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Review

Persistent and Recurrent Primary Hyperparathyroidism: Etiological Factors and Pre-Operative Evaluation

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Abstract

Primary hyperparathyroidism (pHPT) is the most common cause of hypercalcemia and currently the only definitive treatment is surgery. Although the success rate of parathyroidectomy is over 95% in experienced centers, surgical failure is the most common complication today. Persistent HPT (perHPT) is defined as persistence of hypercalcemia after parathyroidectomy or recurrence of hypercalcemia within the first 6 months, and recurrence of hypercalcemia after a normocalcemic period of more than 6 months is defined as recurrent HPT (recHPT). In the literature, perHPT is reported to be 2–22%, and the rate of recHPT is 1–15%. perHPT is often associated with misdiagnosed pathology or inadequate resection of hyperfunctioning parathyroid tissue, recHPT is associated with newly developing pathology from potentially pathologically natural tissue left in situ at the initial surgery. In the preoperative evaluation, the initial diagnosis of pHPT and the diagnosis of perHPT or rec HPT should be confirmed in patients who are evaluated with a pre-diagnosis (suspect) of perHPT and recHPT. Surgery is recommended if it meets any of the recommendations in surgical guidelines, as in patients with pHPT, and there are no surgical contraindications. The first preoperative localization studies, surgical notes, operation drawings, if any, intraoperative PTH results, pathological results, and post-operative biochemical results of these patients should be examined. Localization studies with preoperative imaging methods should be performed in all patients with perHPT and recHPT with a confirmed diagnosis and surgical indication. The first-stage imaging methods are ultrasonography and Tc99m sestamibi single photon tomography Tc99mMIBI SPECT or hybrid imaging method, which is combined with both single-photon emission computed tomography and computed tomography (SPECT/CT). The combination of USG and sestamibi scintigraphy increases the localization of the pathological gland. In the secondary stage, Four-Dimensional computer tomography (4D-CT) or dynamic 4-dimensional Magnetic Resonance Imaging (4D-MRI) can be applied. It is focused on as a secondary stage imaging method, especially when the lesion cannot be detected by conventional methods. Positron Emission Tomography (PET) and PET/CT examinations with 11C-choline or 18F-fluorocholine are promising imaging modalities. Invasive examinations can rarely be performed in patients in whom suspicious, incompatible or pathological lesion cannot be detected in noninvasive imaging methods. Bilateral jugular vein sampling, selective venous sampling, parathyroid arteriography, imaging-guided fine-needle aspiration biopsy, and parathormone washout are invasive methods.

Keywords: Persistent primary hyperparathyroidism, primary hyperparathyroidism, recurrent primary hyperparathyroidism

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Primary hyperparathyroidism (pHPT) is the third most common endocrinological disease after diabetes mellitus and thyroid diseases and it affects 0.25%–0.66% percentage of population.[1,2] pHPT is the most common cause of hypercalcemia and it's only curative treatment is surgery.[2,3] The success rate of parathyroidectomy is above 95% in experienced centers independent from preoperative localization methods and surgical technique.[4] However, in the present surgical failure is the most common complication.[3,5]

The persistent disease rate is reported in between 2% and 22% and the recurrent disease rate is reported in between 1% and 15% in literature.[6-11] According to the data of The American College of Surgeons National Surgical Quality Improvement Program between 2008 and 2011, the annual reoperation rate for all parathyroidectomies varies between 3.6 and 4.8%.[12] In addition, 5–20% of all parathyroid surgeries performed for pHPT in reference centers are reoperations for persistent and recurrent disease.[5,13-22]

Etiology

Definition of surgical cure after parathyroidectomy is providing reestablishment of normal calcium homeostasis after surgery for at least 6 months. In normocalcemic pHPT, on the other hand, for the definition of cure, normal PTH levels together with the normal calcium level should be provided 6 months after the operation. The 6-month postoperative period for hypercalcemia is used to differentiate between persistent HPT (perHPT) and recurrent HPT (recHPT). perHPT is defined as the persistence of hypercalcemia or reappearance of hypercalcemia within the first 6 months after parathyroidectomy, and recurrence of hypercalcemia after a normocalcemic period of more than 6 months is defined as recHPT.[3] In generally, perHPT is related to missed pathological parathyroid gland or incomplete resection of hyperfunctional parathyroid tissue. However, recPTH is related to parathyroid gland which is not resected in first surgery and has a potential pathological nature.[23-25] The incidence of perHPT is more common than recHPT; in several studies the rate of perHPT varies 60-85% and the rate of recHPT is 15–40%.[5,6,20]

