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Review Article

Persistent and Recurrent Primary Hyperparathyroidism: Intraoperative Supplemental Methods, Basic Principles of Surgery, and Other Treatment Options

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ABSTRACT

Reoperative parathyroid surgery is challenging even for experienced surgeons. Cure rates are lower than primary surgery. Good anatomical and embryological knowledge is important. Preoperatively, a comprehensive surgical strategy should be planned. Pre-operative imaging modalities should be used extensively to find the overlooked gland to have a possibility to perform focused parathyroid surgery to avoid possible complications. One of the important developments is the new ancillary methods to find overlooked parathyroid glands. Orthotopic and possible ectopic locations should be known well by the surgeon to increase the surgical success rate. Reoperative parathyroid surgery needs a distinctive approach compared to primary parathyroid surgery. Basic principles include the selection of the incision and route for entering the thyroid region, use of ancillary methods, and intra-operative nerve monitoring and also require a meticulous dissection. Obtaining a surgical cure is difficult and high surgical caution is needed. Post-operative complication rates are higher compared to primary parathyroid surgery. Other treatment methods and medical treatment options may be evaluated in a patient who cannot undergo surgery.

Keywords: Intraoperative auxiliary methods, persistent hyperparathyroidism, primary hyperparathyroidism, recurrent hyperparathyroidism, reoperative parathyroid surgery

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Reoperative surgical intervention is performed in patients who have a confirmed diagnosis of persistent (perHPT) and recurrent (recHPT) hyperparathyroidism with surgical indication. Reoperation may be required in up to 10% of patients operated for primary hyperparathyroidism (pHPT).[1] Reoperation in pHPT is still challenging for both the patient and the surgeon. Pre-operative localization studies should be performed and operation should be performed by an experienced surgeon with an extensive knowledge of anatomy and embryology. Reoperative parathyroid surgery is an important cause of stress even for experienced surgeons due to the technical difficulty associ-

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ated with the operation, the higher complication rate, and the lower cure rate compared to the primary intervention.

For optimal surgical success in reoperative parathyroid surgery, a high-volume surgeon with a good knowledge of parathyroid anatomy and embryology is required. Anatomy and embryology knowledge has a critical role in forming the strategy about which gland or glands are overlooked and where to look for them.[2,3]

In this study, we aimed to review the intraoperative adjunctive methods and surgical strategy that can be used in the reoperative surgery.

Intraoperative Auxiliary Methods

Intraoperative methods that might contribute to the operation of pHPT have been extensively discussed in our previous review.[4]

Intraoperative Parathormone (IOPTH) Measurement

Among them, the most effective method is intraoperative parathormone (ioPTH) measurement. Especially in reoperative parathyroid surgery, ioPTH measurement is recommended.[5] During reoperative parathyroidectomy, when focused surgery (FS) guided by pre-operative localization studies is performed, ioPTH can predict the surgical cure with high sensitivity, and it prevents unnecessary exploration of the scar tissue and reduces the rate of the complications.[6,7]

Other ioPTH Measurement Options

ioPTH may contribute to intraoperative lateralization, differentiating parathyroid tissue from other tissues, and recognizing normal and pathological glands. If reoperative surgery is to be performed in patients whose pre-operative localization studies are negative or incompatible, ioPTH can be checked by taking blood from the right and left jugular veins after anesthesia induction. In case of detecting a gradient of more than 10% between the two sides, then the surgery can be started from the side with higher PTH. When the pathological gland is found and removed on the first explored side, the rate of unilateral exploration or FS can be increased by terminating the operation without additional exploration in patients with adequate reduction in ioPTH values.[8]

ioPTH may contribute to distinguish whether the excised tissue is parathyroid or not. It can contribute to the differentiation of the removed tissue with fine-needle aspiration and PTH washout, or by taking a 1 mm^3 tissue sample from the removed tissue and measuring ioPTH levels. Especially in a tissue biopsy, the PTH level being over 1000 pg/mL was found to be 99% sensitive and appropriate in separating parathyroid tissue.[9]

The amount of tissue required for PTH measurement is significantly less than that of required for frozen examination, providing an advantage of cost and time. This method can be defined as a biochemical frozen examination and used as an alternative to pathological frozen examination.[4].

