



Application of indocyanine green in the parathyroid detection and protection: Report of 3 cases

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ABSTRACT

Background: It was thought that identifying the parathyroid gland during surgery was difficult for surgeons. It may be critical to locate the parathyroid for surgeons during thyroidectomy or parathyroidectomy due to the significant function of the parathyroid in calcium balance. According to recent reports, intrinsic fluorescence of the parathyroid has been found. There is some evidence to suggest that new equipment can detect the intrinsic fluorescence via imaging technology. In this case reports, a newly-invented intraoperative fluorescence imaging system and indocyanine green dye were applied to detect the parathyroid gland and evaluate the vascularization of parathyroid.

Case presentation: From July 1st to August 8st, 2018, 3 patients underwent total thyroidectomy in Zhuhai People's Hospital. The 3 subjects were recruited into our research. Indocyanine green angiography was performed on all the three participants. By ICG angiography, parathyroid glands were identified and protected. In the 3 patients, postoperative PTH levels were in the normal range. No one of them developed transient hypoparathyroidism.

Conclusions: This study has identified that the fluorescence imaging system applied with indocyanine green is a safe, easy and effective method to protect the parathyroid and predict postoperative parathyroidism.

1. Background

In modern times, the indocyanine green (ICG) angiography system is essential for a wide range of surgical procedures. ICG angiography was initially used in macular degeneration. After that, ICG was widely applied in angiography to identify sentinel lymph nodes in cervical cancers [1]. Also, it was used to determine the resection region of hepatic carcinomas [2]. Studies over the past decade have provided important information on the utility of ICG angiography in various surgical procedures, such as cholecystectomies (including robotic and laparoscopic), colectomies, resections, nephrectomies, kidney autotransplantation, lymph node dissection in various locations, and many other kinds of surgeries [3].

ICG angiography is fundamental to complete a successful thyroidectomy surgery, since the prevention of postoperative hypoparathyroidism has a pivotal role in patients undergoing thyroidectomy. In conventional methods, measurements of calcium or parathormone (PTH) are frequently prescribed for patients after total thyroidectomy. In many medical centers or hospitals, postoperative calcium or PTH supplementation plays a vital role in the metabolism of postoperative

thyroid surgery patients and the amount of PTH or calcium supplementation depends on the calcium level or symptoms of patients [4]. However, ICG angiography has emerged as powerful platforms for predicting the function of parathyroid immediately after thyroidectomy. At the same time, the fluorescence imaging system is fast becoming a key instrument in surgeries like thyroidectomy and parathyroidectomy. Postoperative paresthesia is common for hypocalcaemia symptoms, and is one of the most widely seen complaint of patients after thyroid surgery. There is a growing body of literature that recognises the importance of ICG angiography to prevent post-thyroidectomy hypoparathyroidism. In fact, few methods preventing post-thyroidectomy hypothyroidism has been reported before ICG angiography. The use of intravenous methylene blue in identifying the parathyroid was reported in 1971. But the results were not so obvious [5]. In the following years, the techniques used to locate the parathyroid did not function well. ICG angiography is an important component in the thyroid and parathyroid surgeries and plays a key role in protecting parathyroid.