Causes of perHPT

The most common cause of development of perHPT is due technical problems in first surgery.[25] Lack of experience of surgeon: The most common cause of perHPT is lack of experience of surgeon. An inexperienced surgeon may not even be able to localize the parathyroid gland in its normal position.[20] In experienced centers surgical cure rate is reported above 95% although failure rate can be reached to 30% in surgeons who perform <10 operation per year.[3,22,25,26] Although inadequate surgical treatment is 13–22% preventable in high-volume centers, it is significantly higher in low-volume centers, 77–89%.[27,28]

Missed Parathyroid Adenoma: Missed solitary parathyroid adenoma is the major cause of perHPT in low volume centers.[18,27] In patients with negative exploration where no glands are seen or only normal glands are seen on exploration, this is usually related to an adenoma still waiting to be found.[25]

The pathological gland can be in orthotopic or ectopic localization. Above %50 of the missed parathyroid glands may be found in orthotopic position.[5,15,17,20] While the rate of ectopic localization is 5.3% in patients without parathyroid disease and 17.5% in patients with primary and secondary HPT, this rate has been reported to be 24–53% in patients with perHPT and reHPT and is higher.[5,18,20,21,29]

In generally, in patients who need secondary intervention ectopic pathological gland are in the neck in half of patients and in mediastinum in other half of patients.[20] Most of mediastinal parathyroid glands are localized in thymus.[30] In 80% percentage of ectopic parathyroid glands, cervical incision can be sufficient in secondary interventions.[29]

Supernumerary parathyroid glands: Supernumerary parathyroid glands can be rarely cause of perHPT.[31] In the last meta-analysis, the incidence of supernumerary glands was reported as 4.9% in healthy individuals, and the mean of secondary HPT, hereditary HPT and primary HPT series was 6.3%.[30] The prevalence of supernumerary parathyroid glands is significantly higher in patients with secondary HPT (16.5–32%). This is out of our scope.[32-34]

Although the prevalence of supernumerary glands in HPT patients with MEN1 is not as frequent as in patients with secondary HPT, it is not uncommon and has been reported as 12.2%.[35] The incidence of supernumerary HPT among sporadic primary HPTs is low, reported as 0.7%.[36,37]

In primary HPT, approximately 60% of the supernumerary glands are located in the mediastinum, often in the thymus.[35] However, in series with neck reexploration for perHPT or recHPT, the ratio of supernumerary parathyroid glands is higher and varies between 7.4 and 39.5%.[38-40]

Especially in the presence of 4 normal sized glands in the neck and histology, the possibility of possible supernumerary glands should be considered.[35]

Incomplete resection of parathyroid adenoma: In some cases, incomplete resection of parathyroid gland can be cause of perHPT. If this situation is noticed intraoperatively, the remnant of the adenoma should be investigated by the surgeon. The remnant is usually embedded in the thyroid.[25]

Multi Gland Disease: The inappropriate resection of multi

gland disease is another cause of perHPT. The major cause of surgical failure in high-volume centers is multigland disease, and the rate of multigland disease for perHPT is significantly higher in high-volume centers than in low-volume centers.[18,27,41] In inappropriate resection, pathological parathyroid tissue was found, but its hyperfunctional nature was not evaluated correctly and a large amount of hyperfunctional tissue was left in place. Sporadic or familial multiglandular disease (MGD) is the main cause of inappropriate resection.[36] Although sporadic MGD is more common than hereditary diseases, most of perHPT and recHPT patients are MEN 1, MEN 2, and other forms of familial HPT patients. These patients may have been diagnosed with sporadic HPT because of negative family history or asymmetric parathyroid involvement.[22]

Patients with MEN 1 who have undergone more limited parathyroidectomy than subtotal parathyroidectomy have a higher risk of perHPT. In the last meta-analysis, the perHPT rate was 4.4% in patients who underwent subtotal parathyroidectomy, while it increased to 23% in patients who underwent more limited resection than subtotal resection.[42] Despite all the developments in imaging methods, at least 30% of multiple gland diseases cannot be detected preoperatively.[43] The sensitivity of imaging methods is low in both double adenoma and multiglandular hyperplasia patients and misleading results were reported often.[22] Neither the combination of preoperative imaging modalities nor the application of further imaging modalities can reliably rule out multiple gland disease.[44]