Sometimes the size of the pathological gland is borderline and it may be difficult to distinguish it from the normal parathyroid gland. Preservation of normal parathyroids is important in terms of post-operative hypoparathyroidism risk. In reoperative parathyroid surgery, an ioPTH value above 1000 pg/mL from an aspirate of an intraoperative suspicious gland is a strong indicator of the pathological gland. Its sensitivity of predicting the pathological gland is 87%, specificity is 75%, positive predictive value is 74%, and negative predictive value is 88%.[10].

Use of Intraoperative Ultrasonography (USG)

Intraoperative USG can be applied in reoperative parathyroid surgery, depending on the experience and the conditions of the center.[1,11]

Due to the neck extension and muscle relaxation, anatomical localization of the pathological parathyroid may change compared to the pre-operative localization, the pathological gland can be determined by USG at the beginning of the operation, the skin incision can be made directly on the lesion, and the gland can be reached with less dissection.[12]

In patients with discordant pre-operative imaging, intraoperative USG before incision may contribute to the solution of this problem and allow FS.[13] If the gland localized in pre-operative imaging cannot be explored, the gland can be localized with intraoperative USG.[4] The accuracy of USG is related to the operator's ability and experience, the patient's body mass index, the size of the pathological gland, the presence of thyroid pathology, and previous neck surgery. Although intraoperative USG is recommended as an additional method in the guidelines and its possible advantages, there is no study in the literature evaluating the role of USG and intraoperative USG in reoperative parathyroid surgery.

Intraoperative Gamma-Probe Application

The use of intraoperative gamma-probe in the localization of the pathological gland in parathyroid surgery is also recommended among the additional intraoperative methods.[11] However, there is no clear consensus on the use of gamma-probes in parathyroidectomy. Although some studies have reported that the use of gamma-probe will make a significant contribution to parathyroidectomy, other studies have reported that the contribution of gamma-probe to parathyroidectomy is limited.[4] While it is recommended not to use the gamma-probe routinely in various publications, it is also reported that it may be useful in reoperative parathyroidectomy.[14] As a result of retention of Tc99m-sestamibi in hyperfunctional parathyroid tissue, it is aimed to detect the pathological gland with gamma-probe in surgery. In the study suggesting the use of intraoperative gamma-probe in reoperative parathyroidectomy, it is reported that the gamma-probe allows the pathological gland to be localized intraoperatively and removed with minimal dissection in the area having fibrotic changes and dense scar tissue. It has been reported that with this approach, parathyroidectomy can be performed with low complication rates similar to the initial parathyroidectomy.[15]

Radio-guided Occult Lesion Localization (ROLL) Approach

In solitary lesions with negative scintigraphy, positive pre-operative USG, and confirmed to be parathyroid with PTH washout, it has been reported that gamma-probe application by ROLL technique can be performed with occult lesion marking. Macroaggregate albumin labeled with mCi Tc99m is injected into the suspected gland. The lesion site is marked on the skin with a gamma-probe before the operation, and the lesion is excised with a gamma-probe through an incision made over the lesion. It has been stated that ROLL application does not impair the post-operative histopathological examination.[16]

It is reported that the ROLL technique can be used especially in reoperative parathyroid surgery, providing a great advantage in localizing and removing the pathological lesion with less dissection in the neck region with adhesions due to the previous intervention.[17]