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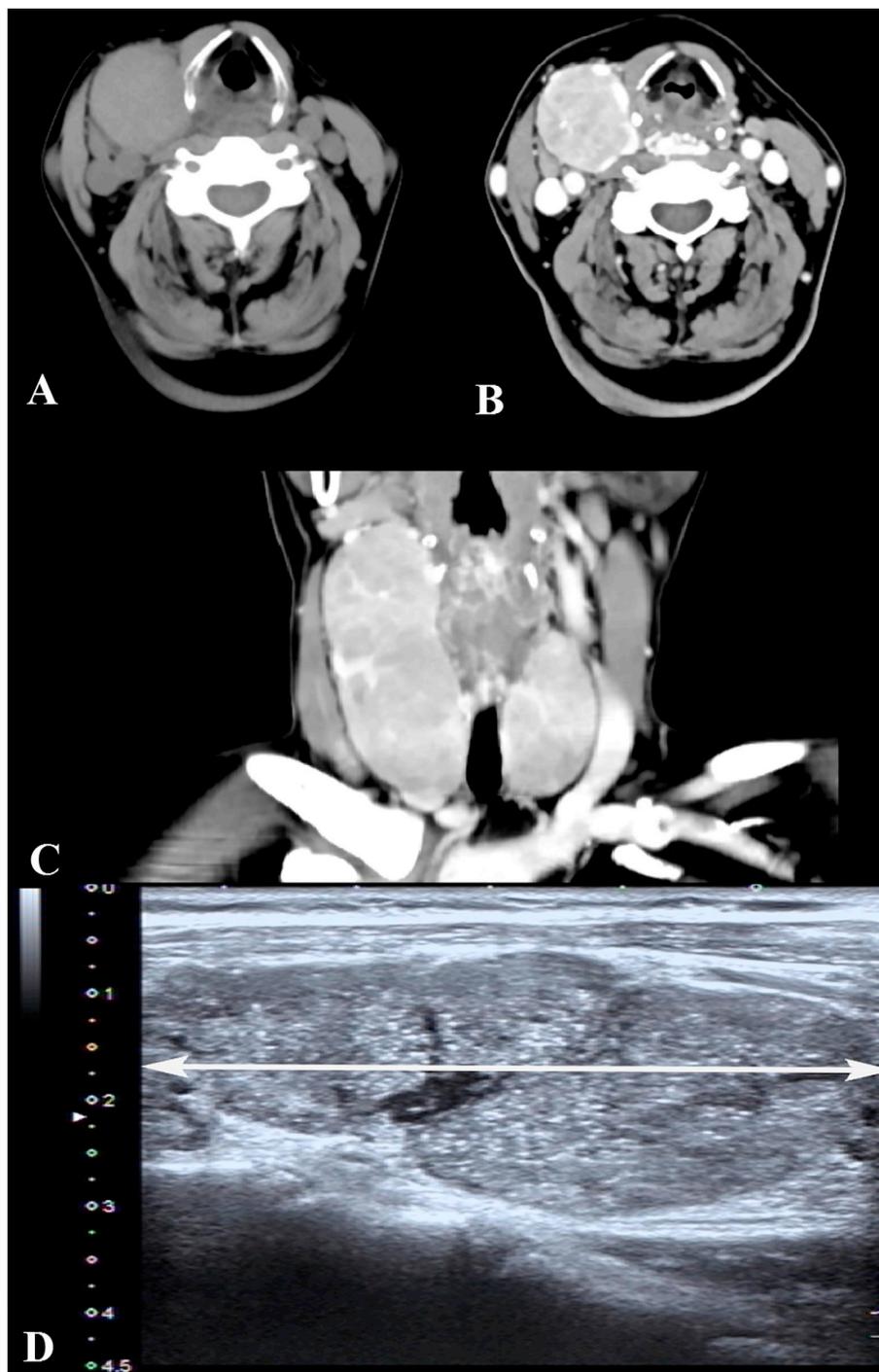


Fig. 1. Imaging features of case 1. A. CT image of thyroid; B. Enhancement CT image of thyroid; C. Coronal CT image of thyroid; D. Ultrasound image of thyroid.

1.1. Case 1

All of the cases were approved by [Zhuhai People's Hospital] as one of the prospective study. A 39-year old woman with Graves' disease and hypertensive disease. The patient was admitted to the hospital because of palpitation and disturbance in respiration lasting half a year. The palpitation was heavier when the patient was overworked. The symptoms were paroxysmal, and the patient took nifedipine, indapamide, propylthiouracil and thyrozol orally. Upon physical examination, trachea was displaced to the left. A neck mass was noted in the right thyroid region. The volume of the mass was about $5 \times 4 \times 4$ cm. The left thyroid and neck lymph nodes swelling were not detectable. The

neck computerized tomography (CT) examination image of the patient showed extensive swelling in bilateral thyroid region (more obvious in the right thyroid) as presented in Fig. 1. The neck ultrasound (US) examination image of the patient showed similar result as presented in Fig. 2. Her serum calcium was 2.31 mmol/L (normal range = 2.11–2.52 mg/dL), PTH 3.80 pmol/L (normal range = 1.60–6.90 pmol/L). Serum phosphorus 3.6 mg/dL (normal range = 2.5–4.5 mg/dL). Her 24-hour urine calcium was 279 mg (normal range = 100–300 mg/24 h) and a 24-hour creatine of 1060 mg. The patient was diagnosed as nodular goiter.