Another cause of perHPT is leaving one of the adenomas with inappropriate resection in double adenoma patients. In general, the reason for perHPT in patients with double adenomas is probably related to the early termination of exploration by applying focused surgery or unilateral exploration, since it is evaluated as a single adenoma in the preoperative period. Especially in patients with double adenoma, the rate of persistent disease is higher than in patients with single adenoma and hyperplasia.[8,9]

Although double adenoma 9–11% and multiglandular gland disease 9–13% in large study series conducted in recent years, multi-gland disease is the reason in 14–70% of patients who develop persistent and recHPT.[8,9,22]

Normocalcemic HPT: Normocalcemic HPT is one of the three phenotypes of pHPT. In one of the latest studies, normocalcemic HPT was found to be related with perHPT and the incidence of perHPT was demonstrated higher than non-hormona and classic HPT (18.8%, 2.8%, 1.2%, p<0.001, respectively).[45] In another study, the 6th month cure rate was 45% in normocalcemic HPT, and it was reported to be significantly lower than non-hormonal (84%) and classical (93%) HPT.[46]

The incidence of multigland disease is higher in normocalcemic patients and is reported to be 45–64%.[46-48]

In the evaluation of 7569 patients in the American The Collaborative Endocrine Surgery Quality Improvement Program database, the rate of single parathyroid resection was found to be lower in normocalcemic patients compared to hypercalcemic patients (47.5% vs. 73.3%, respectively; p<0.05), and the rate of multiple gland disease was found to be higher in pathology reports (43.1% vs. 21.9%, respectively, p<0.05), the rate of remedial surgery was higher (6.4% vs. 4.5%, respectively; p<0.05).[49]

A higher rate of perHPT in normocalcemic HPT is associated with possible inappropriate resection of multiple gland disease.

Parathyroid Cancer: Parathyroid cancer is a rare tumor, accounting for <1% of primary HPTs. In patients with parathyroid cancer, perHPT may develop due to incomplete resection.[50,51]

If a post-operative histological diagnosis is made and the disease persists, local residual disease or distant metastasis should be suspected.[25]

Causes of recHPT

Multigland disease: The most common cause of the recHPT is the patients with hereditary MGD who underwent due to multiglandular hyperplasia with family history. recHPT could be occurred after first operation due to both in patients with remnant hyperplasia after subtotal parathyroidectomy performed or hyperplasia development in the autotransplate graft after total parathyroidectomy; or could be occurred due to supernumerary parathyroid gland in both situations.[25,50] Recurrence rate is lower in sporadic MGD than hereditary MGD. Although, data about recHPT prevalence in sporadic MGD is conflicted in literature; according to high volume series the general opinion is recurrence rates are similar in between sporadic MGD and single gland disease.[52]

It is believed that double adenoma is a different phenomenon from single gland disease and MGD. In patients with double adenoma, when both glands are resected, the long-term high cure rate is similar to single gland disease, which is the best evidence that double adenoma is a different disease.[52] In the other hand, according to the high volume serie by Alhefdhi et al.,[8] the recurrence rate was higher in double adenoma (7.3%) than MGD (4.4%) and single adenoma (1.7%). These results suggest double adenoma could represent asymmetric or asynchronous hyperplasia in some patients. However, this is very rare situation and MGD is occurred synchronously in generally. Therefore, in patients who are suspected with double adenoma, the sur-

geon should have high suspicion about possibility of MGD in intraoperative and/or post-operative period. The intraoperative biopsy from normal parathyroid gland could be considered if necessary.[52]

The development of a metachronous second adenoma from the normal parathyroid gland in patients who have a single adenoma excised in the first operation is a rare condition and is usually seen in patients with a history of radiation.[53]

Parathyroid Carcinoma: The recurrence could be occurred in 50% of patients after initial successful surgery due to parathyroid carcinoma. The recurrence rate is getting higher in patients with lymph node metastasis or distant metastasis. Recurrence is locoregional in generally. In addition, distant metastasis could be developed in 25% of parathyroid carcinoma patients.[51]

Parathyromatosis: Parathyromatosis is a rare cause of recHPT in pHPT. The main reason for this pathology is the implantation of the enlarged parathyroid gland into the surrounding tissue due to capsular rupture during manipulation in the first operation. Parathyromatosis in pHPT is very rare and the number of cases reported so far in the English literature is <25 (Table 1).[54,55]