Localization with Ultrasound-Guided Methylene Blue Injection

In patients who will undergo reoperative parathyroidectomy, it is recommended to remove the lesion after applying 0.2 mL of 0.2% methylene blue to the parathyroid lesions determined by USG under the guidance of pre-operative USG. In two studies on this subject, it has been reported that it is a cheap, effective, and safe method for removing the lesion in reoperative parathyroidectomy. No local or systemic complications related to methylene blue have been reported.[18,19] In addition, it has been reported that with the intravenous administration of methylene blue, the pathological parathyroid glands can be identified quickly by calorimetrical measurement. However, false-positive staining has been reported in normal parathyroid glands, lymph nodes, thyroid tissue, thymic tissue, and fatty tissue.[20]

Frozen Section Technique

Considering the limitations of frozen examination and the widespread use of other methods such as intraoperative PTH measurement today, and the limitations of frozen examination, routine use of frozen section examination is not recommended. It can be said that it is a more rational option to use it in selected cases where the surgeon macroscopically suspects whether a nodule is a parathyroid tissue.[4]

Parathyroid Imaging with Optical Technologies

Recently, new methods with optical technologies have been described in the literature to increase the localization of the parathyroid glands and evaluate their viability. These are autofluorescent parathyroid imaging, indocyanine green fluorescent, methylene blue, 5-aminolevulinic acid, optical coherence tomography, laser speckle contrast imaging, dynamic optical contrast imaging, and Raman spectroscopy.[4] All of these methods are newly developing methods and have no routine use. Near-infrared autofluorescence, which has received increasing attention recently, has been described in one of the last meta-analyses as an excellent indicator to identify the parathyroid gland in thyroid and parathyroid surgery.[21] These results give great hope for future studies. It has been reported in a limited number of cases that infrared fluorescent imaging can be used in the localization of the pathological gland in reoperative parathyroid surgery.[22] There is a need for new clinical studies to provide clear recommendations on the use of these new methods.

Intraoperative Nerve Monitoring (IONM)

Although visualization is the gold standard for preserving the recurrent laryngeal nerve (RLN) in thyroid and parathyroid surgery, it is difficult to visualize the RLN, especially in secondary thyroidectomy and parathyroidectomies.[23] There is consensus on the use of IONM in reoperative parathyroid surgery.[1]

In thyroid reoperations, it has been reported that 80% of the RLN route changes secondary to the first operation and the nerve travels within the scar tissue in approximately 60% of the cases. IONM makes an important contribution to the finding and mapping of RLN in the scar tissue.[24] In general, the RLN is anterior and more superficially to the enlarged upper parathyroids, posterior, and deep to the lower parathyroids.[1] Especially secondary to scar tissue, enlarged parathyroid and RLN are closely related. Most of the time, the RLN can be observed to be adherent to the enlarged parathyroid. Early detection and visualization are important for the preservation of the RLN in the dissection of parathyroids. In these cases, the IONM can contribute significantly to the identification and mapping of the RLN before visualization.

Possible Locations of Overlooked Glands

When evaluating where the overlooked parathyroid glands might be, parathyroid embryology and anatomy should be well-known. While most of the overlooked pathological glands are located in the orthotopic position, the majority of those located in the ectopic position can be reached from the cervical route.[25,26]

Normal Location of the Parathyroids

The upper parathyroids are located in the region of the cricothyroid joint between the inferior aspect of the thyroid cartilage and the cricoid cartilage, in the posterolateral aspect of the upper and middle 1/3 of the thyroid, at a rate of 80–85%. This region is an area of 2 cm in diameter, in which the central point is 1 cm superior point to the intersection of the inferior thyroid artery (ITA) and the RLN.[27]

Approximately 60–70% of the lower parathyroid glands are located posterior, lateral, or anterolateral to the lower pole of the thyroid in an area within 1 cm diameter. About 26% of the lower parathyroids can be located in the thyrothymic ligament region.[26] In general, the upper parathyroids are 80%, the lower parathyroids are 70% symmetrical, and the relative symmetry of both the upper and lower parathyroids is 60%.[28]

