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Review

Intraoperative Adjunct Methods for Localization in Primary Hyperparathyroidism

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Abstract

Primary hyperparathyroidism (pHPT) is a frequently seen endocrine disease, and its main treatment is surgery. In the majority of pHPT, the disease involves only a single gland, and the majority of the pathological glands can be determined by preoperative localization methods.In addition to preoperative localization studies in parathyroidectomy, the use of adjunct methods to improve intraoperative localization in order to increase success of surgery is becoming widespread. These methods include different approaches, mainly intraoperative parathyroid hormone (PTH) measurement, followed by intraoperative gamma probe application, intraoperative ultrasonography, parathyroid imaging with methylene blue, and frozen section examination. Recently, especially promising new imaging methods have been described in the literature with various optical technologies to increase the localization of the parathyroid glands and to evaluate their viability. These methods include parathyroid imaging with autofluorescence, indocyanine green imaging with autofluorescence, autofluorescence imaging with methylene blue, autofluorescence imaging with 5-aminolevulinic acid, optical coherence tomography, laser speckle contrast imaging, dynamic optical contrast imaging, and Raman spectroscopy. Currently, minimally invasive parathyroidectomy has become the standard treatment for selected pHPT patients with the aid of preoperative imaging and intraoperative auxiliary methods . The aim of the present study was to evaluate the routinely used new promising intraoperative adjunct methods in pHPT.

Keywords: Intraoperative adjunct methods; minimally invasive parathyroidectomy; multigland disease; primary hyperparathyroidism; parathyroid adenoma.

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The curative treatment of primary hyperparathyroidism (pHPT) is surgery. The causative agent of the disease in pHPT is parathyroid adenomas originating from a single gland in 80–85% of the cases. After the third quarter of the last century, preoperative imaging methods have been rapidly developed, most of the pathological glands could be determined. In addition, intraoperative gamma probe application, ultrasonography (USG), methylene blue, and/or frozen section examination are being used to increase the success in parathyroidectomy. Recently, promising studies regarding different parathyroid imaging modalities with optical technologies to identify the intraoperative parathyroid glands have been noteworthy. Currently, bilateral neck exploration (BNE) is the gold standard in the surgical treatment of pHPT.[1]

However, with the contribution of imaging modalities and especially intraoperative parathyroid hormone (PTH) mea-

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surement, surgical treatment has shifted from BNE to minimally invasive parathyroidectomy (MIP). MIP has become the gold standard treatment for seleced patients with pHPT who have positive preoperative imaging findings.[1]

Intraoperative Measurement of PTH

Nussbaum et al.[2] described the intraoperative PTH measurements to demonstrate the suitability of resection after the removal of the hyperfunctioning parathyroid gland.[2] In 1991, Irvin et al.[3] reported rapid intraoperative PTH assay.

PHPT is mostly (80–85%) related to a single gland disease. Intraoperative PTH monitorization is based on the intraoperative measurement of PTH with a half-life of 3–5 minutes at certain intervals so as to verify biochemical cure in parathyroidectomy and to demonstrate decreases in PTH. More than 90% of high-volume parathyroid surgeons in the US are using intraoperative PTH monitoring as a guide to determine the extent of parathyroidectomy.[4] A chemiluminescence method has been developed for rapid intraoperative PTH assay, and a kit of this method is available in the market.[5] This method can yield results within approximately 10 minutes in the operating room.[6] However, this method is more expensive than other PTH assays performed in the central laboratory and cannot be performed in many centers.[7]

PTH measurements in blood samples collected during surgery can be performed in the central laboratory as an alternative method for portable rapid PTH assays realized in the operating room. The sensitivity, specificity, and suitability of this method are similar to those detected for rapid PTH assays.[8] The most important disadvantage of this method is that it has a turnaround time of 25–30 minutes compared with rapid PTH assay.[6, 8] The turnaround time of this method is almost equal to intraoperative histopathological analysis that may last for 25–35 min. It can eliminate the need for histopathological examination performed within the same period.[8] As a result, rapid PTH assay cannot be performed in many centers, and rapid PTH analysis in the central laboratory is used as an intraoperative PTH measurement.