Surgical procedures: For thyroidectomy procedure, patients received general anesthesia with endotracheal intubation. After that they



Fig. 2. Image of parathyroid of case 1 and the ICG angiography equipment. A. Image of parathyroid of case 1. Light white indicates parathyroid gland. B. The ICG angiography equipment; C. The fluorescence detector of the ICG angiography equipment.

were placed in a supine position with their necks slightly extended. A 4–6 cm incision was made on the superior border of the sternum. Platysma myoides were abstracted to expose the TN. The thyroid goiter was dissected with an ultrasound knife (Johnson&Johnson Inc., New Brunswick, NJ, USA). According to the patient's situation, a total thyroidectomy was performed.

ICG injection and the fluorescence imaging system manipulation were prepared according to the protocols used by Desmettre T et al. [6].

Intravenous injection of 5 mg ICG dye was given to patients during the surgical procedure adequate exposure of each central neck compartment was acquired. In 2 min, the parathyroid glands took up the dye and stay fluorescent up to 20 min. The injection could be repeated until a maximum regimen of 5 mg per kg per day was reached. Images were acquired with a fluorescence imaging system named INTRAOPERATIVE NAVIGATION SYSTEM (Digi-MIH-I-001, Digital Precision Medicine Technology Co., Ltd., Beijing, China)(Fig. 2). ICG is a kind of anionic,

water-soluble tricarbo-cyanine molecule, which would emit fluorescence when it was excited by a near-infrared (NIR) fluorescence with a wavelength of 800 nm. ICG has a mean (s.d.) half-life of 3.4(0.7) min [7]. When injected intravenously, ICG could rapidly bind plasma lipoproteins. Previous research has found that as the ICG is excreted through the hepatic system at once via first-pass effect and ICG does not possess any toxic or other kinds of side effects [3].

Intraoperative intact PTH level decreased from a pre-excision level of 118 pg/mL to 26 pg/mL, 10 min after excision. On postoperative day (POD) 1, her serum calcium was 9.8 mg/dL, PTH was 23 pg/mL, and phosphorus was 3.4 mg/dL. The patient was discharged home uneventfully on POD 1. At 2 week follow-up her serum calcium was 9.5 mg/dL, PTH was 48 pg/mL, and phosphorus was 3.5 mg/dL.

1.2. Case 2

A 36-year old male with cancerous goiter and diabetes mellitus. The patient was admitted to the hospital because of weakness and marasmus lasting 3 months. The patient found a neck mass 5 years ago and underwent thyroid radiofrequency ablation in the same year. The patient underwent US-guided fine needle aspiration cytology one month ago in our hospital and the result showed a cancerous goiter. In the recent 3 months, the weight loss is about 15 Kg.

Upon physical examination, a neck mass was noted in the left thyroid region and a smaller mass was noted in the right thyroid region. Redness, swelling, fever and pain were not detectable around the two masses. The masses were smooth, tough and mobilizable with swallowing. The volume of the left mass was about $2 \times 1 \times 1$ cm and the volume of the right mass was about $1 \times 1 \times 1$ cm. A submaxillary lymph node swelling were detectable. Swelling of neck lymph nodes on other positions were not detectable. The neck CT examination image of the patient showed a cancerous goiter in the left thyroid region (probably thyroid malignant tumor) and a small nodule in the right thyroid region as presented in Fig. 3. The neck ultrasound examination image of the patient showed similar result as presented in Fig. 3. His serum calcium was 2.25 mmol/L (normal range = 2.11–2.52 mg/dL), PTH 4.20 pmol/L (normal range = 1.60–6.90 pmol/L). Serum phosphorus 4.1 mg/dL (normal range = 2.5–4.5 mg/dL). His 24-hour urine calcium was 282 mg (normal range = 100–300 mg/24 h) and a 24-hour creatinine of 1080 mg.

Total thyroidectomy procedure was performed as case 1, in which ICG angiography was performed to locate the position of parathyroid glands (Fig. 4). Postoperative pathological result showed thyroid papillary carcinoma.

Intraoperative intact PTH level decreased from a pre-excision level of 126 pg/mL to 32 pg/mL, 10 min after excision. On POD 1, his serum calcium was 9.7 mg/dL, PTH was 25 pg/mL, and phosphorus was 3.3 mg/dL. He was discharged home uneventfully on POD 1. At 2 week follow-up his calcium was 9.6 mg/dL, PTH was 49 pg/mL, and phosphorus was 3.4 mg/dL.