The expected relationship of both the upper and lower parathyroids with the RLN can be described within an imaginary rectangular prism area at the thyroid gland location when the thyroid lobe is rotated anteromedially. It is formed by the coronal plane, which passes the posterior surface of the prism tangent to the anterior surface of the esophagus, and the coronal plane, whose anterior surface is tangential to the anterior surface of the trachea. The upper surface of the prism is formed by the transverse plane passing through the highest point of the thyroid lobe, and the lower surface by the transverse plane passing 4 cm below the lowest point of the thyroid lobe. The outer surface of the prism is the vertical plane passing through the carotid artery edge, and the medial surface is the vertical plane passing through the anterolateral edge of the trachea. The normal course of the RLN divides the defined rectangular prism into 2 triangular prisms dorsal and ventral to the nerve. Accordingly, the upper parathyroids are located in the dorsal triangle above-posterior of the RLN, and the lower parathyroids are located in the anterior-lower prism, ventral to the RLN.[27,29]

Another definition; In the coronal plane passing through the trace of the RLN, the upper parathyroids remain in the deep plane in the dorsal plane and the lower parathyroids in the ventral plane in the superficial plane.[30] Therefore, the course of RLS can be a guide in determining the localization of the parathyroids during surgery. This is a more reliable relationship than the relationship between ITA position and parathyroids.

Ectopic Localization of Parathyroids

Congenital ectopia that develops during embryological migration in parathyroids and acquired ectopia due to migration of enlarged parathyroids may develop. At the 6th gestational week, the lower parathyroid gland develops from the dorsal part of the third pharyngeal pouch, the primitive thymus from the ventral part, the upper parathyroid from the dorsal part of the fourth pharyngeal pouch, and the ultimobranchial body (lateral thyroid) with cells from the neural crest from the ventral part. Congenital ectopia may develop due to abnormal migration of parathyroids during their migration to their normal anatomical localizations in the neck.

Since the migration path of the upper parathyroids is shorter, the embryological migration of the upper parathyroids is less than that of the lower parathyroids. About 13% of the upper parathyroid glands are located posterior to the upper pole of the thyroid, lateral to the cricoid cartilage and the pharynx, or at the intercricothyroid area between the thyroid and cricoid cartilage. They are located behind the esophagus, pharynx, or larynx in 1–4% of cases. Rarely, (1–2%) it may be located in the cranial part of the upper pole or in a more superior localization. Approximately 4% of the upper parathyroids are blocked caudal to the ITA, which can be perceived as lower parathyroids. The upper parathyroids may rarely be located lateral to the carotid sheath.[27]

Most of the ectopic localizations of the upper parathyroids are acquired ectopia. Enlarged upper parathyroid glands may be displaced due to regional dynamics such as repetitive muscle contractions during swallowing, intrathoracic negative pressure, cervicomediastinal fascial planes, and gravity. Enlarged upper parathyroid glands, up to 40%, can descend to the inferior of the neck, and even to the posterior mediastinum, as the paraesophageal and retroesophageal parathyroids, within the porous tissue on the prevertebral fascia. These glands are usually located posterior to the ITA and posterolateral to the RLN.[27]

The embryological migration path of the lower parathyroids is longer than the upper parathyroid, and the probability of congenital ectopia is higher, and most of the lower parathyroid ectopias are congenital ectopias. Due to the long embryological migration route, they can be located in any region between the corner of the mandible and the pericardium. Due to inadequate migration of the upper parathyroids, they can be located in the cranial part of the ITA at a rate of about 3% and may be perceived as the upper parathyroid. In the 2% of the lower parathyroid glands due to migration defect can be located along the carotid sheath from the corner of the mandible to the level of the lower pole of the thyroid.[25]

