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HOW-I-DO-IT ARTICLES

Enhanced visualization of parathyroid glands during video-assisted neck surgery

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Abstract

Purpose Visualization and precise dissection of the parathyroid glands are a crucial step of thyroidectomy. Moreover, identification of parathyroid adenoma in patients with primary hyperparathyroidism can be challenging due to the possible abnormal location of the enlarged parathyroid. Near-infrared fluorescence (NIR) can be adopted during video-assisted neck surgery in addition to standard endoscopic magnification to enhance the visualization of the parathyroid tissue.

Methods Between July and August 2017, five patients (one male, four females) underwent video-assisted neck surgery at our hospital. One patient suffered from primary hyperparathyroidism. The four remaining patients underwent thyroidectomy for multinodular goiter or Graves' disease. The parathyroid glands were firstly identified by the video-assisted approach and then confirmed by the NIR visualization of the endogenous autofluorescence of the parathyroid tissue. Low-dose (2.5 mg/ml) indocyanine green was administered to visualize the vascular supply during and/or after the dissection. The standard dose of 2.5 mg (1 ml per injection) was used to allow repeated injection during the same procedure.

Results An endogenous parathyroid autofluorescence could be visualized by the NIR camera in all patients. The right upper parathyroid adenoma could be detected prior to fully dissection of the gland from the surrounding tissue. Twelve out of 16 parathyroid glands have been visually identified during four total thyroidectomies. Eleven glands showed an autofluorescence prior to indocyanine green (ICG) injection. Further, ICG injection has been used for guiding the dissection of the gland in three cases and for confirmation of the vascular supply at the end of the procedure in the remaining cases. There were neither intraoperative nor postoperative complications.

Conclusion The 5-mm 30° NIR camera allows for enhanced visualization of the parathyroid tissue during video-assisted thyroidectomy. This promising tool can become standard for video-assisted neck surgery.

Keywords Parathyroid · Video-assisted thyroidectomy · MIVAT · Indocyanine green · Near-infrared fluorescence

Introduction

Postoperative hypoparathyroidism is the most common complication of thyroid surgery. The incidence varies according to the definition that could follow clinical criteria (definition of symptomatic patients) or biochemical parameters (blood samples for calcium and/or intact parathormone). In general, the incidence of transient hypoparathyroidism is assumed to be around 20%, while the incidence of permanent hypoparathyroidism is about 1–2% [1]. Intraoperative identification and evaluation of the functionality of the parathyroid tissue during thyroid and parathyroid surgery are crucial to ameliorate the current results of endocrine neck surgery. Up to now, the intraoperative assessment of the parathyroid gland viability has been made by visual observation of the vascularization of the gland after dissection. Nevertheless, even experienced endocrine surgeons cannot always surely well define the vascularity of the dissected gland(s) and therefore avoid the occurrence of postoperative hypocalcemia. Intraoperative PTH measurement can be used to evaluate the function of the parathyroid glands but this method can only predict which patients will develop the complication during the postoperative course [2, 3].

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Video-assisted thyroidectomy (MIVAT) has been described in 1999 [4, 5]. Instead of the magnification of the parathyroid glands achieved by the endoscopic view, the incidence of postoperative hypoparathyroidism is not reduced after video-assisted surgery [6, 7]. Nevertheless, the video-assisted technique is, due to its excellent cosmetic results [8], meanwhile widely accepted and adopted as well for thyroid as for parathyroid surgery. Video-assisted parathyroidectomy (MIVAP) has been described prior to thyroidectomy as primary hyperparathyroidism represents the ideal indication for focused approach to the neck [9]. Even if the preoperative localization is supposed to be clear according to the preoperative imaging studies, the intraoperative search for the hyperfunctioning gland can be challenging. Our group demonstrated that the indications for the video-assisted approach can be extended also to cases with uncertain localization due to the possibility to perform a bilateral exploration by the MIVAP approach [10, 11], and therefore, this technique has become our standard for all patients, affected by primary hyperparathyroidism. Recently, near-infrared light (NIR) technology has been introduced in many fields of laparoscopic surgery and used in combination with intravenous injection of indocyanine green (ICG), an inert, water-soluble contrast agent that is bound to plasma proteins. ICG has different clinical uses ranging from the evaluation of the perfusion of skin flaps to hepatobiliary and colorectal surgery as well as different oncologic operations allowing for the identification of sentinel lymph node [12–14]. In the present study, we evaluate the feasibility and results of the NIR/ICG visualization of the parathyroid glands during video-assisted neck surgery.