Table 1. Causes of recHPT and perHPT

Causes of Persistent HPT
Inexperience of the surgeon
Overlooked parathyroid adenoma
Orthotopic Localization
Ectopic Localization
Supernumerary Parathyroid Adenoma
Incomplete Parathyroid Adenoma Excision
Multiple Gland Disease
Inappropriate Resection of Multipl Gland Disease
Normocalcemic HPT
Inappropriate Double Adenoma Resection
Inappropriate Resection of Parathyroid Cancer
Causes of Recurrent HPT
Multiple Gland Disease
Inappropriate Resection of Multiple Gland Disease
Recurrence from Remnant After Subtotal Resection
Recurrence from The Transplanted Graft in Patients with Total Parathyroidectomy and Autotransplantation
Recurrence from Supernumerary Gland
Parathyroid Cancer
Parathyromatosis
Metachronous Parathyroid Adenoma
Metachronous Second Adenoma with Radiation History

HPT: Hyperparathyroidism; recHPT: Recurrent hyperparathyroidism; perHPT: Persistent hyperparathyroidism.

Predictive Factors for perHPT and recHPT

Demographic, clinical, radiological, and biochemical features have evaluated for predicting persistence and recurrence disease in some studies. Yeh et al.[6] determined age >70 years as an independent risk factor for development of perHPT (OR 1.80, 95% confidence interval [95% CI] 1.13–3.11, p<0.05). High volume hospitals (>100 cases) were determined as a factor which decrease the recurrence risk. Furthermore, the patients with suspicious and negative sestamibi results were related to perHPT risk.

In multivariable analysis, double adenoma was found to be associated with increased persistent/recurrent disease.[56]

According to the study of Shirali et al.[57]; age >66.5, calcium level 9.8 mg/dL and PTH 80 pg/mL at 6 months are independent factors related to the increased risk of recurrence. In addition, in patients who underwent minimally invasive parathyroidectomy, at least 1 pre-operative imaging and/or findings inconsistent with intraoperative findings are associated with an increased risk of recurrence in patients (hazard ratio 4.93, 95% confidence interval 1.25–16.53, p=0.016).[57] Similarly, in another study, Ca levels >9.7 mg/dL at 6 months and an increase in PTH with normocalcemia at 6 months were found to be independent risk factors for late recurrence.[11]

However, in the other study, advanced age was a protective factor for recurrence (hazard ratio 0.97, 95% confidence interval 0.94–0.99, p=0.034), intraoperative PTH drop more than 70% (HR 0.45, 95% CI 0.20–0.98, p=0.046) were found to be independent protective factors for recurrence. Double adenoma was determined as an independent risk factor for recurrence. (hazard ratio 3.52, 95% confidence interval 1.23–10.08, p=0.019).[10] Similarly, in another study, a higher decrease in intraoperative PTH was protective against recurrence (HR = 0.96; 95% CI = 0.93–0.99; p=0.03), and a higher PTH value at post-operative 1–2 weeks was significantly associated with recurrence (HR = 1.03; 95% CI = 1.02–1.05; p<0.01).[58]

In the one of latest studies, the lowest intraoperative PTH level was found to be a very weak predictive factor for recurrence but the early biochemical respond was determined as the strongest predictor. Compared to complete response in the early postoperative period (within 2 weeks postoperatively); The recurrence risk was found to be 2.727 (95% CI 1.490–4.991) (p<0.02) in patients with early partial response with increased PTH and Ca, whereas the risk of recurrence was 4.297 in patients with early partial response with increased PTH and normal Ca value (95% CI 2.570–7.186) (p<0.02).[59]

According to the Lim et al.[48], normocalcemic HPT and fam-

ily history were determined as significant predictive factors for multigland disease which is the most important factor for persistent and recurrent disease.

In the study in which 9114 patients who underwent parathyroidectomy were evaluated from The American College of Surgeons National Surgical Quality Improvement Program data between 2008 and 2011, obesity rate in reoperative parathyroidectomy compared to first parathyroidectomy (48.5 vs. 40.0%, p=0.009, respectively) and ASAIII patient rate (40.7% vs. 30.3%, p=0.001), and both obesity and ASAIII score were associated with reoperation.[12]