The inability to separate from the thymus during migration may result in lower ectopia due to further migration. Secondary to this, the probability of being in the upper and middle part of the thymus is 2%, and the rate of localization in the mediastinum, which is more inferior to the thymus, is reported as 3%. Rarely, it can be found more inferiorly on the pericardium. If there is a thymus remnant around a parathyroid that gland should be considered as a lower parathyroid.[27]

Lower parathyroids may be localized to a lesser extent in acquired ectopic conditions. Enlarged lower parathyroids may migrate to the anterior mediastinum, rarely posterior mediastinum, usually through the thyrothymic ligament and thymus for the reasons mentioned above.[27]

Parathyroids can be ectopically located intrathyroidally. According to autopsy series, thyroid surgery specimens, and parathyroid series, the incidence of true intrathyroidal parathyroid is 0.5–4%. Both the upper and lower parathyroids can be located intrathyroidally. However, parathyroids can be located capsular or subcapsular.[30]

Parathyroids other than true intrathyroidal parathyroid may be located capsular or subcapsular and these should be differentiated from true intrathyroidal parathyroid. Especially in nodular goiter, the nodule surrounds these capsular and subcapsular parathyroids and can be considered as intrathyroidal parathyroid.[25,30] It is reported that the subcapsular parathyroid can be seen at a rate of approximately 15%.[27]

In the meta-analysis including cadaver and hyperparathyroidism series in which parathyroid anatomy was examined, 15.9% of the parathyroid glands are located ectopically, 11.6% of ectopic localizations are located in the cervical region, and 4.3% in the mediastinum. Of the parathyroids located ectopically in the cervical region, 31.4% are in the retroesophageal, paraesophageal region, 20.3% are intrathyroidal, 17.7% are in the carotid sheath, 17% are in the thyrothymic ligament, 5.1% are in the tracheoesophageal groove, and 8.4% are in other areas (thyroid cartilage and adjacent to the hyoid bone, retropharyngeal area). It has been determined that most of the mediastinal parathyroids are located in the thymus.[31] In this meta-analysis, supernumerary parathyroids were found in 4.9% of cadaver series and 6.3% of patients with hyperparathyroidism.[31]

Supernumerary parathyroid glands are often found within the thymus. In addition, an important part of ectopic localizations such as the pyriform sinus, adjacent to the vagus nerve or inside the vagus nerve, in the carotid sheath, in the posterior cervical triangle, in the aortopulmonary window (in front of the pulmonary artery, behind the aortic arch and tracheal carina), pericardium and diaphragmatic dome, and laryngeal submucosa are where the pathological parathyroids detected during surgery for hyperparathyroidism.[25,27,30]

Basic Principles in Reoperative Parathyroid Surgery

Due to the scar formation and deteriorated anatomy secondary to previous surgery, reoperative parathyroid surgery is more challenging, it is more difficult to reveal the pathological gland and the risk of complications is significantly higher. A surgical strategy that can provide the highest cure with the least dissection and the least morbidity should be determined. Therefore, reoperative parathyroid surgery should be performed by a knowledgeable surgeon who is experienced in both decision-making and technique.[26]

Before reoperative parathyroid surgery, the diagnosis of primary HPT should be confirmed, and the indication for surgery should be established according to the patient's symptoms and target organ involvement.[32]

Although the rate of multi-gland disease is higher in persistent and recurrent patients than in primary surgery, the major cause is adenoma. Pre-operative imaging is mandatory in patients with surgical indications. It should be aimed to obtain at least 2 positive and concordant localization studies.[1,25,32] Reoperation should be applied to patients with positive localization studies. Approximately 95% of abnormal glands can be localized, especially when imaging modalities are combined.[33] Pre-operative localization studies can increase surgical success and reduce morbidity.[33,34] FS should be performed in imaging-positive patients.[11]

Blind exploration without imaging should not be performed in these patients. Selected severely symptomatic patients with negative imaging can be reoperated. If reoperation is to be performed on these patients, reoperation should be performed by a surgeon with high experience.

