MODERN METHODS OF INTRAOPERATIVE FLUORESCENT IMAGING OF THE PARATHYROID GLANDS IN ENDOCRINE SURGERY: A LITERARY REVIEW

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Abstract

Hyperparathyroidism (primary, secondary and tertiary) is a common endocrine disease, often occurring with pronounced symptoms, in most cases caused by adenoma (rarely several adenomas) in primary hyperparathyroidism (pHPT) and chronic renal failure in patients on programmed hemodialysis with secondary (sHPT) and tertiary (tHPT) hyperparathyroidism. To date, the only radical treatment for hyperparathyroidism (HPT) is surgical removal of pathologically altered parathyroid glands. In this regard, there is a need to improve diagnostic search algorithms, including intraoperative ones, for altered parathyroid glands. The main objective of the review is to study current trends and techniques of intraoperative imaging of the parathyroid glands, compare these methods and evaluate their effectiveness. The use of qualitatively new technologies for the topical diagnosis of altered parathyroid glands, such as identification by autofluorescence in the near infrared spectrum (NIRAF), the technique of using indocyanine green (ICG) and 5-aminolevulinic acid under UV radiation, make it possible to visualize the localization of the parathyroid glands with more than 90% accuracy. However, the issue of their priority use remains open and unresolved.

Key words: primary, secondary, tertiary hyperparathyroidism, parathyroid gland, imaging, surgical treatment, ICG, NIRAF, 5-ALA.

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МЕТОДЫ ИНТРАОПЕРАЦИОННОЙ ФЛУОРЕСЦЕНТНОЙ ТОПИЧЕСКОЙ ДИАГНОСТИКИ ПАРАЩИТОВИДНЫХ ЖЕЛЕЗ: ЛИТЕРАТУРНЫЙ ОБЗОР

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Резюме

Гиперпаратиреоз (первичный, вторичный и третичный) – распространенное эндокринное заболевание, часто протекающее с выраженной симптоматикой, в большинстве случаев обусловленное аденомой (реже несколькими аденомами) при первичном гиперпаратиреозе (пГПТ) и хронической почечной недостаточностью у пациентов на программном гемодиализе при вторичном (вГПТ) и третичном (тГПТ) гиперпаратиреозе. На сегодняшний день единственный радикальный метод лечения гиперпаратиреоза (ГПТ) – хирургическое удаление патологически измененных паращитовидных желез. В этой связи возникает необходимость совершенствования алгоритмов диагностического поиска, в том числе интраоперационного, измененых паращитовидных желез. Основная задача обзора – изучить современные тенденции и методики интраоперационной визуализации паращитовидных желез, сравнить данные способы и оценить их эффективность. Применение качественно новых технологий топической диагностики измененных паращитовидных желез, таких как идентификация путем аутофлюоресценции в близком инфракрасном спектре (NIRAF), методика использования индоцианин-зеленого (ICG) и 5-аминолевулиновой кислоты при УФ-излучении позволяют с более чем 90% точностью визуализировать локализацию паращитовидных желез. Однако вопрос их приоритетного использования остается открытым и не решенным.

Ключевые слова: первичный, вторичный и третичный гиперпаратиреоз, паращитовидная железа, визуализация, хирургическое лечение, ICG, NIRAF, 5-АЛК.

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Introduction

Today, primary hyperparathyroidism (pHPT) after diabetes mellitus and thyroid diseases is the third most common disease of the endocrine organs, which occurs in 1% of the world's population [15]. Chronic kidney disease in the terminal stage is the cause of secondary hyperparathyroidism (sHPT) and tertiary hyperparathyroidism (tHPT), which is associated with a violation of phosphorus-calcium metabolism, altered metabolism of cholecalciferol due to a violation of its hydroxylation in the affected kidneys [1]. In this case, the secretion of parathyroid hormone (PTH) becomes independent of the concentration of calcium and phosphate ions. Together, this leads first to sHPT, and then to tHPT, which is expressed morphologically in the formation of autonomous hyperfunctioning adenomas of the parathyroid glands (PTG). Drug therapy of HPT in the form of taking drugs that suppress the synthesis of PTH from the cinocalcet group is quite effective in the early stages of sHPT, but has a number of significant drawbacks: 1) high cost; 2) the effectiveness does not extend to pHPT, tHPT and long-term persistent sHPT. Thus, surgical treatment remains the only effective treatment option for the latter category of patients [1].