Materials and methods

This was an IRB-approved prospective study conducted between July and August 2017. Five patients (one men, four women) underwent video-assisted neck surgery using a 5-mm 30° ICG endoscope and the Modular IMAGE1 S™ Camera Platform with OPAL™ technology for NIR/ICG imaging (Karl Storz Endoskope, Tuttlingen, Germany®). One patient suffered from primary hyperparathyroidism and underwent focused parathyroidectomy. Ultrasound and sesta-MIBI scintigraphy were performed prior to surgery and were positive and concordant showing a right enlarged parathyroid gland. The four remaining patients underwent total thyroidectomy for multinodular goiter or Graves' disease. The video-assisted procedure has been performed according to the original description by Miccoli [15] and modified in our setting as previously described [16]. Informed consent was obtained from all patients prior to surgery.

The parathyroid glands were visually identified by video-assisted approach, and subsequently, their identification was confirmed by near-infrared (wavelength 700–900 nm) light due the endogenous autofluorescence of the parathyroid tissue. In a second step, low-dose (2.5 mg/ml) indocyanine green was administered to visualize the vascular supply during and/or after the dissection of the parathyroid gland(s). Preservation of parathyroid gland was carried out by meticulous extracapsular dissection and individual ligation or bipolar coagulation of the terminal branches of the thyroid arteries. To allow repeated injection of indocyanine green during the same procedure, 1 ml per application was injected. Therefore, the standard dose of 2.5 mg was injected independently from the body weight in all patients. This dosage allowed us to perform at least three consecutive injections during the same procedure coupled by the visual evaluation of the parathyroid vascularization by means of NIR/ICG imaging. Complete blue staining of the surgical field has been observed after injection of 10 mg indocyanine green (four injections) or more per patient. The time interval between the injection and the visual identification of the gland(s) ranged from 30 to 70 s. One side (two parathyroids) has been evaluated for each injection. The data were prospectively collected including postoperative PTH and calcium levels. Postoperative hypoparathyroidism was defined by a serum calcium level < 2 mmol/l (normal range 2.1–2.5 mmol/l) and/or PTH levels below 10 pg/ml (normal range 10–65 pg/ml). Supplementation therapy with calcium and vitamin D was started in case of symptoms or by biochemical evidence of hypoparathyroidism.

Results

The endogenous parathyroid autofluorescence could be visualized by the NIR camera in all patients. The right upper parathyroid adenoma could be detected prior to full dissection of the gland from the surrounding tissue guiding the surgeon for further dissection (Fig. 1). Twelve out of 16 parathyroid glands have been visually identified during four total thyroidectomies. Eleven glands showed an autofluorescence prior to ICG injection (Fig. 2). In one case, autofluorescence could not be evocated, probably due to only partial exposure of the gland (covered by fatty tissue). Further, ICG injection has been used for guiding the dissection of the gland in three cases (Fig. 3) and for confirmation of the vascular supply at the end of the procedure in the remaining cases (Figs. 4 and 5). According to the finding of the intraoperative ICG angiography, one parathyroid gland has been auto-transplanted at the end of the operation. The intensity of the autofluorescence was not different between normal glands and the adenoma. The mean operating time was 62 min (range 50–80 min). There were no intra or postoperative complications, including allergic reaction to ICG. The patients were routinely discharged on the second postoperative day. Characteristic of the patients, extent of surgery, and postoperative PTH and calcium levels are shown in Table 1.