The main surgical indications of intraoperative PTH monitorization include the following:

- verification of removal of all hyperfunctioning parathyroid glands without seeing normally functioning glands,
- demonstration of inadequate reduction in PTH and additional hyperfunctioning parathyroid gland,
- determination of the need for additional exploration for surgical success,
- distinguish parathyroid tissue from other tissues,
- bilateral jugular vein sampling and lateralization of the hyperfunctioned gland.[9]

Blood samples are obtained from the patient at certain times to evaluate PTH changes depending on the half-life of PTH. Blood samples can be collected from the peripheral veins by an anesthetist or from the internal jugular vein in the surgical field by a surgical team.[10]

Immediately before anesthesia induction for baseline value, blood samples are collected for PTH measurement at the time of skin incision. Blood samples are obtained at different times, such as 5, 10, 15, and 20 min, after the removal of the pathological parathyroid gland, and PTH levels are measured.[9]

Approximately 20–30% of the patients may experience sudden PTH increases due to intraoperative manipulations. If PTH is not measured at the time of excision, these sudden peaks may be overlooked, and unnecessary bilateral exploration may be made considering that there is not enough decrease in PTH (false-negative result) relative to the baseline value obtained at the first measurement of PTH.[11, 12]

The Miami, Halle, Rome, Vienna, and Charleston criteria were defined according to the data of the centers to be able to predict the success of treatment in intraoperative PTH monitoring.[9] Among these, the Miami criteria are the most commonly used. First, in 1993, >50% decrease at the 10th minute after the excision of the suspected gland compared with the preoperative PTH values was defined as the best value in predicting postoperative normocalcemia.[13] Then, these criteria were revised as >50% decrease at the 10th minute value after the excision of the suspected gland relative to the highest preoperative or preexcisional PTH value.[14]

In the literature, 97%–98% accuracy rates have been reported for predicting postoperative normal or low calcium values according to the Miami criteria.[9]

Barczynski et al.[15] retrospectively evaluated the data of 260 patients for whom they performed preoperative USG and sestamibi scan consistent with sporadic pHPT and MIP. They also evaluated the Halle, Miami, Rome, and Vienna criteria, and they determined the indicated rates of compatibility with the Miami (97.3%), Vienna (92.3%), Rome (83.8%), and Halle (65%) criteria. They found that the Rome and Halle criteria were better in determining multigland disease (MGD). Since their negative predictive values are low (Rome: 26.3% and Halle: 14.2%), they can only marginally contribute to the success of the primary operation, leading to a high number of unnecessary negative BNEs when these criteria are applied to patients undergoing preoperative imaging modalities. Routine intraoperative PTH use increases the cure rate in MIP.[16, 17]

It is thought that intraoperative PTH does not have any additional contribution in patients who underwent MIP based on the results of USG and scintigraphy.[18] In the review evaluating 17 studies that included 4280 image-positive patients, it was indicated that intraoperative PTH measurements increased the success rate of MIP from 96.3% to 98.8%, but only a marginal increase in cure rates was achieved.[19]

However, in some previous studies, it has been reported that even in 4–6% of the patients with compatible preoperative USG and scintigraphy findings, unexpected findings might be encountered, and intraoperative PTH could contribute to the prediction of cure rates in these patients.[16, 20]

The additional contribution of intraoperative PTH increases to 19% in patients with single positive imaging findings.[16]

Using a combination of USG and scintigraphy, Sugg et al.[21] could predict multiple parathyroid hyperplasia in 30% of the cases. While intraoperative PTH measurement could detect 83% of MGD, but in 17% of the cases, it led to misdiagnosis after single gland excision. However, the combined use of USG, scintigraphy, and PTH measurement could predict MGD in 89% of the patients.

In a previous study evaluating >2000 cases from two centers, unilateral exploration was performed, and in 15.2% of the cases where the parathyroid gland was normal on the side of the pathological gland, a contralateral pathological gland was detected. If surgery was terminated in this group without intraoperative measurement of PTH, the expected cure rate would be 87%, and owing to intraoperative PTH measurement without seeing the other parathyroid gland on the side of the excised pathological gland, the cure rate increased to 98%. Intraoperative PTH measurement can optimize cure rates when compared with unilateral exploration.[22]

In a recent study, it has been indicated that intraoperative PTH measurement increased cure rates in 11% of the patients with compatible preoperative USG and scintigraphy findings, in 11% of the patients with single positive imaging method, in 33% of the patients in whom two incompatible imaging methods visualized different aspects of the neck, and in 24% of the patients in whom two imaging modalities yield negative and incompatible results. In addition, it was stated that the additional contribution rates were 11% in MIP, 24.6% in BNE, 12.4% in initial surgery, and 32.6% in secondary surgery.[23]

