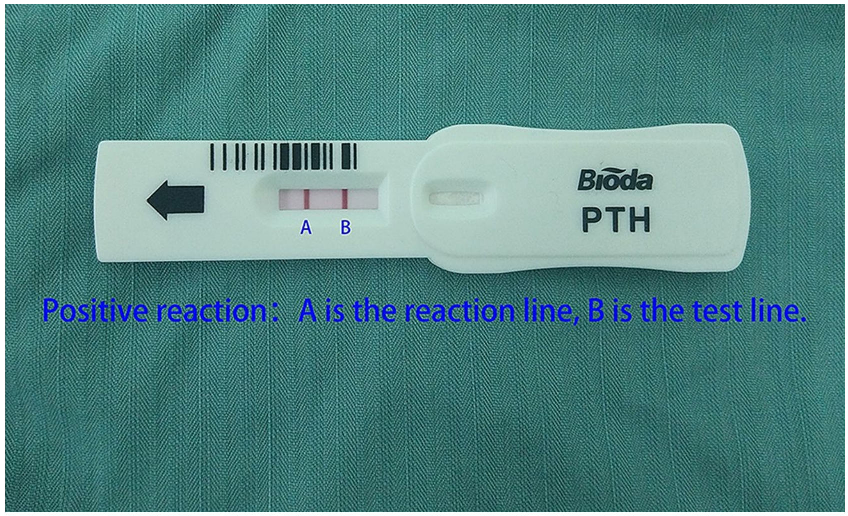

Fig. 8 Upon confirmation of parathyroid tissue, a reaction line was displayed

Table 1 PTH level and survival rate of parathyroid glands in patients with different numbers of PG auto-transplantation

Variable (pmol/L)	Time points of postoperative review	One IPG auto transplantation	Two IPG auto transplantation	*P* value
Right-hand PTH level	pre-operation	3.95 ± 1.52	4.3 ± 1.98	0.092
	1 days after surgery	2.90 ± 1.36	2.57 ± 1.24	0.349
	2 months after surgery	3.90 ± 1.81	2.86 ± 1.05	0.026
	6 months after surgery	3.59 ± 1.56	3.38 ± 1.12	0.587
Left-hand PTH level	6 months after surgery	23.46 ± 12.54	35.46 ± 20.65	0.045
Survival rate of PG auto-transplantation	6 months after surgery	122/176 (86.36%)	16/16 (100%)	0.007

Note Measurement unit for PTH level is pmol/L

For SPG recognition, identification rate was 100% (236/236), while the auto-transplantation rate was 8.47% (20/236). For IPG recognition, identification rate was 97.88% (231/236), with an auto-transplantation rate of 74.46% (172/231). The rate of one or two PG auto-transplantations was 67.80% (160/236) and 6.80% (16/236), respectively. The overall PG survival rate was 86.36% (152/176). However, survival rate significantly differed depending on the number of PGs transplanted: the survival rate for one PG was 85%, while for two PGs it was 100%.

Additionally, PTH level measured from the right-hand and left-hand glands in the two PG auto-transplantation group were found to be higher than those in the one PG auto-transplantation group at both the 2-month and 6-month postoperative follow-ups. (Table 1)

Risk factors in patients with IPG unidentified during the operation

We found IPG in most patients during operation, but some (5/236) were still missing. Meanwhile, our postoperative paraffin pathology results revealed that there were 15 patients with accidental removal of IPG, except the previous five cases. We suspected the IPG found in postoperative paraffin specimens may be the fifth PG. Further analysis also showed the IPG unidentified was mainly related to the age($P = 0.013$), but not associated with.