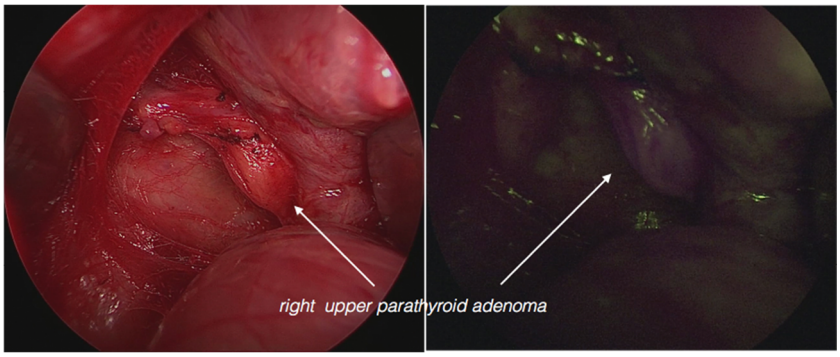

Fig. 1 Right upper parathyroid adenoma identified switching to the near-infrared filter due to endogenous parathyroid autofluorescence without ICG injection

Discussion

The present study demonstrates the combined use of NIR light and ICG angiography during video-assisted neck surgery for the first time. We registered neither intra- nor postoperative complications as well as complications related to ICG injection. The feasibility of NIR/ICG visualization of the parathyroid has been demonstrated; the use of low-dose ICG (2.5 mg/injection) allows for repeated evaluation of the perfusion instead of background fluorescence. According to this protocol, at least three consecutive injections were possible before staining of the surgical field has been observed. The small number of patients included may represent the main limitation of the present study and this observation needs to be confirmed in a larger cohort of patients. Moreover, the small volume of the thyroid selected in accordance to the inclusion criteria for video-assisted surgery (< 30 ml) could have facilitated the intraoperative visualization of the parathyroid glands (12 out 16 parathyroids) and cannot probably be generalizable to larger goiters.

Postoperative hypoparathyroidism is the most common complication of thyroid surgery [17]. The small dimension and variable location of the parathyroid glands as well as the difficulty to distinguish in some cases the parathyroids from thyroid tissue or lymph nodes are the logical explanation for this observation. Moreover, the vascular supply can easily be compromised during dissection of the thyroid lobe. The only reliable and objective method for intraoperative identification of the parathyroid gland is tissue biopsy. Nevertheless, this procedure can be itself reason for damage to the gland or the feeding vessels.

The first description of near-infrared (NIR) autofluorescence of the parathyroid tissue was performed in a pilot study on 21 patients undergoing endocrine surgery in 2011 [18]. The fluorescence intensity of the parathyroid gland was found to be consistently greater than that of the thyroid and all other tissues in the neck. In particular, parathyroid fluorescence was two to 11 times higher than that of the thyroid tissues with peak fluorescence occurring at 820 to 830 nm [18]. The identity of the fluorophore is not known. There are no reports of biological fluorophores with peak fluorescence around 800 nm. The hypothesis formulated by McWade and coworkers is that the NIR autofluorescence in the parathyroid is caused by the calcium-sensing receptor (CaSR) [19]. CaSRs are involved in controlling synthesis and secretion of PTH and calcitonin. The greatest levels of CaSR expression are found in parathyroid cells, and smaller concentrations are found in the C-cells of the thyroid but nowhere else in the muscle, fat, or lymph of the neck region. This provides a fluorophore that is present in high concentrations in parathyroid tissue and low concentrations in thyroid tissue making CaSR a highly probable candidate for the observed fluorescence.

This and other methods of NIR visualization of the parathyroids cannot be performed during endoscopic surgery and are reserved for conventional surgery [20]. The implementation of the conventional endoscopic white light source with the near-infrared light and the possibility to switch between to

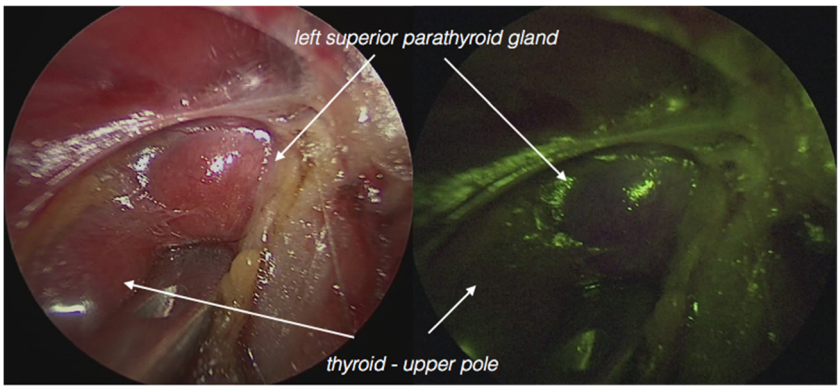

Fig. 2 Identification of the left upper parathyroid gland by near-infrared autofluorescence