1.3. Case 3

A 36-year old male with neck mass. The patient was admitted to the hospital because of neck mass lasting 10 years. The patient found a neck mass 10 years ago without discomfort and had never received any kind of treatment.

Upon physical examination, trachea was displaced to the left slightly. A neck mass was noted in the right thyroid region and a smaller mass was noted in the right thyroid region. The masses were smooth, tough and mobilizable with swallowing. The volume of the right mass was about $5 \times 4 \times 3$ cm and the volume of the left mass was about $1 \times 1 \times 1$ cm. The neck CT examination image of the patient showed a cancerous goiter in the right thyroid region (probably thyroid malignant tumor) and some small nodules in the left thyroid region as presented in Fig. 5. The neck US examination image of the patient

showed similar result as presented in Fig. 3. His serum calcium was 2.31 mmol/L (normal range = 2.11–2.52 mg/dL), PTH 3.80 pmol/L (normal range = 1.60–6.90 pmol/L). Serum phosphorus 3.6 mg/dL (normal range = 2.5–4.5 mg/dL). Her 24-hour urine calcium was 279 mg (normal range = 100–300 mg/24 h) and a 24-hour creatinine of 1060 mg.

Total thyroidectomy procedure was performed as case 1, in which ICG angiography was performed to locate the position of parathyroid glands (Fig. 6). Postoperative pathological result showed thyroid papillary carcinoma.

Intraoperative intact PTH level decreased from a pre-excision level of 120 pg/mL to 27 pg/mL, 10 min after excision. On POD 1, serum calcium was 9.9 mg/dL, PTH was 20 pg/mL, and phosphorus was 3.2 mg/dL. He was discharged home uneventfully on POD 1. At 2 week follow-up her calcium was 9.8 mg/dL, PTH was 43 pg/mL, and phosphorus was 3.2 mg/dL.

2. Discussion and conclusion

This report describes a potential utility of ICG fluorescence imaging in parathyroid surgery. In this report, we used a INTRAOPERATIVE NAVIGATION SYSTEM, with which ICG angiography was used to detect the fluorescence of the ICG injection.

Recently, there has been renewed interest in ICG. Traditionally, ICG has been subscribed to the belief that it is a kind of anionic, water-soluble tricarbo-cyanine molecule and when injected intravenously, ICG could rapidly bind plasma lipoproteins. And ICG would emit fluorescence when it was excited by a near-infrared (NIR) fluorescence with a wavelength of 800 nm [6]. One of the most important events of the 1956 was that ICG was first approved by the Food and Drug Administration for human use to study the hepatic and cardiac system [7]. Since then, ICG has been attracting a lot of interest. Some researchers in Japan applied the ICG angiography to the ophthalmic field [3]. At the same time, a considerable amount of literature has been published on ICG in the USA. These studies highlight the potential application of ICG angiography in clinical treatment of patients with occult choroidal neovascularization [8]. In the late 1980s, there has been an increasing interest in technological innovations, which enabled high-resolution digital imaging systems and cameras specifically designed for infrared photography utilizing ICG dye. The academic literature on ICG in 1990s has revealed the scope, nature and adverse effects related to ICG. Early examples of research into ICG included Reichel et al., concluding that ICG dye had an absorption peak of 805 nm, similar to the emission peak of the diode laser and NIR light (810 nm). In 1992, it was reported that Hope-Ross et al. performed over 1 million tests utilizing ICG for over 30 years and the conclusion is that ICG is extremely safe and well tolerated [9].

There is a growing body of literature that recognises the timing and dosing of ICG administration are of significant importance of for a successful surgical procedure. For cholecystectomy, colectomy and rectectomy, the suggested regimen is 4 mg which is given 15 min preoperatively. For lymphadenectomy, the recommended regimen is 5 mg which is given to patients 20 min preoperatively [3]. The existing body of research on ICG angiography utility in parathyroid identification suggests that injection of 3.75 to 8.75 mg during the operation procedure is effective in thyroid or parathyroid surgeries. In thyroid surgeries, injection should be given after thyroid glands being dissected and parathyroid being exposed. In 2 min, the parathyroid glands take up the dye and stay fluorescent up to 20 min.