Despite the fact that PTG surgery has been developing since the mid-20th century, generally accepted indications for parathyroidectomy are accepted only for pHPT; a unified and standardized surgical method, volume, and timing of the intervention for sHPT and tHPT have not yet been developed [1, 2, 3]. The most commonly used approaches are subtotal parathyroidectomy and total parathyroidectomy with autotransplantation. Thus, the analysis conducted by Triponez et al. proves a confident decrease in PTH levels in the postoperative period in patients with total parathyroidectomy, in contrast to patients who underwent subtotal resection [2]. Rothmund et al. also found a low rate of hyperparathyroidism recurrence in patients who underwent total parathyroidectomy with autotransplantation [3]. It is worth noting that autotransplanted PTG tissue will not function fully until it undergoes neovascularization, so transient hypoparathyroidism is more common and pronounced after such radical operations than after subtotal parathyroidectomy. Autotransplantation of PTG can also fail and lead to long-term hypoparathyroidism [4].

For adequate parathyroidectomy, a clear understanding of the PTG localization is necessary. Preoperative PTG visualization techniques such as ultrasound and PTG scintigraphy have not lost their importance to this day. Overweight patients, recurrent HPT, multiple lesions, atypical parathyroid gland location can reduce the accuracy of these methods. All these disadvantages are inherent in intraoperative ultrasound and gamma detection [5,6]. In this review, we discuss in detail the issues of intraoperative fluorescence navigation of the PTG when all available preoperative diagnostic methods have been exhausted.

One of the first methods of visual navigation of the PTG was the intravenous administration of a methylene blue solution in the preoperative period with the development of blue staining of the PTG [7]. However, according to a number of authors, methylene blue stains less than half of all PTG [8], and in some cases can lead to the development of acute neurological disorders [9,10]. Today, this technique is not used due to the above-mentioned shortcomings.

The use of indocyanine green (ICG) as a fluorescent dye has attracted the attention of surgeons due to its ability to improve the visualization of anatomical structures. ICG was first synthesized in 1955 and was initially used in ophthalmology to assess vascular perfusion. One of the first significant studies devoted to the use of ICG in PTG surgery was a study conducted in 2016 by Fortuny et al. [11]. Richard et al. showed that the use of ICG significantly increases the accuracy of PTG identification compared to traditional visualization methods and reaches, according to the authors, 94%. This is especially important in cases where the anatomical position of the glands may vary [12]. Raffaelli et al. found that the use of ICG in parathyroidectomy reduces the number of complications (persistent hypoparathyroidism up to 9%, persistence of HPT up to 5%) [13]. However, this method also has its drawbacks in use: 1) the need for appropriate fluorescence imaging systems, which are not available in most medical institutions; 2) reduced efficiency of ICG imaging in cicatricial and tumorous changes in the anatomic location of the PTG; 3) the need for expensive training of medical staffl in the ICG imaging technique. The most important advantage of ICG over other techniques is the ability to determine the preservation of PTG vascularization with 99% sensitivity. This helps to determine which glands are functioning normally, which is important for improving calcium control after surgery [14, 15, 16, 17, 18, 19]. Fortuny et al. demonstrated that ICG angiography can reliably predict PTG vascularization and eliminate the possibility of persistent hypoparathyroidism. Using this technique in 13 patients with HPT, it was possible to visualize all 4 PTGs in all cases. A correlation was obtained between perfusion of the parathyroid remnant and its function in the postoperative period [20].