In a large series, cure rates were determined to be 99.4% with intraoperative PTH-guided focused surgery and 97.1% with BNE.[24]

Intraoperative PTH contributes to the confirmation of cure achieved with focused pHPT and the prediction of the presence of multiple glands without seeing other glands. MIP under the guidance of intraoperative PTH measurement is widely performed by parathyroid surgeons. In particular, it may increase the success rate in focused surgery and minimize the conversion rates to BNE.[9] Its contribution is still questioned in cases where results of both imaging modalities are compatible. In these patients, the use of intraoperative PTH measurement depends on the choice of the center. However, it may contribute to the application of MIP in patients whose single imaging findings obtained are positive or incompatible. Therefore, intraoperative PTH is recommended in centers with available facilities.[25] Owing to intraoperative PTH measurements, MIP can be safely performed with higher success rate and lower morbidity than more invasive BNE.[26]

Other uses of Intraoperative PTH Measurement

Intraoperative Lateralization

Bilateral jugular venous sampling used for lateralization and PTH measurement can be performed intraoperatively and in combination.[27, 28] This method is used to increase the rate of unilateral exploration, especially in patients with preoperative-negative and incompatible imaging findings.[29]

Differentiating Parathyroid Tissue from Other Tissues

Sometimes it may be difficult to separate the parathyroid tissue from the thyroid tissue or the lymph node. Intraoperative PTH measurement is used to differentiate parathyroid tissue from other tissues. Fine needle aspiration biopsy (FNAB) is performed from the excised tissue, and the biopsy material is washed with 1 mL of saline and its PTH content is measured (PTH washout test). This is an effective method, and when the lower limit of PTH for parathyroid tissue is obtained as 1610 pg/mL, the sensitivity and specificity of the test have been reported as 97% and 100%, respectively.[30]

It has been indicated that optimally, FNAB materials should be obtained from the excised tissue for at least five times to minimize the false negativity rate.[31] In another prospective study, FNAB was performed for 10 and 20 times, and 1 mm parathyroid tissue was excised to assess the presence of suspicious parathyroid tissue and then PTH measurements were performed. The median PTH levels were significantly higher in parathyroid tissue specimens than in non-parathyroid tissue specimens in all three methods. However, when the threshold value of 1000 pg/mL was taken into consideration, the compatibility rates of the three methods were reported as 71%, 81%, and 99%, respectively.[32]

The measurement of PTH from the tissue samples and aspirates may be defined as "biochemical frozen examination." This method can provide time and cost advantage relative to pathological frozen examination. It can be used as an alternative to pathological frozen section examination and may allow pathological examination to be applied in a more limited number of selected patients.[33]

Differentiation Between Normal and Pathological Parathyroid Glands

Sometimes the size of the pathological gland is limited, and it may be difficult to separate it from the normal parathyroid gland. Preservation of the normal parathyroid glands is important with respect to postoperative risk of hypoparathyroidism. In reoperative parathyroid surgery, the intraoperative PTH value of >1000 pg/mL in aspirate obtained from the suspected gland has been reported to have a strong predictive value as for the presence of a pathological parathyroid gland.[34]

Intraoperative use of a Gamma Probe

As in scintigraphic examination, it is aimed to detect Tc99m-sestamibi that is retained in the hyperfunctioning parathyroid tissue using a gamma probe during surgery. Several different protocols according to differences in injection doses and injection times have been defined for the gamma probe-guided parathyroidectomy. In some centers, 20–25 mCi (740–925 MBq) Tc99m-sestamibi is injected via the intravenous (iv) route, and dual-phase scintigraphy is performed within 3 hours. Then, gamma probe-guided parathyroidectomy is conducted on the same day.[35] Scintigraphy is performed prior to surgery to select the suitable patient for gamma probe-guided parathyroidectomy and to ensure higher effectiveness of the method in many centers. On a separate day, parathyroidectomy is performed with the aid of a gamma probe by administering sestamibi again on the day of surgery.[36]

In some centers, 10–20 mCi iv Tc99m sestamibi is administered 1–2 h before the operation.[37, 38]