Several systematic animal experiments of ICG have been undertaken by Suh et al. [10]. Historically, their research investigating the effects associated with ICG has focused on the utility of ICG as a fluorescent agent for identifying parathyroid during thyroid surgeries in dogs. Their evidence suggests that the intensity peak occurred at 50 s after injection. 50 s after injection, the parathyroid gradually lost its fluorescence, but could remain fluorescent and was able to be distinguished.

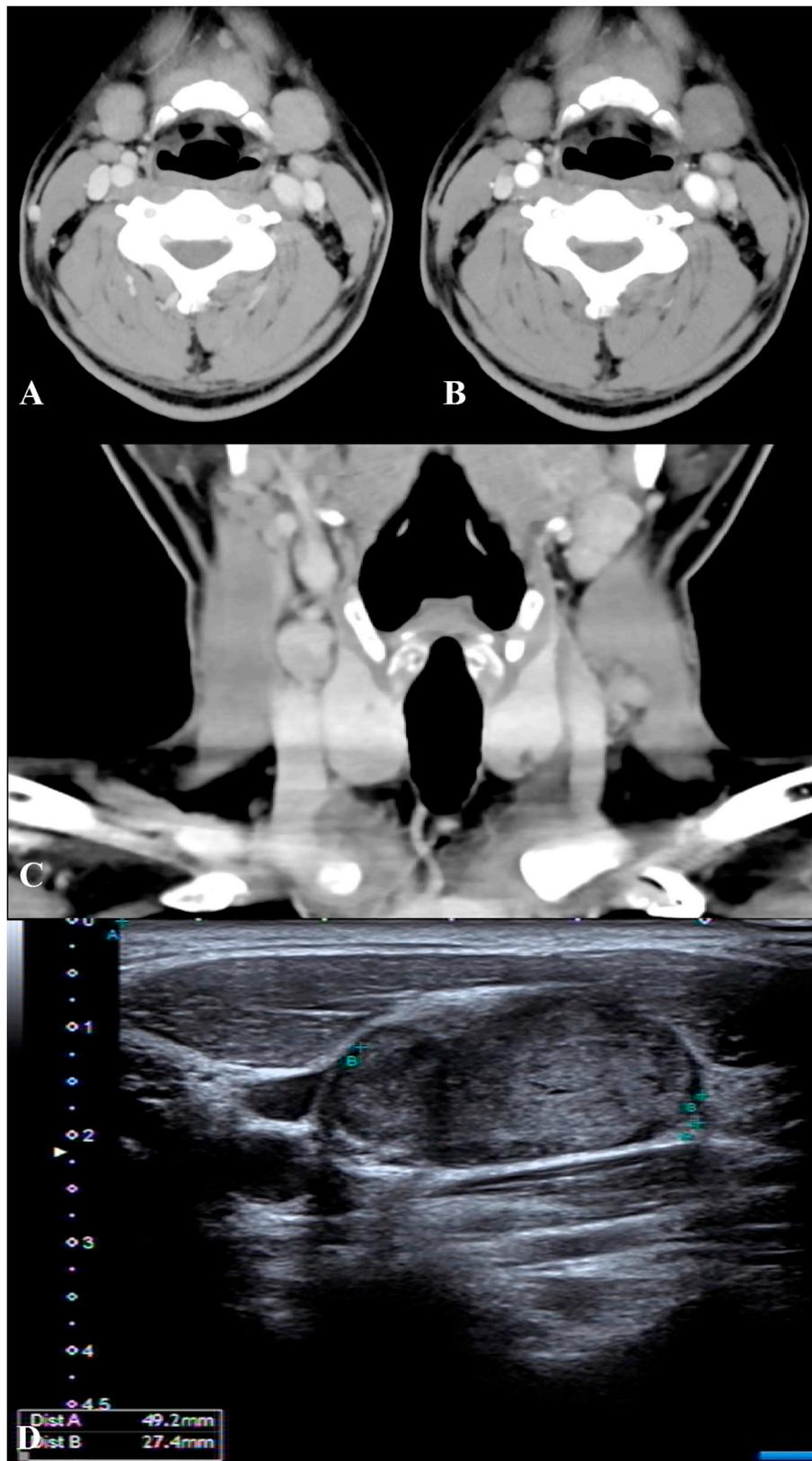


Fig. 3. Imaging features of case 2. A. CT image of thyroid; B. Enhancement CT image of thyroid; C. Coronal CT image of thyroid; D. Ultrasound image of thyroid.