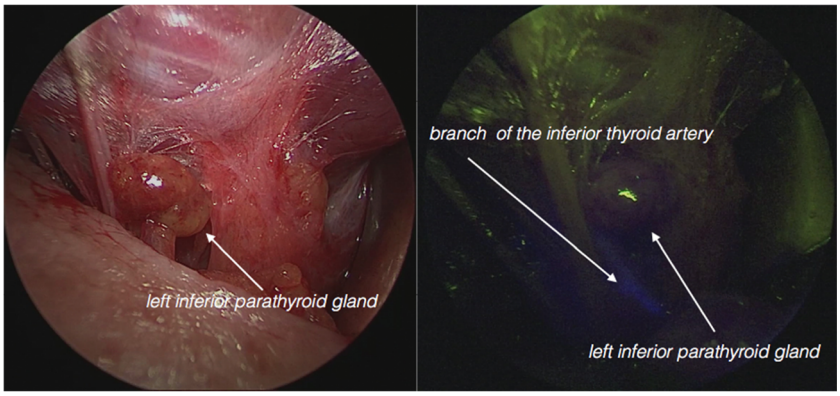

Fig. 3 The ICG injection allows for identification and preservation of the vascular supply of the parathyroid gland guiding further dissection of the gland

the two options is the essential step to make this technology useful for minimally invasive surgery. The results of a preliminary study using the NIR/ICG endoscopic system for intraoperative parathyroid visualization was performed by Ladurner and coworkers [21]. The authors noticed a considerable interference of light in the blue channel overlying the autofluorescence and therefore modified the light source by interposing additional filters. According to this modification, 27 out 35 parathyroids from 25 patients were correctly identified. Intravenous application of a contrast agent has not been performed. Nevertheless, it could improve the visualization of the parathyroid glands.

The first use of a contrast agent-guided parathyroidectomy was published in 1971 [22]. Methylene blue (MB) was administered at a calculated dose of 5 mg/kg body weight in 500 ml of 5% glucose and 1/5 normal saline. In this first experience, intravenous administration of methylene blue resulted in staining of both normal and abnormal parathyroid glands. Sixty-eight parathyroids were looked for and 41 found and confirmed by histology. The administration of high-dose MB can be associated with serious adverse events such as toxic metabolic encephalopathy and can lead to blue staining of the complete surgical field due to leakage of dye into the tissue when the operation takes a long time [23]. Alternatively, other fluorescence-inducing substances can be adopted. In 2006, the first description of a minimally invasive videoscopically assisted parathyroidectomy after photosensitization with aminolevulinic acid has been published [24]. Under special fluorescence illumination by the D-light, the parathyroid could be identified and successfully resected. The problem of this substance is that the patient has to avoid direct light exposure for 48 h because of possible photobleaching and phototoxic reactions. This feature makes this agent not suitable for the clinical practice. Low-dose methylene blue in combination with NIR fluorescence imaging obtained by the Mini-FLARE imaging system has been recently described in surgery for primary hyperparathyroidism [23]. The authors reported the results of parathyroidectomy in 13 patients and conclude that in patients in whom difficult identification of the parathyroid adenoma is expected or when normal glands have to be identified, the administration of methylene blue may improve surgical outcome, as in 10 of 12 patients with a histologically proven adenoma, the adenoma was fluorescent during surgery.