In some other centers, preoperative scintigraphy is performed, and a low dose (1 mCi/37 MBq) of sestamibi was administered a few minutes before the surgery to patients with presumptive parathyroid adenoma who are also scheduled for surgery, and then parathyroidectomy is performed under the guidance of a gamma probe. It is aimed to preclude minimal radiation exposure of the surgeon and the operation room staff due to the administration of a very low dose of radioactive agent just before surgery and also false-negative results that may occur due to rapid washout (clearance of radioactive substance from the gland) from some hyperactive gland.[39]

You and Zapas compared the effects of standard and low-dose sestamibi. In a previous study, the effects of 25 mCi iv sestamibi administered 1.5 hours and 5 mCi iv sestamibi given 1 h before the surgery were evaluated, and diagnostic suitabilities were determined as 96% for standard and 98% for low doses. Moreover, they recommended gamma probe-guided parathyroidectomy with the administration of low-dose sestamibi as an alternative method.[40]

MIP is usually performed through a 2.5–3 cm incision in the gamma probe-guided parathyroidectomy. In some centers, the midline approach is used so as to easily switch to BNE, whereas in other centers, the lateral approach made in front of the sternocleidomastoid muscle is used. In addition, surgery is performed through an incision made over the radioactive hot spot determined by a gamma probe in various centers. During the exploration of the loge, generally, >50% of background activity is retrieved in vivo from the suspected parathyroid lesion.[10]

Murphy and Norman performed gamma probe-guided parathyroidectomies in 345 patients with sporadic pHPT and evaluated ex vivo radioactivity and background activity counts in 1290 tissue specimens they extracted within 3.5 hours after the injection of sestamibi and described the 20% rule. Radioactivity in the lymph node, normal parathyroid gland, and adipose tissue is not >2.2% of background radioactivity. In their study, background activity was 7.5% in the thyroid tissue and 5.5% in the hyperplastic parathyroid tissues, but they did not find >16% of background activity in none of the thyroid glands and hyperplastic tissues.

However, radioactivity in parathyroid adenomas was 59%, +9% of background radioactivity, and ranged between 18% and 136%, which was significantly higher than that in other tissues. In a previous study, the radioactivity count detected by a gamma probe in parathyroid adenomas in patients with positive sestamibi uptake who were thought to have solitary parathyroid adenomas was >20% of background radioactivity. The authors stated that the 20% rule in these patients could reduce the need to explore other glands and to perform frozen section and intraoperative PTH measurement.[41]

In another previous study, a success rate of 97.1% was reported in gamma probe-guided parathyroidectomy using the 20% rule.[42] Rubello et al.[43] reported a 97.9% success rate in gamma probe-guided parathyroidectomy with low-dose sestamibi administration. In their study, they obtained radioactivity counts >40% of background activity in all parathyroid adenomas and in at least one of the dominant glands removed from patients with multiple gland diseases.

Chen et al.[37] reported that using the ex vivo 20% rule, the gamma probe provides equal efficacy and information in the detection of both parathyroid adenomas and hyperplastic glands.

Tobin et al. evaluated the contribution of a gamma probe to the differentiation of parathyroid adenoma from MGD according to background activity in the firstly removed parathyroid gland. They stated that an uptake of 50% of background activity was the best threshold value in the identification of MGD, 69.4% of the cases of MGD radioactivity were below the threshold of 50%, and only 6.8% of the cases of activity counts were >100% of background activity. For the 50% threshold, the positive and negative predictive values for MGDs were 42.1% and 89.9%, respectively, and 72% of the whole study group could be classified correctly. When the threshold value was accepted as 100%, the positive predictive value for single adenoma was 93.2%. Although lower ex vivo activity counts could not clearly differentiate MGD, they stated that they could help the surgeon to wait for intraoperative PTH measurement or to continue exploration because of the high likelihood of MGD. In addition, ex vivo high count is an indication of adenoma, and it is not possible to have additional pathological gland.[44]

However, in other previous studies, it has been reported that the gamma probe cannot differentiate between adenoma and hyperplasia and therefore cannot help to exclude MGD.[45, 46]

In previous studies, the rates reported for the lesions may vary according to background activity, depending on the amount of radioactive material, time of administration, the area where the background activity is estimated, and the use of different gamma probes. Background activity has been reportedly retrieved from different regions in different studies. The radioactivity counts have been estimated from the bed where the lesion is removed, from the area of the thyroid tract through the skin, or from the lung apex on the opposite side of the arm where the radioactive material is injected after the lesion was removed.[36]