In 2012, Chissov V.I. et al. proposed a method for intraoperative identification of parathyroid gland using derivatives of 5-aminolevulinic acid (5-ALA) (Patent of the Russian Federation No. 2458689 Chissov V.I. et al., 2012). The method is based on the 5-ALA oral administrastion in the preoperative period at a dose of 30 mg/kg of body weight and a surgery performed 120-180 minutes after administration with irradiation of the surgical field with polarized blue light [21]. According to the results of the study by Dolidze et al., conducted as part of a study of the pre-, intra- and postoperative period of surgical treatment with intraoperative visualization in patients with PTG adenomas, it was proven that visualization of the PTG was achieved in 94% of patients. Normalization of ionized calcium levels was also noted within 6 months in 100% of patients, a decrease in PTH levels by more than 50%, and due to clear visualization of the PTG, no recurrent nerve injury was recorded in any of the cases. According to the authors, this approach significantly improves the results of surgical treatment of solitary PTG adenoma in patients with pHPT [22].

In 2020, Zinchenko S.V. et al. described a technique similar to the technique described by Chissov V.I. et al. (Patent of the Russian Federation No. 2019142608). The authors reported that high doses of the drug (10 mg/kg body weight of 5-ALA when administered orally) are not required for adequate parathyroidectomy in patients with sHPT and tHPT, since the excretion of 5-ALA is significantly slowed down in dialysis patients [23]. The promise of this visualization method is undeniable and many studies confirm this thesis. Kalashnikov A.A. et al. conducted a study in which they compared the technique of using 5-ALA in patients with parathyroid adenomas, 95% of which were visualized [24]. Vshivtsev D.O. et al. in their study of intraoperative visualization of the PTG using 5-ALA demonstrated that the fluorescence intensity of altered and hyperfunctioning glands was subjectively higher than that of unchanged glands. In all patients in the sample, the PTH level decreased to normal values within 24 hours after surgery. However, the authors of the study noted the development of a phototoxic reaction was detected in 2 patients with oral administration of 5-ALA at a rate of 30 mg/kg body weight [25].

The most “young” method of PTG visualization is near infrared autofluorescence (NIRAF). In 2011, Paras et al. presented a new technique for PTG detection in the near infrared range. The study demonstrated that the fluorescence intensity of PTG is higher than that of thyroid tissue [26]. In 2014, MacWade et al. presented the possibility of PTG visualization in the near infrared range using a modified Karl Storz camera [27]. Subsequently, a number of studies confirmed these findings that near infrared fluorescence can help in detecting PTG tissue during thyroid surgery. Early studies using near-infrared fluorescence imaging allowed surgeons to scan the surgical field for parathyroid tissue using a camera with a 25 cm field of view, but this requires turning off the operating room lights due to interference between ambient light and the light emitted by the intrinsic fluorophores of the PTG [28,29]. Despite the interest of surgeons in developing the technique, research studies are limited by small patient samples. Rossi et al. conducted a study on the use of NIRAF in parathyroidectomy in 11 patients with primary hyperparathyroidism. Histopathologic examination of 15 resected specimens confirmed 14 PTG adenomas and one schwannoma. All adenomas had a heterogeneous NIRAF pattern, distinct from the homogeneous pattern seen in the schwannoma. A bright "cap" was detected in 9 of 14 (64.3%) PTG adenomas, which proves the high efficiency of the method [30]. A large monocentric prospective study by Akgun et al., which examined NIRAF images in 1506 normal and 597 altered PTG, indicates that there are differences between the luminescence intensity of normal and hyperplastic PTG glands [31]. Despite the high sensitivity and accuracy (92-99%) declared by the authors, cases of negative use of the method have been described. Thus, small adenomas can be verified by the surgeon as normally functioning PTGs. Lee et al. in their study examined NIRAF data in patients with a history of parathyroidectomy. From 2017 to 2021, 151 parathyroidenomas were removed from 131 patients with pHPT. The mean intensity of PTG autofluorescence in the near infrared range had a negative correlation with the weight of patients and a positive correlation with age (glands in elderly patients fluoresced more strongly). However, no correlations were found with the level of calcium in the blood before surgery, PTH, BMI, or gender [32].