However, the rate of negative and inconsistent imaging methods in multi-gland disease is high. Reoperation should be performed in severely symptomatic patients from patients with a high suspicion of multiple gland disease.[25]

To optimize surgical success, all pre-operative imaging findings from the first operation, operative findings, pathology reports, and final pre-operative imaging should be carefully evaluated and an operative strategy should be determined. All patients should undergo pre-operative vocal cord examination. The previous surgical complications and current health status of the patient should be evaluated.[32]. Before the reoperation, it should be tried to predict whether there is a single or multiple gland disease, the locations of the abnormal gland or glands, the number of normal parathyroid glands removed, whether the pathological gland is the only gland remaining, and a surgical strategy should be determined accordingly.[26]

Except for extreme cases, FS should be performed under the guidance of pre-operative localization studies. An approach should be preferred in such a way that the pathological gland is reached through the region having the least scar tissue. The operation should be performed under the guidance of IONM. Intraoperative PTH measurement in the operation should confirm surgical success. According to the conditions of the center and the surgeon's preference, the above mentioned intraoperative contributing techniques should be used. In the case of post-operative hypoparathyroidism, primary autotransplantation should be performed. If technical facilities are available in the operation center, cryopreservation should be performed.[1,35]

Which Surgery to Whom?

Since the surgical methods and technical details to be applied in parathyroidectomy were given in detail in our previous study, some details will be emphasized in this section.[27]

Bilateral exploration may be required according to the initial surgery data of the patient who is planned to be reoperated with the diagnosis of multiple gland disease. If bilateral exploration was performed in the first operation and no gland was removed or a single hyperplastic gland was removed, bilateral exploration may be required. Exploration can be done by widening the anterior border of the sternocleidomastoid muscle laterally on both sides through the same incision. When entered from the midline, previous operative adhesions may cause difficulties until reach the thyroid gland. Alternatively, the thyroid gland can be reached with a lateral approach by entering between the anterior border of the sternocleidomastoid muscle and the lateral border of the strap muscles separately from the right and left sides. Hyperplastic parathyroid glands can usually be found in the orthotopic position. Both areas can be explored, pathological glands revealed, and subtotal parathyroidectomy can be performed. With this approach from the lateral, if necessary, thymectomy can be performed from both sides in terms of an ectopic gland or an accessory gland in the thymus.

If three normal glands were removed in the first operation, subtotal resection of this gland can be performed if there is only one pathological gland in the patient. It is often difficult to predict and extract the amount of tissue that would allow a desired reduction in PTH levels before hypoparathyroidism develops. It should also be taken into account that, although perhaps lowering PTH levels sufficiently, at least for a time, the remaining tissue is pathological and may regrow and cause recurrent hyperparathyroidism in the future. In this case, a difficult reoperation from a scarred area may be required.[35]

An alternative approach is the total removal of the remaining pathological gland and a portion of the gland implanted into the sternocleidomastoid muscle or subcutaneous tissue near the incision and marked with a polypropylene suture or clip. The success rate of parathyroid autotransplantation is uncertain; the patient may develop permanent hypoparathyroidism. In addition, if possible, the remaining parathyroid tissue can be preserved by cryopreservation. If the autotransplanted tissue does not function, the parathyroid tissue stored by freezing can be reimplanted. It should be noted that secondary autotransplantation after cryopreservation is not equally successful.[35] In patients who develop post-operative hypoparathyroidism, secondary autotransplantation should not be performed immediately and should be waited for a while. Some hypoparathyroidism may improve over time.[25]