Indocyanine green seems to be the most suitable agent for intraoperative angiography. This agent has been used with promising results in thyroid [25] and parathyroid surgery [26]. In a recent study, Vidal Fortuny et al. described the results of intraoperative ICG in 36 patients undergoing total thyroidectomy [27]. At least one well-

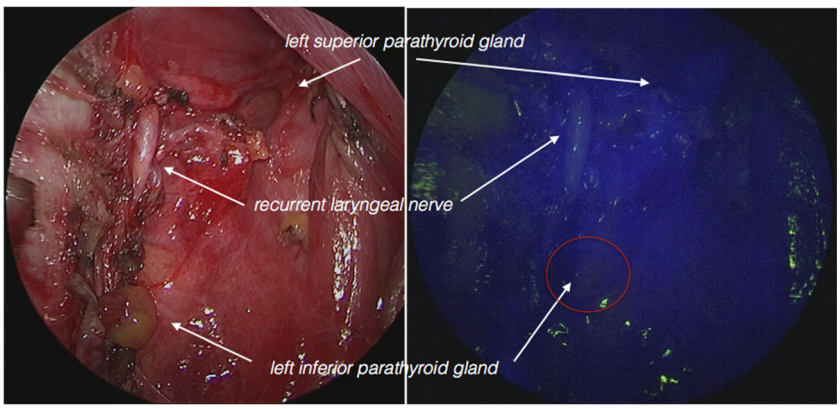

Fig. 4 Final view on the recurrent laryngeal nerve and both apparently well-vascularized parathyroid glands after left lobectomy. The ICG injection revealed a well-vascularized left upper parathyroid and a non-vascularized left inferior gland (red circle)

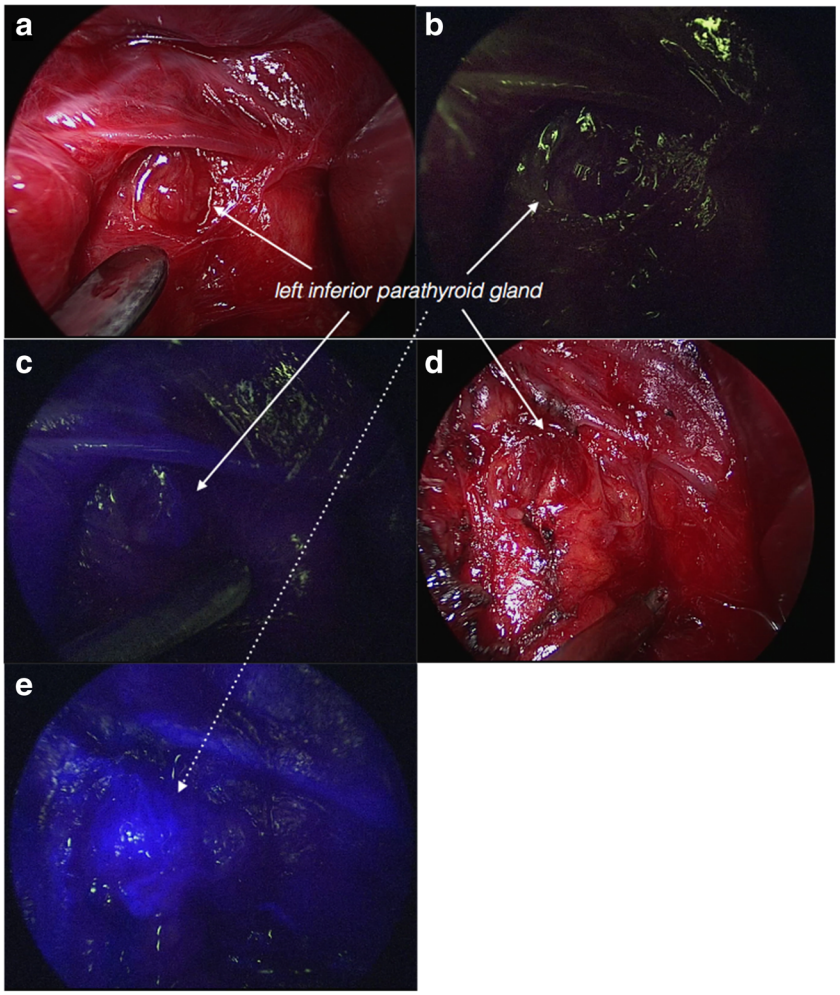

Fig. 5 The combination of NIR view and ICG injection enhances the visualization of the parathyroid glands. In this sequence, the parathyroid is first visualized by white light (**a**); the autofluorescence of the parathyroid tissue is confirmed by NIR light (**b**); ICG is injected prior to dissection with the intent to identify the vascular supply of the gland (**c**); the dissection has been completed (**d**) and the repeated ICG injection allows for confirmation of an excellent perfusion of the gland (**e**)