Таблица 1.
Сравнение методик интраоперационной визуализации паращитовидных желез
Table 1.
Comparison of intraoperative imaging techniques for parathyroid glands

Методика Methodo-logy	Преимущества Advantages	Недостатки Disadvantages	Чувстви-тельность Sensitivity	Специ-фичность Specificity	Точность Accuracy
Метиленовый синий [7,8,9,10] Methylene blue [7,8,9,10]	Достаточно четкая визуализация. Sufficiently clear visualization.	Может приводить к развитию острых невро-логических нарушений после операции. Can lead to the development of acute neurological disorders after surgery.	Чувстви-тельность 46% Sensitivity 46%	–	–
ICG [11-20] ICG [11-20]	Улучшенная идентификация анатомических структур. Снижение риска после-операционных осложнений. Интраоперационная оценка васкуляризации. Минимизация инвазивности и сокращение времени операции. Improved identification of anatomical structures. Reduced risk of postoperative complications. Intraoperative assessment of vascularization. Minimization of invasiveness and reduction of surgical time.	Возможен риск воз-никновения аллергической реакции у пациентов с аллергией на йод. Для проведения методики требуется специальное оборудование. Возможно ограничение визуализации при наличии анатомических особенностей. Possible risk of allergic reaction in patients with iodine allergy. Special equipment is required to perform the technique. Visualization may be limited in the presence of anatomical features.	85%–100%	90%–100%	93%–98%
5-АЛК [21-25] 5-ALA [21-25]	Высокий уровень интра-операционной визуализации. Визуализация гипер-плазированных ПЩЖ выше, чем у нормальных. Относительно низкий процент осложнений, минимизация инвазивности, оптимизация времени операции. High level of intraoperative visualization. Visualization of hyperplastic PTG is higher than that of normal ones. Relatively low percentage of complications, minimization of invasiveness, optimization of surgical time	Ограниченная доступность Наличие возможного осложнения в виде фотодерматозов Требует особых условий проведения, учета времени введения препарата Limited availability Presence of a possible complication in the form of photodermatoses Requires special conditions for implementation, taking into account the time of drug administration	85%–95%	90%–98%	88%–95%
NIRAF [26-32] NIRAF [26-32]	Для визуализации ПЩЖ не нужен контраст. Сравнительно большая глубина проникновения спектра. Визуа-лизация не зависит от патологического статуса. Отсутствие побочных эффектов. No contrast needed for PTG imaging. Relatively large spectrum penetration depth. Visualization is independent of pathological status. No side effects.	Ограничивает оценку перфузии ПЩЖ. Требуются особые условия освещения во время операции. Высокие экономические затраты, несовершенное оборудование. Limits PTG perfusion assessment. Requires special lighting conditions during surgery. High economic costs, imperfect equipment.	85%	80%–90%	90%–95%

The resulting data on the comparison of existing methods of intraoperative visualization of the PTG are presented in Table 1.

Conclusion

The main method of treating HPT (primary, secondary and tertiary) remains surgical. Even for an experienced surgeon, visualization of the PTG and their complete removal is often an impossible task. Despite the large number of scientific papers on the topic of intraoperative navigation of the PTG, the cheapest and most effective method of fluorescent visualization of the PTG are techniques using 5-ALA. They do not require the purchase of expensive equipment and fluorescent agents, and are associated with low rates of side effects and complications. Further research on this issue is necessary in order to minimize side effects and improve the effectiveness and safety of surgical treatment of pHPT, sHPT and tHPT

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