Ideal candidates for gamma probe-guided parathyroidectomy are patients undergoing first-time or redo parathyroid surgery, patients with non-nodular thyroid disease or a single gland disease based on scanning results, and patients with sporadic pHPT whose single gland disease was confirmed with USG.[47] The potential advantages of gamma probe-guided surgery are facilitation of especially surgery particularly focused parathyroidectomy, shortening of operative time, identification of the pathological ectopic parathyroid gland, and its ability to confirm surgical success.[47, 48] In the center where MIP was routinely applied with the aid of a gamma probe, its suitability rates were reported as 10% for single gland disease and 50% for hyperplastic gland and switching to BNE, with a total suitability rate of 83%.[49] However, in some previous studies, its use in MGD, in nodular thyroid disease or goiter, and in patients with negative scintigraphy is being questioned.[49]

Although the use of a gamma probe has been thought to be effective in sestamibi-positive patients, Chen et al.[50] from Wisconsin University found that all enlarged parathyroid glands, including parathyroid glands in ectopic localization in sestamibi-negative patients, can also be localized with a gamma probe at a sensitivity similar to that of scintigraphy-positive patients. They claimed that the gamma probe plays an important role in parathyroid localization in patients with negative scintigraphy. The same center reported that the gamma probe was also effective in reoperative neck surgery, and that reoperative surgery could be performed with a cure rate of 96% and also comparable complication rates relative to the primary parathyroidectomy.[51] In other studies of the University of Wisconsin, where the gamma probe is being routinely used, the gamma probe has been reported to be applicable and effective in the parathyroid glands in mediastinal localization, familial hyperparathyroidism, recurrent parathyroid cancer, and secondary and tertiary hyperparathyroidism.[49]

The precise contraindications to gamma probe-assisted parathyroidectomy are pregnancy, allergy, and sensitivity to Tc99m-sestamibi.[47, 48]

In some previous studies, it has been reported that the gamma probe does not facilitate surgery in 15%–48% of the cases with or without intraoperative PTH monitoring.[46, 52] There is no clear consensus on the use of gamma probes in parathyroidectomy. Some researchers have reported that the use of gamma probes will contribute significantly to parathyroidectomy.[41–44, 49] In other previous studies, a limited contribution of the gamma probe to parathyroidectomy has been reported.[46, 53]

The use of gamma probes is not recommended since preoperative imaging and intraoperative PTH monitoring are developed and are widely used.[52] Higher cure rates have been reported in pHPT (99.4% for MIP and 97.1% for BNE) in experienced centers with preoperative imaging and intraoperative PTH monitoring without the use of a gamma probe.[24]

Limitations of gamma probe application include logistic difficulties related to isotope application time, equipment problems, counts of radioactivity creating confusion, and easy identification of abnormal glands without using a gamma probe.[48] At the beginning of the 2000s, only 14% of the members of the International Association of Endocrine Surgery stated that they performed gamma probe-guided parathyroidectomy.[50] In their latest review article, Noureldine et al.[48] indicated that gamma probe-guided parathyroidectomy is thought to be considered by many surgeons in patients with ectopic parathyroidectomy or in patients who had undergone thyroidectomy previously. In addition, it has been reported that the pathological gland is localized intraoperatively with the help of a gamma probe, and that it allows the removal of fragile, fibrotic changes and dense scar tissue with minimal dissection. Therefore, its use can be considered in redo parathyroid surgery.[51]

Radio-guided Occult Lesion Localization Using a Gamma Probe

In patients with typical or suspicious parathyroid pathology detected on preoperative USG, preoperative occult lesion localization (ROLL) can be performed in patients with parathyroid gland as confirmed by PTH washout. In this method, 0.1–0.15 mL/0.1–0.15 mCi Tc99m-labeled macroaggregated albumin is injected into the lesion that is thought to have parathyroid pathology using a USG-guided tuberculin needle. Before the operation, the lesion site is marked with a gamma probe, and the lesion is removed with an incision made through the lesion.