In the majority of patients, IPGs were identified during the operation. But in a small subset (5/236) IPG was still undetected. Additionally, postoperative paraffin pathology results revealed 15 patients in whom IPG had been accidentally removed, aside from the previous 5 cases. We suspected that the IPG found in postoperative paraffin specimens could potentially represent the fifth parathyroid gland. Further analysis indicated that the failure to identify IPG during surgery was mainly associated with age ($P = 0.013$), but no significant associations were found with other factors such as: IPG anatomical type, Body mass index, Tumor size, Total number of lymph nodes, Number of lymph node metastases, Diabetes, Hypertension, Thyroid disease. (Table 2)

Comparison of serum PTH and calcium levels between patients with different characteristics

We observed that PTH level in patients with IPG orthotopic retention were higher than that in patients who underwent IPG auto-transplantation. This difference was

Table 2 Risk factors in patients with IPG unidentified during operation

Variable	IPG identified 231 cases	IPG un-identified 5 cases	Chi-square or T value	*P* value
Age	45.06 ± 11.14	57.06 ± 9.76	-2.496	0.013
Tumor side	106/125	1/4	/	0.381
Body mass index (Kg/m^2)	23.00 ± 2.69	22.59 ± 5.54	0.165	0.877
Years(≤ 55y/>55y)	189/42	3/2	/	0.234
Sex (Male/Female)	58/173	1/4	/	1.000
Total number of lymph nodes	9.42 ± 8.14	8.6 ± 2.88	0.223	0.824
Numbers of lymph node metastases	1.09 ± 1.99	0.60 ± 1.34	0.544	0.587
Diabetes	18/231	1/5	/	0.345
Hypertension	30/231	2/5	/	0.137
Thyroid disease (Hashimoto or nodular goiter)	194/231	3/5	/	0.192

statistically significant at 1 day and 6 months after surgery. However, no statistical difference was found in the serum calcium level between the two groups at any postoperative time point. (Table 3)

We further analyzed PTH level and serum calcium level in three types of IPG orthotopic retention. No significant differences were found in either PTH level or serum calcium level at any of the three time points after surgery when analyzed by single-factor analysis of variance (ANOVA). Additionally, no significant differences were observed in the pairwise comparisons between any two of the three groups. (Table 4)

We found that PTH level in patients with SPG and IPG orthotopic retention was significantly higher than that in patients with SPG and IPG auto-transplantation at all three postoperative time points. Also, no significant difference in the serum calcium levels between the two groups at any of these time points after surgery. (Table 5)

Side effects and operative complications

A few patients experienced complications following surgery, including postoperative bleeding (1/236), transient hypoparathyroidism (3/236), transient recurrent laryngeal nerve palsy (6/236). Patients with transient hypoparathyroidism did not exhibit symptoms of hypocalcemia, and their PTH level returned to normal within two weeks. Additionally, patients who developed transient vocal cord dyskinesia (due to recurrent laryngeal nerve palsy) showed complete recovery within two months, as confirmed by electronic laryngoscopy.

Discussion

In this study, a novel approach was employed to locate IPG using RIPPT. Our results demonstrated a high success rate in identifying IPGs and performing auto-transplantation, with rates of 97.88% and 74.46% respectively.

Table 3 Comparison of serum PTH and calcium level between patients with IPG orthotopic retention and auto-transplantation after surgery

Variable	IPG orthotopic retention	IPG auto-transplantation	Chi-square value	*P* value
PTH (pre-operation)	3.98 ± 1.30	4.00 ± 1.58	-0.074	0.941
PTH (1 days after surgery)	3.36 ± 1.31	2.89 ± 1.36	2.424	0.016
PTH (2 months after surgery)	3.82 ± 1.12	3.83 ± 1.79	-0.041	0.968
PTH (6 months after surgery)	4.18 ± 1.47	3.57 ± 1.52	2.767	0.006
Ca (pre-operation)	2.34 ± 0.07	2.35 ± 0.17	-0.185	0.853
Ca (1 days after surgery)	2.21 ± 0.10	2.19 ± 0.10	1.268	0.206
Ca (2 months after surgery)	2.39 ± 0.11	2.38 ± 0.11	0.448	0.654
Ca (6 months after surgery)	2.42 ± 0.35	2.35 ± 0.10	1.678	0.098

Note Measurement unit for PTH level and serum calcium level is pmol/L, mmol/L respectively

Table 4 PTH level and serum calcium level among patients with different IPG types of orthotopic retention