In the reoperation, if midline intervention was performed in the first operation and the pathological gland is thought to be the upper parathyroid gland, the intervention can be performed from the area where there is no scar tissue with a lateral approach. This approach can also be preferred in patients who have had a previous thyroidectomy. The carotid sheath is exposed by entering between the anterior border of the sternocleidomastoid muscle and the lateral border of the strap muscles. Vagus stimulation (V1) is obtained with IONM in the carotid sheath. The carotid sheath is taken laterally and the anatomical space of the thyroid gland is entered. If the cross-sectional imaging points to the upper parathyroid, especially in the orthotopic position, the parathyroid can be easily accessed by opening the prethyroid fascia, which is the middle leaf of the superficial layer of the deep neck fascia originating from the anterior surface of the carotid sheath. With this approach, it is not necessary to dissect the thyroid. RLN can be easily identified and mapped with IONM. If the parathyroid is located at the paraesophageal or retroesophageal space, this region can be easily seen and explored after the deep leaf of the superficial layer of the deep neck fascia (pretracheal fascia) is opened. The upper parathyroids can usually descend paraesophageally. It is usually located behind the ITA and can be found in this region. However, lower parathyroids can be explored with this incision. To reach the parapharyngeal upper parathyroid located in the cranial part of the thyroid space, around the thyroid upper pole or in the upper pole cranial, it may be necessary to separate the thyroid upper pole vessels and release the upper pole. Upper pole release can be done with this incision. For this purpose, cutting the omohyoid muscle may provide additional benefits.[27]

It is not uncommon for overlooked parathyroids to be located medial to the entrance of the RLN to the larynx, adjacent to the ligament of Berry. This region cannot be seen well without separating the upper pole vessels and mobilizing the lobe medially. Sometimes, adenomas in this region can be removed by dissection along the RLN without separating the upper pole.[36]

If the first operation was performed with a lateral approach or if an operation such as anterior cervical discectomy was performed before, these patients can be approached from the midline. However, this area can be entered by carefully dissecting the scar tissue with the lateral approach. Meticulous dissection should be performed as there is a risk of injury to the RLN, esophagus, and trachea due to adhesions in this area. IONM should be used routinely to reduce the complication rate and sharp dissection should be applied instead of blunt dissection. After the vagus stimulation is received, RLN can be found by searching the operation area with the IONM probe.

The lower parathyroid glands located anterior to the trachea, or the lower parathyroids located in the upper mediastinum extending to the thymus, can be explored with an incision reached from the midline, and medial aspect of the lower lobe and thyrothymic region can be explored and thymectomy can be performed from this incision. It is not necessary to dissect the lower pole on both sides to explore this area.[1] If the lower parathyroid gland is lateral to the lower pole of the thyroid gland and toward the posterior mediastinum, this area can be entered with a lateral approach. The lower pole of the thyroid lobe is released and pulled medially and superiorly. The RLN can be identified and the parathyroid can be searched around the lower pole medial to the RLN. With the lateral approach, the area around the lower pole can be explored and thymectomy can be performed.

An overlooked parathyroid adenoma may be intrathyroidal. Most of them may have remained in the subcapsular area and within the nodular thyroid tissue. These subcapsular lesions can be removed without lobectomy. True intrathyroidal adenoma is rare. It can be confirmed with FNAB and PTH washout when pre-operative intrathyroidal parathyroid adenoma is suspected. Lobectomy may be necessary for true intrathyroidal parathyroid adenoma.[36]

Parathyromatosis is a rare condition. In patients with parathyromatosis, all parathyromatosis tissue should be aimed to be removed. The only curative treatment is en bloc removal of all foci. However, it is difficult to provide a cure in these patients.[37]

In particular, it can be very difficult to separate the parathyroid tissue from the RLN. Whenever possible, attempts should be made to dissect foci from the RLN. The patient should be informed that the risk of RLN paralysis is high.[33]

Up to 50% of patients with parathyroid cancer develop local recurrences. Surgery is still the only effective treatment. Therefore, residual tissue should be removed *en bloc*, if necessary, together with adjacent invading organs.[25,33]