vascularized parathyroid gland was demonstrated by ICG angiography in 30 patients and none of them had parathyroid hormone levels below the normal range on postoperative days 1 and 10. Only one patient exhibited asymptomatic hypocalcaemia on the first postoperative day, although all patients received standard calcium and vitamin D supplementation, postoperatively. In this study, the ICG angiography was used only as a tool for predicting the postoperative hypocalcemia.

The NIR visualization of the parathyroid by endogenous autofluorescence implemented by the ICG-guided evaluation of the perfusion, as performed in the present study, could represent the best possible combination to reduce the rate of postoperative hypoparathyroidism. The present study describes this technique during video-assisted neck surgery for the first time. The magnified visualization of the parathyroid gland by means of the endoscope has been implemented by the autofluorescence of the parathyroid tissue and the

Table 1 Characteristics of the patients and postoperative outcome

Patient	Age/sex	Diagnosis	Video-assisted operation	Postoperative calcium (mmol/l)	Postoperative PTH (pg/ml)	Symptoms
N.1	77/male	Primary hyperparathyroidism	Parathyroidectomy	–	29 pg/ml	No
N.2	45/female	Multinodular goiter	Total thyroidectomy	2.4	34	No
N.3	50/female	Multinodular goiter, hypercalcitoninemia	Total thyroidectomy	2.3	10	No
N.4	52/female	Multinodular goiter	Total thyroidectomy	2.2	25	No
N.5	57/female	Graves' disease, hyperthyroidism refractory to medical therapy	Total thyroidectomy	2.1	13	No

Calcium normal range 2.1–2.5 mmol/l; PTH normal range 10–65 pg/ml

functional evaluation of the perfusion after ICG injection. Moreover, ICG angiography has been used for guiding the dissection and allows for a safe preservation of the vessels feeding the parathyroid tissue. Promising results of intraoperative ICG have been recently published for the bilateral axillo-breast approach (BABA) robotic thyroidectomy [28]. In a case-control study on 22 patients scheduled to undergo BABA robotic thyroidectomy for papillary thyroid carcinoma, the authors demonstrate a significantly lower rate of incidental parathyroidectomy in the ICG group than the control group (0 vs. 15.9%, $P = 0.048$). The ICG and control groups had similar rates of transient hypoparathyroidism (36.4 vs. 40%, $P = 0.842$) and permanent hypoparathyroidism (9.1 vs. 5%, $P = 0.657$). The last observation highlights the main limitation of the NIR technology. In fact, there is at the moment no objective model to quantify the intensity of the fluorescence and evaluation by surgeon's eyes represents only a subjective method for the visualization of the parathyroid viability after ICG injection. The laser speckle contrast imaging (LSCI) technique for real-time assessment of parathyroid viability has been recently described with the intent to overcome this limitation [29]. Taking an experienced surgeon's visual assessment as the gold standard, LSCI has been used to distinguish between well-vascularized ($n = 32$) and compromised ($n = 27$) parathyroid glands during thyroid surgery with an accuracy of 91.5%. Results showed that this technique could be promising for detecting parathyroid gland devascularization before it is visually apparent to the surgeon.

We report the first experience of combining NIR/ICG fluorescent imaging of the parathyroid glands during video-assisted neck surgery. Besides the excellent cosmetic results, this can become another advantage of the video-assisted and in general of endoscopic neck surgery. Although the ability of the NIR/ICG to reduce the rate of postoperative hypoparathyroidism when compared with the simple visualization has not been yet demonstrated, this technology seems in our opinion to be promising and needs certainly further evaluation in a larger cohort of patients.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Disclosure Karl Storz GmbH & Co. KG provided an endoscopic NIR/ICG system free of charge for performing the present study.

Conflict of interest The authors declare that they have no conflict of interest.

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