Variable	IPG types of orthotopic retention			F value	*P* value
	Type A	Type B	Type C		
PTH (pre-operation)	3.64 ± 1.07	4.33 ± 1.61	3.88 ± 0.90	1.577	0.204
PTH (1 days after surgery)	3.35 ± 1.38	3.44 ± 1.44	3.30 ± 0.88	0.138	0.937
PTH (2 months after surgery)	3.83 ± 1.08	3.87 ± 1.21	3.68 ± 1.20	0.074	0.974
PTH (6 months after surgery)	4.04 ± 1.28	4.24 ± 1.53	4.38 ± 1.94	0.203	0.894
Ca (pre-operation)	2.34 ± 0.06	2.36 ± 0.07	2.31 ± 0.08	1.339	0.270
Ca (1 days after surgery)	2.19 ± 0.10	2.23 ± 0.10	2.20 ± 0.08	1.136	0.342
Ca (2 months after surgery)	2.38 ± 0.10	2.40 ± 0.12	2.40 ± 0.11	0.306	0.821
Ca (6 months after surgery)	2.35 ± 0.12	2.39 ± 0.10	2.37 ± 0.07	0.641	0.591

Note Measurement unit for PTH level and serum calcium level is pmol/L, mmol/L respectively

Table 5 Comparison of PTH level and serum calcium level between patients with SPG and IPG orthotopic retention vs. auto-transplantation

Variable	SPG and IPG orthotopic retention	SPG and IPG auto transplantation	Chi-square value	*P* value
PTH (pre-operation)	4.02 ± 1.33	4.30 ± 1.98	-0.546	0.592
PTH (1 days after surgery)	3.44 ± 1.29	2.57 ± 1.24	2.422	0.018
PTH (2 months after surgery)	3.90 ± 1.10	2.86 ± 1.05	3.388	0.001
PTH (6 months after surgery)	4.23 ± 1.44	3.37 ± 1.12	2.203	0.031
Ca (pre-operation)	2.34 ± 0.07	2.28 ± 0.31	0.871	0.397
Ca (1 days after surgery)	2.21 ± 0.09	2.19 ± 0.07	0.943	0.349
Ca (2 months after surgery)	2.38 ± 0.11	2.34 ± 0.11	1.121	0.266
Ca (6 months after surgery)	2.37 ± 0.10	2.31 ± 0.10	0.712	0.053

Note Measurement unit for PTH level and serum calcium level is pmol/L, mmol/L respectively

Notably, these rates were higher than those reported in previous studies [21–23]. The anatomical relationship between the IPG and the thymus was observed in 77.97% of patients (184/236). Furthermore, the survival rate following auto-transplantation of one PG or two PGs was 85% and 100%, respectively. These findings suggested that the majority of patients have a clear anatomical connection between IPG and thymus, even in cases where 5 out of 236 unidentified IPGs and 15 out of 236 IPGs were accidentally removed. The anatomical relationship between IPG and thymus can be attributed to their shared embryological development, which supports the feasibility of using RIPPT to identify thymus during surgery.

RIPPT was effective in quickly identifying IPGs, but it remains uncertain whether IPG orthotopic retention offers significant benefits for its functional preservation. In this study, we found that PTH level in patients with IPG orthotopic retention were significantly higher than that in patients with IPG auto-transplantation both 1 day and 6 months post-surgery. However, we did not observe significant differences in PTH and serum calcium level among the three IPG anatomical types with orthotopic retention. This lack of difference might be attributed to our clinical decision-making process regarding IPG auto-transplantation. Specifically, we opted for orthotopic retention when we were confident in blood supply; otherwise, auto-transplantation was performed. The question of whether auto-transplantation or orthotopic retention is preferable for protecting IPG function when it is identified may be partially answered by our findings. We observed higher PTH level in patients with SPG and IPG orthotopic retention compared to those with auto-transplantation, suggesting that orthotopic retention may offer functional advantages under certain conditions.

More importantly, RIPPT not only enhances the efficiency of IPG protection but also simplifies thyroid surgical procedure. During surgery, we first separated the external surface of the thyroid gland before searching for thymus, taking care to manage the middle and lower thyroid veins on the superficial surface of the common arterial sheath to prevent bleeding that could compromise the surgical field. We then quickly identified and protected RLN, reducing the risk of damage during IPG search, which was a challenge with previous methods.