Most mediastinal parathyroid adenomas are located in the anterior and posterior mediastinum above the aortic arch and can be removed by the cervical course.[25] Most of those in the anterior mediastinum are associated with the thymus. It can be delivered from the mediastinum by traction from the upper end of the thymus from the cervical route and carefully blunt dissection around it. Blind sharp dissection of the mediastinum should not be performed.[36] However, a mediastinal approach may be indicated in 1–2% of mediastinal adenomas. Mediastinal parathyroid adenomas are often located in the aortopulmonary window and are a good indication for video-assisted thoracoscopy.[33] A blind thoracic approach should not be used in imaging-negative patients.[26]

Surgical Outcomes

Surgical cure rates are lower in reoperative parathyroidectomy.[1] The surgical cure rate was reported as 82–98% in the literature.[11] If the first surgery is performed by an inexperienced surgeon, a surgical cure rate of up to 95% can be achieved without any localization studies.[33] However, it should not be forgotten that the key to a high cure rate in reoperative parathyroidectomy is optimal pre-operative imaging.[38,39] In reoperations performed by experienced teams, high cure rates comparable to primary surgery can be achieved.[2,38-40]

Post-Operative Complications

Complication rates are higher in reoperative parathyroidectomy. Compared to primary surgery, vocal cord paralysis is 6 times higher and post-operative bleeding is 2 times higher.[41] Post-operative hypocalcemia rates of up to 82% have been reported. Permanent hypoparathyroidism rates are reported between 5 and 13.6%.[2,39,41] It has been demonstrated that the use of intraoperative PTH may reduce the development of post-operative permanent hypoparathyroidism. Richards et al. have reported that with intraoperative PTH measurement in reoperative parathyroidectomy, the rate of permanent hypoparathyroidism reduced from 13% to 3% compared to patients without intraoperative PTH monitoring.[7] Temporary and permanent RLN paralysis rates are reported as 11.4 and 6.8–9%, respectively.[2,39,41]

In a study evaluating parathyroidectomies performed between 2008 and 2011 from the American College of Surgeons National Surgical Quality Improvement Program database, the presence of obesity in patients who underwent reoperative parathyroidectomy compared with those who underwent first surgery (48.5% vs. 40.0%, p=0.009) and ASA class 3 ratio (40.7% vs. 30.3%, p=0.001) were higher. Median operation time is longer in reoperative cases (101 min vs. 76 min, p<0.001), hospital stay (median days until discharge 1, IQR: 1.1 vs. 1, IQR: 0.1, p<0.001) was longer. The rate of re-admission to the hospital within 30 days of reoperation was higher (12.7% vs. 2.6%, p<0.001).[42]

Other Treatment Methods

Recently, some studies have reported that thermal ablation methods including ultrasound-guided microwave ablation and radiofrequency ablation are safe and can be applied in the treatment of primary HPT. The surgical cure rate of both methods is around 80%, which is lower than that of the primary surgical treatment. In these methods, the complication rate for hoarseness was reported as 5%.[43,44] It has been reported that 73% of normocalcemia was achieved with percutaneous ethanol injection in patients with recurrent HPT in MEN 1 syndrome. It has been reported that ethanol injection is an effective method and can be applied with low hypocalcemia rates.[45]

These ablative methods are rarely used in patients with perHPT and recHPT who cannot undergo surgery. These thermal ablation and percutaneous ethanol injection methods can be considered as alternatives in patients for whom secondary surgery is not appropriate.

Medical Treatment Options

Medical treatment in perHPT and recHPT should be reserved for patients who have an indication for parathyroid surgery but will not undergo parathyroid surgery. Specific pharmacological therapy should be reserved for situations where there is an indication to increase bone mineral density (BMD) and/or decrease serum calcium concentration. Evidence in the literature indicates that it should be used when there is a clinical indication to reduce serum calcium and/or increase BMD. Cinacalcet is likely to normalize serum calcium levels and lower PTH levels. Alendronate, denosumab, vitamin D, and estrogen therapy increase BMD.[46]

Disclosures

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