It has been reported that this method is safe and effective in patients with single adenoma, especially in patients with negative scanning results. Histopathological examination of the removed glands revealed bleeding, congestion, subcapsular hematoma, fibrin, and neutrophil and leukocyte infiltration. However, the authors stated that ROLL application did not intervene with postoperative histopathological examination.[55] They reported a significant advantage in the removal of the pathological lesion from the previously intervened neck region with less dissection by localizing the pathological lesion.[56]

Intraoperative USG

Some surgeons, if available, also use high-resolution USG intraoperatively. Intraoperative USG can make significant contributions to the surgeon at different stages of surgery.[48] USG is the cheapest and the least invasive technique among all imaging modalities that does not use radiation, and it is also reproducible at any time if desired. The examination is performed on both the transverse and sagittal planes. The pathological parathyroid glands are well-defined, oval, and generally seen as solid nodules. In addition, the relationship between these pathological lesions and important vascular structures, such as internal jugular vein and carotid, can be evaluated.[48]

Since the anatomical localization of the pathological parathyroid gland may vary with the extension of the neck if focused surgery is to be performed, the skin incision can be made directly on the lesion identified by the parathyroid USG.[48] If the parathyroid gland cannot be found during surgical exploration, it can be searched by intraoperative USG.[49]

Furthermore, bilateral jugular vein sampling with preoperative USG can be performed, and the side of the exploration and the selection of the incision can be made according to PTH values.[49] USG-guided FNAB is performed for the hypoechoic structure suspected to be a parathyroid gland in the neck or thyroid, and then PTH level can be measured to determine if the lesion is a parathyroid gland or not.[49]

The suitability of USG is related to the surgeon's ability and experience, body mass index of the patient, size of the pathological gland, and presence of thyroid pathology, together with previous history of neck surgery. Knowing the limitations of USG and evaluating the possible ectopic sites of the parathyroid gland are important for a successful USG examination.

The fact that the air in the tissue disrupts the anatomical appearance limits its intraoperative usefulness in intraoperative USG.[49] Despite the possible advantages of intraoperative USG, there is no study in the literature evaluating the intraoperative role of USG, and there is no clear suggestion that it can be used as an additional method in parathyroid surgery.[49]

Methylene Blue

The colorimetric localization of the parathyroid gland with the use of iv methylene blue for the rapid identification of the parathyroid gland was first described by Dudley in 1971.[57] Later, some surgeons used methylene blue to identify the parathyroid glands. To date, there is no prospective randomized study performed with methylene blue.

In a review of the literature performed by Patel et al.,[58] 39 studies until 2012 were evaluated, and 33 of these studies did not have a control group. The percentage of staining of the pathological gland ranged from 83% to 100% (median 100%) in 243 patients with single gland disease. In 13 studies with 144 patients with MGD, it ranged from 67% to 100%, with a median of 100%. False-positive staining is reported in the normal parathyroid glands, lymph nodes, thyroid tissue, thymic tissue, and adipose tissue. A total of seven studies in patients with normal parathyroid glands showed a staining rate of 22%–100%. In four studies on thyroid tissue, in 24 (14.4%) of 167 patients, the uptake of methylene stain was reported.[58] Undesirable effects, such as blue staining of the urine and skin, are common, but they are self-limiting and harmless.[58] Methylene blue demonstrates additional and synergistic effect with anesthetic agents, reduces the need for anesthetic agent, and prolongs arousal time. It may cause transient neurological dysfunction in the early postoperative period. Overdose of anesthesia can contribute to the development of methylene blue encephalopathy. Brain monitoring in patients exposed to methylene blue and neurological examination in the first postoperative hours are recommended.[59]

However, neurotoxicity may be rarely seen, leading to hypertension, tachycardia, agitation, and disorientation. Almost all of these neurotoxicities have been reported in patients receiving serotonin reuptake inhibitor antidepressants (serotonin reuptake inhibitors).[58] These neurological effects are due to serotonin toxicity. The mechanism of serotonin toxicity is associated with the inhibition of monoamine oxidase that metabolizes serotonin when methylene blue is used.[60] Although there are studies reporting that methylene blue is still utilized, it has a lower popularity due to its potential neurological side effects.[1] Methylene blue should be avoided, especially in patients receiving serotonin reuptake inhibitors.[58] Strong, high-level evidence supporting the use of methylene blue so as to significantly increase the cure rate or reduce the risk of persistent and recurrent disease is lacking.[47, 58] Currently, the routine use of methylene blue, excluding prospective studies, is not recommended.[47]

Localization with Methylene Blue Injected Under Ultrasound Guidance

Removal of the lesion using 0.2 mL of 0.2% methylene blue under USG guidance in patients who previously experienced neck surgery and had parathyroid lesion detected on USG has been recommended. In two studies with a limited number of cases, it has been reported that it is an inexpensive, effective and safe method for the removal of the lesion in redo parathyroidectomy. No local or systemic complications associated with methylene blue have been reported.[61, 62]