Our approach prioritized IPG protection and orthotopic retention, while also emphasizing that auto-transplantation should be performed when IPG could not be preserved in situ. Furthermore, after ensuring the protection of RLN and IPG, the use of RIPPT helped simplify the dissection of LNs, avoid RLN injury, and prevent damage to PGs. This not only reduced the complexity of the surgery but also saved time during the examination of resected specimens. Therefore, RIPPT is a simple and safe technique, particularly beneficial for less experienced surgeons. However, it is important to note that this study's findings are applicable only to PTC patients undergoing unilateral or bilateral surgery, and the technique is most suitable for use in central neck dissection (CND). As the guidelines for CND become more restrictive, the indications for RIPPT may also become more limited.

As for complications, some criteria define permanent postoperative hypoparathyroidism as a condition with consistently low PTH level for 12 months [24]. In our study, we considered postoperative hypoparathyroidism generally, using a PTH level below 1.3 pmol/L at six months after surgery as an indicator. However, we did not assess PTH level and serum calcium level for all patients at the 12-month mark. Secondly, we performed thyroid lobectomy with central lymph node dissection for all PTC patients in accordance with Chinese guidelines, which is also a procedure used in the combined treatment of anaplastic thyroid carcinoma [25]. Additionally, hypocalcemia and low PTH level on POD1 are often observed after total thyroidectomy for PTC and hyperparathyroidism [24, 26]. Our results showed no cases of hypocalcemia, suggesting that RIPPT can effectively reduce the risk of low PTH and serum calcium levels after surgery.

Wang JB proposed a method for detecting the blood supply to IPG based on the concept of thymus-blood vessel-inferior parathyroid gland layer [27]. Wang X, on the other hand, introduced a meticulous thyrothymic ligament dissection technique to explore IPG. Both approaches are challenging in terms of preserving the branches of inferior thyroid artery, making them less suitable for widespread adoption in primary hospitals [28]. On the contrary, our study focused on identifying IPG using RIPPT and deciding whether to retain it in situ based on its type. Since IPGs with blood supply from thymus are more likely to survive, we opted for a more aggressive auto-transplantation approach in patients with Type D IPG and reduced the time spent on IPG searching to minimize the risk of functional impairment [29].

Although RIPPT technology has been widely implemented in our hospital, several areas for improvement remain. These include: (1) Further validation is needed to confirm the blood supply or subsequent microcirculation development in IPG orthotopic retention; (2) PTH level in our study was influenced by IPG auto-transplantation and contralateral PG compensation, which could impact the interpretation of results; (3) A higher number of IPG auto-transplantations were performed in patients with Type D IPG, limiting the ability to compare PTH level between Type C and Type D IPG. An active strategy of IPG in situ retention in Type D IPG requires further validation; (4) Total thyroidectomy is commonly used in the treatment of PTC, MTC and hyperparathyroidism. An extended study evaluating the effectiveness of RIPPT in total thyroidectomy for different diseases would be beneficial in the future.

Conclusion

Retrograde inferior parathyroid protection technique (RIPPT) prioritizes the protection of IPG during thyroid surgery. Based on short-term data, RIPPT proves beneficial for the rapid identification of IPG and its functional preservation. As a result, we present this promising approach that could be considered for widespread adoption in hospitals to safeguard the function of inferior parathyroid gland during thyroid surgery.

Abbreviations

PTC	Papillary thyroid carcinoma
RLN	Recurrent laryngeal nerve
PG	Parathyroid gland
SPG	Superior parathyroid gland
IPG	Inferior parathyroid gland
PTH	Parathyroid hormone
TC	Thyroid carcinoma
IONM	Intraoperative neuromonitoring
TRIPG	Thymus-related inferior parathyroid gland
RIPPT	Retrograde inferior parathyroid protection technique
LN	Lymph node
POD1	Postoperative day 1

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Author contributions
No editorial services were used for this manuscript. Wenxin Zhao contributed to the concept of study design and final approval of the work. Shouyi Yan contributed by writing and data analysis. Yuhan Chen contributed through the collection and analysisof data, preservation of original data, and preparation of the manuscript. Liyong Zhang contributed by review of data and analysis of data. Shaojun Cai contributed through data acquisition. All authors read and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are not publicly available due to the complexity and amount of data, which requires special processing software. However, data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Fujian Medical University Union Hospital (2019KY122), and consent obtained was written. All patients provided informed consent. All experiments were performed in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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