ICG angiography plays a critical role in the maintenance of post-operative patients' calcium and parathyroidism. On the other hand, ICG angiography can play an important role in addressing the issue of preventing damage to the parathyroid intraoperation, to allowing surgeons protecting the parathyroid vascularization and eventually

preserving the parathyroid glands. Also, ICG angiography is the most potential method known as allowing each parathyroid gland being evaluated separately and the evaluation of parathyroid function at the same time. There is evidence that ICG angiography plays a crucial role in reimplanting the parathyroid glands. Moreover, ICG angiography has



Fig. 4. Image of parathyroid of case 2. Light white indicates parathyroid gland.

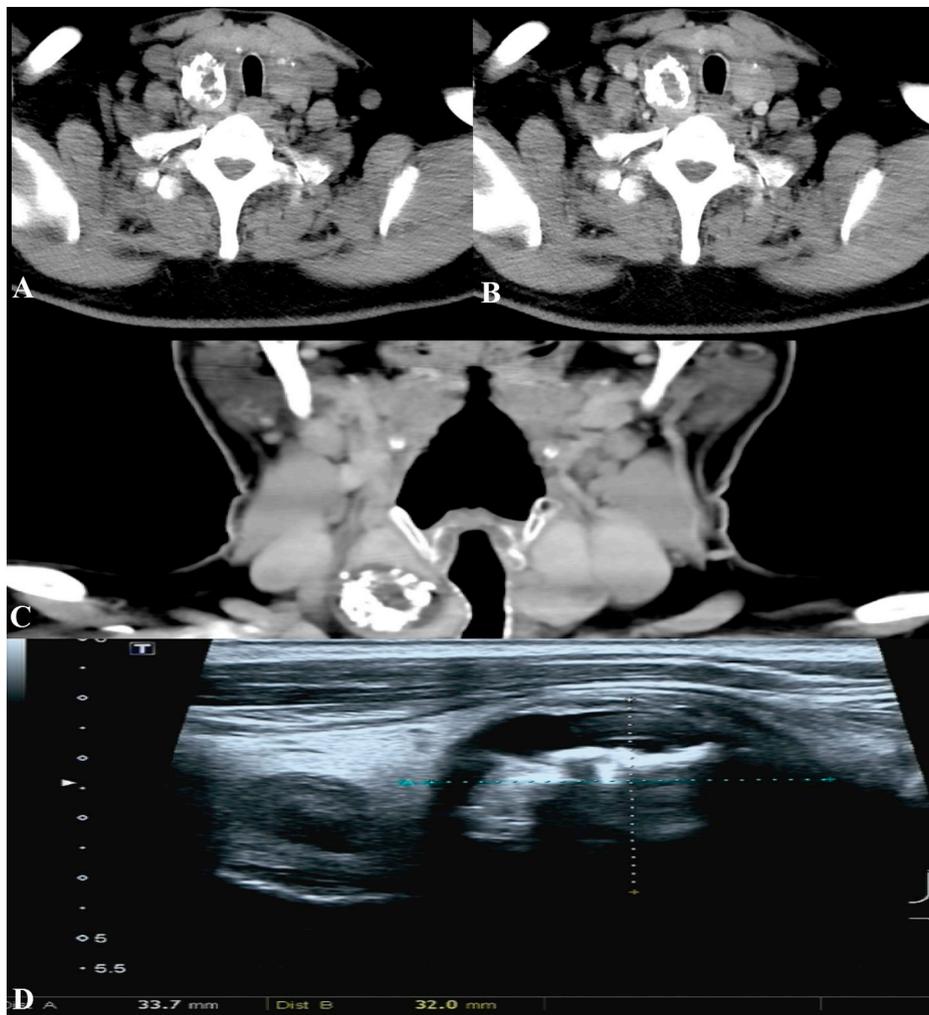


Fig. 5. Imaging features of case 3. A. CT image of thyroid; B. Enhancement CT image of thyroid; C. Coronal CT image of thyroid; D. Ultrasound image of thyroid.