Frozen Section Examination

Frozen section examination has long been used to confirm that the resected tissue is the parathyroid tissue. Three types of cells, such as chief, oxyphilic, and water clear cells, are found in the parathyroid tissue. Chief cells may be confused with thyroid follicle cells, and oxyphilic cells cannot be differentiated from Hurthle cells. Although the parathyroid tissue can be differentiated from other tissues, it may be difficult to differentiate between the thyroid tissue and parathyroid tissue in the frozen section examination. However, follicles and colloid-like materials are rarely found in the parathyroid tissue. The suitability of frozen examination was evaluated as 99.2% in a previous study where >1500 frozen section examinations were assessed. However, it has been also reported that frozen section examination has caused misdiagnosis.[63]

The routine use of frozen section examination is not recommended.[47] Considering the limitations of frozen section examinations and use of other methods, such as intraoperative PTH measurement, it appears to be a more rational option to use the frozen section in selected cases where a surgeon macroscopically suspected a parathyroid tissue.

Frozen section examination is not a reliable method for differentiating parathyroid adenoma from multiple gland hyperplasia.[47] Differentiation between hyperplasia and adenoma may not be based on pathological examination, but can be made according to operative findings, such as localization, size, color, and total macroscopic appearance of the glands. The pathologist may make the diagnosis of hypercellular parathyroid tissue in a frozen examination of a parathyroid gland. If only the gland is enlarged and hypercellular, the diagnosis of adenoma can be established reliably. When biopsy is obtained from a parathyroid gland, the pathologist cannot determine the cellular structure of other parathyroid glands that are not biopsied.[48, 49] The routine biopsy of all parathyroid glands to determine the status of other glands is associated with a higher rate of hypoparathyroidism.[1] Frozen section examination may play a role in pHPT, MGD, and secondary or tertiary hyperparathyroidism. In these cases, it is important to confirm the parathyroid tissue regarding the tissue to be left as a remnant or stored for autotransplantation or cryopreservation. In these cases, frozen examination may be used.[64]

Parathyroid Imaging Using Optical Technologies

Recently, new imaging technologies have been described in the literature to increase the localization of the parathyroid glands and to evaluate the viability of the parathyroid gland, especially in thyroid surgery. These include parathyroid imaging by autofluorescence, indocyanine green (ICG) with autofluorescence, methylene blue, 5-aminolevulinic acid (5-ALA), optical coherence tomography (OCT), laser speckle contrast imaging (LSCI), dynamic optical contrast imaging (DOCI), and Raman spectroscopy.

Surgeons need a technology that can identify the parathyroid glands, evaluate the viability of the glands, and identify the features that can distinguish the pathological gland from the normal glands to obtain better results. None of the methods evaluated here are able to meet all of these properties, and it is necessary to reach the parathyroid glands through a dissection to view all of them.[65]

These methods are all recently emerging methods. These techniques will be reviewed in light of the evidence in the literature, although they are not in routine use.

Detection of the Parathyroid Gland using the Autofluorescence Technique

The parathyroid gland has an autofluorescent property in the infrared spectrum.[66] The high fluorescent signal of the pathological or normal parathyroid gland continues after resection. The parathyroid gland has a higher fluorescence density than the thyroid, lymph node, and adipose tissue. The authors reported that this method could be used in the localization of the parathyroid tissue, and the verification of the parathyroid tissue can be used for the verification of the parathyroid tissue after its removal.[67]

Combination of Autofluorescence with Methylene Blue Staining

In parathyroid imaging, the combination of autofluorescence with low-dose (0.4–0.5 mg/kg) methylene blue has been reported in studies since 2013.[65] It has been reported that this method may help the intraoperative localization of parathyroid adenoma and normal parathyroid glands. The intensity of fluorescence in the parathyroid glands is higher than that in the thyroid and surrounding tissues.[68, 69]

Combination of Autofluorescence with 5-ALA

The 5-ALA is the natural precursor of protoporphyrin with fluorescence characteristics involving the synthesis pathway. High 5-ALA uptake in the parathyroid gland is explained by the high number of mitochondria in the parathyroid cells.[70, 71]

Prost et al.[70] reported that a total of 92% of the glands in pHPT and secondary HPT can be detected, and that in 48% of the patients, this method accelerated the localization of the pathological glands. It has been claimed to be a simple method in the differentiation between the normal and pathological parathyroid glands.[71] After 5-ALA is applied to prevent the phototoxic effects of the eye and skin, the patient's avoidance of direct light for 24–48 h is its main disadvantage.[70]

Angiography with Intraoperative ICG

One of the most commonly used imaging techniques using optical technologies is the visualization of autofluorescence and ICG.[65] ICG is a fluorescent agent with low toxicity and few side effects when administered systemically and has been approved by the Food and Drug Administration approximately 25 years ago.[65]

Sound et al. reported that in three patients with pHPT who underwent secondary intervention, fluorescein imaging with ICG successfully visualizes the pathological gland. They stated that owing to this method, during the early stages of exploration with the visualization of the pathological gland, the operation time and the stress of the surgeon would be reduced, and focused surgery could be performed with lesser need for dissection.[72]

Zaidi et al. visualized the uptake of ICG with the naked eye in 104 (92.9%) of 112 parathyroid glands in 33 patients with pHPT. They stated that the parathyroid glands could be safely localized with the ICG applied during parathyroidectomy, while at the same time, the perfusion of the glands that were exposed to subtotal resection could be evaluated.[73]

DeLong et al.[74] performed angiography with ICG in 60 patients with pHPT and detected a strong or moderate increase in vascularization in 93.3% of the patients. In addition, in 36 of 54 patients who underwent scintigraphy, parathyroid adenomas could be visualized, and 18 adenomas that could not be detected in scintigraphy could be visualized using ICG. They stated that it aids surgeons in determining the parathyroid pathology in primary surgery. The sensitivity of ICG in secondary HPT was found to be higher (91.1%) than that of preoperative imaging methods. It has been reported that ICG increases the rate of total resection and decreases the rates of persistent HPT and operation time.[75]

However, the emergence of a high fluorescence signal in all vascularized organs after the systemic injection of ICG and the limitation in depth of the camera may limit the pathological parathyroid gland mapping. It may limit its effect, especially in deeply localized or ectopic lesions.[65]

Studies on this issue suggest that ICG and fluorescein angiography with ICG are safe, effective, and easy ways to identify the parathyroid glands.[76]

It has been suggested that this procedure will be widely used in the future because of its contribution to the surgeon in the intraoperative decision-making process.[78] Though only a limited number of studies have been recently conducted on this subject, they are promising trials; thus, further studies are needed. New data are needed to determine whether the contribution of this method will be meaningful, especially in patients who were preoperatively scheduled for localized and focused surgeries. In secondary interventions, preoperative imaging may help the surgeon to reach the lesion with less dissection.

Laser Speckle Contrast Imaging

LSCI is based on the evaluation of intrinsic tissue contrast obtained from dynamic light scattering. In this method, it has been reported that the viability of the parathyroid gland can be evaluated in thyroid and parathyroid surgeries. This method is a non-contrast, non-invasive real-time method. The main disadvantage of the method is that the system is affected with the respiration of the patient and the movement of the surgeon. Studies on this subject are limited, and further studies are needed.[79]

Optical Coherence Tomography

OCT is a non-invasive, high-resolution imaging technique that allows the identification of microarchitectural properties in real time. Its sensitivity in making the differentiation among the thyroid tissue in the parathyroid gland, adipose tissue, and lymph nodes in thyroid and parathyroid surgeries is 69%, and it has been reported that it is not possible to differentiate, especially the lymph nodes, using this method.[79]

Intraoperative imaging of the parathyroid glands is a premature method, and further studies are needed on its usability.[65]

Dynamic Optical Contrast Imaging

DOCI is a method that allows the identification and visualization of specific tissue characteristics according to the automatic measurements of autofluorescence properties obtained from endogenous fluorophores at various wavelengths. The tissues extracted from 81 patients with pHPT were evaluated ex vivo, and it has been reported that the method is capable of differentiating the parathyroid tissue from other tissues. In vivo clinical trials are needed for the efficacy of this method.

Raman Spectroscopy

It has been reported in ex vivo studies that Raman spectroscopy may contribute to the differentiation of parathyroid adenoma from normal parathyroid tissue and also parathyroid hyperplasia from adenoma.[81, 82] The efficacy of this method should also be assessed in in vivo clinical trials.

Disclosures

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