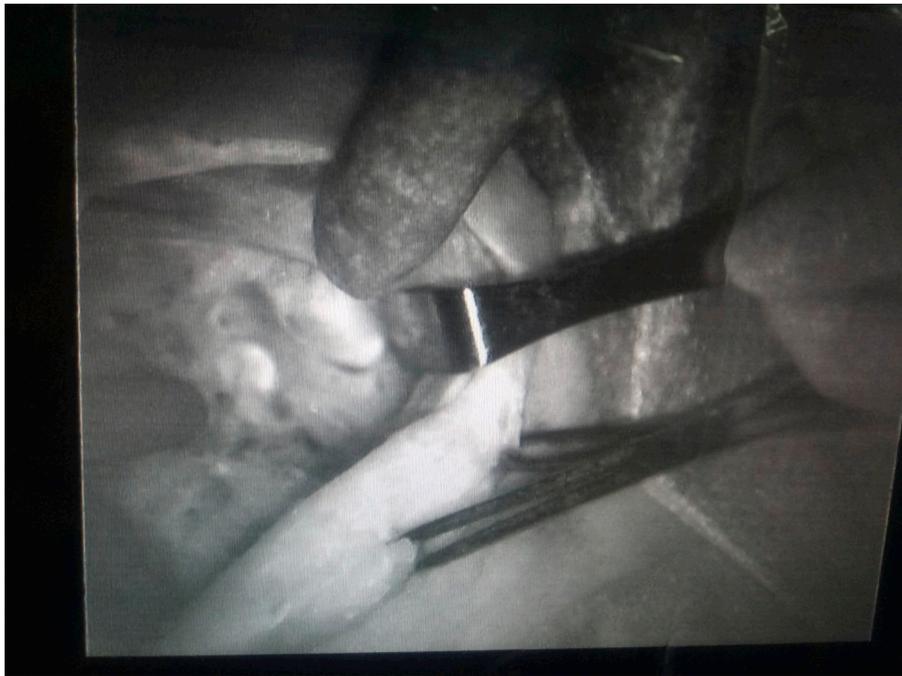


Fig. 6. Image of parathyroid of case 3. Light white indicates parathyroid gland.

considerable impact on the ambulatory surgery and ICG angiography has become a central issue for predicting and preventing post-thyroidectomy hypoparathyroidism. Evidence suggests that ICG is among the most important factors for guaranteeing function of the parathyroid, especially when ICG angiography has not identified a well vascularized parathyroid. And ICG angiography is often performed after one lobe of thyroid has been resected.

This study set out to identify a novel method for the parathyroid protection. In the three cases, parathyroid glands were all detected and protected. No hypoparathyroidism occurred in these patients. One of the more significant findings to emerge from this study is that ICG angiography equipment along with ICG dye provides a good method to detect parathyroid. Although this study focuses on parathyroid detection, the findings may well have a bearing on parathyroid protection and hyperparathyroidism therapy. The findings will be of interest to surgeons on thyroidectomy and parathyroidectomy. One source of weakness in this study which could have affected the study was the small sample size. Although the current study is based on a small sample of participants, the findings suggest that our technique is a safe, effective and easy way to detect the parathyroid glands. More information on ICG and the parathyroid would help us to establish a greater degree of accuracy on this matter. The findings of this study have a number of important implications for future practice.

Abbreviations

CT	Computerized tomography
US	Ultrasound
ICG	Indocyanine green
NIR	Near infrared ray
POD	Postoperative day
PTHq	Parathormone

Conflict of interest

The authors declare no conflict of interest.

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Availability of data and materials

All authors had full access to all the data in the study and Prof. Min Cui takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' contributions

Min Cui, Hao Jin, Kun Liao, Jinrui Fan, Zhuocheng He and Jun Yang undertook the surgical operation, critical revision of the manuscript for important intellectual content, technical support, drafted the manuscript and undertook the statistical support.

Consent for publication.

Consent for publication was obtained by the patient and his legal guardians (patient's spouse or parents in these cases).

Competing interests

The authors have no competing interests to declare.

CRediT authorship contribution statement

Hao Jin: Conceptualization, Data curation, Formal analysis, Funding acquisition, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jinrui Fan:** Investigation. **Jun Yang:** Resources. **Kun Liao:** Methodology. **Zhuocheng He:** Project administration. **Min Cui:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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