Long-Term Follow-Up and Follow-Up for Recurrence

There is a lack of data about long-term recurrence after initial successful parathyroidectomy. In a meta-analysis includes 14 study which have at least 50 patients and more than 1 year follow-up, the cure rate was determined 96.9% (95.5–100%) and recurrence was 1.6% (0–3.5%) for 33.5 months mean.[60] In the long-term (mean: 78 months (21–112 months) follow-up of patients with positive scintigraphy and USG and underwent minimally invasive parathyroidectomy, the recurrence rate was reported as 3.85%.[61] However, data on long-term follow-up and recurrence after the initial successful parathyroidectomy are limited. In recent studies, it is noteworthy that the recurrence rate increases with long-term follow-up. A recurrence rate of approximately 10% was reported in two studies with mean follow-up of 3 years and 5 years.[11,59] Median recurrence times in long-term follow-up were determined as 77 months in a study, 92 months in other study and 12.2 years in another study.[11,61,62]

In a study with median 6.3 years recurrence time (interquartile range 3.4–10.3 years) recurrence rate was determined 14.8% for 10 years; 41.4% of recurrence was occurred in 5 years after initial parathyroidectomy and 23.5% was occurred in between 5 and 10 years and 34.5% was occurred after 10 years of initial parathyroidectomy. As the follow-up period increases, the incidence of recurrence increases.[10] Similarly, the recurrence rate was reported 14% in another study.[62]

recHPT is higher than previously reported recurrence rates, so long-term, even life-long follow-up of patients with primary HPT over 10 years is required.

In the literature review discussed at the 5th international multidisciplinary workshop on primary HPT, the discussion about the 6-month time periods in the definitions of persistent and recurrent disease is increasing, and it is recommended to update these periods and definitions.[23] Although the definition of recHPT is development of hypercalcemia after 6 months normocalcemic period, the main question is whether occurring of a new disease as recHPT after this period or is this period a transient period which masks the perHPT.

In the light of a better understanding of asymmetric hyperplasia and the information obtained from more sensitive third and fourth generation PTH tests and ioPTH monitoring; dormant disease needs to be better understood.[7,23,61,63]

Pre-Operative Evoluation

Biochemical Verification of Diagnosis

In patients evaluated with a pre-diagnosis (suspect) of perHPT and recHPT, the initial diagnosis of pHPT and the diagnosis of perHPT or rec HPT should be verified.

Verification of pHPT Diagnosis: 2–10% of patients with considered with inadequate surgical history could be misdiagnosed. In present, pHPT can be diagnosed with almost 100% accuracy by demonstrating (proving) that the serum intact parathormone (iPTH) level is increased in a patient with an ionized or total calcium increase. The coexistence of hypercalcemia and increased iPTH is almost always associated with pHPT. However, the other causes of hypercalcemia and iPTH increment should be excluded.[25]

The second most common cause of hypercalcemia is malignancy. Hypercalcemia due to malignancy could be occurred with different mechanisms. In generally, this phenomenon is occurred as humoral hypercalcemia due to higher secretion of PTH related protein (PTHrP) from different type of tumors.[64] Hypercalcemia due to ectopic PTH secretion from tumors is rare. Humoral hypercalcemia may very rarely be related to the production of both PTH and PTHrP by tumors. PTH and PTHrP do not cross-react in current measurement methods. This feature makes it possible to make a clear distinction between PTH-mediated, PTHrP-mediated and the very rare cases where both appear simultaneously.[65] Malignancy related hypercalcemia may be occurred from extensive lytic lesions due to malignant tumors. These patients have advanced malignancies and have suppressed PTH due to hypercalcemia, and there is usually no problem in the differential diagnosis with pHPT.[64]

Some malignancies and sarcoidosis, tuberculosis, and other granulomatous diseases can produce excess 1,24(OH) vitD and cause hypercalcemia. Also various endocrine diseases such as thyrotoxicosis, pheochromocytoma, adrenal insufficiency or crisis (Addison's disease), VIPoma, islet cell pancreatic tumors can cause hypercalcemia, too.[64,66] All of this hypercalcemia are characterized by PTH suppression

and can be easily distinguished from pHPT by PTH measurement.[66]

Biotin supplementation may cause falsely low PTH measurements. Therefore, it is recommended to discontinue biotin at least 48 h before PTH measurement.

Familial hypocalciuric hypercalcemia (FHH) biochemical profile is similar to pHPT and should be considered in differential diagnosis to avoid unnecessary surgery. Patients with FHH have life-long hypercalcemia typically below 3.0 mmol/L (12 mg/dL); however, PTH is inappropriately normal in 80% and slightly increased in 20% of these patients also renal function is preserved and inappropriately urinary calcium excretion is determined low. Serum phosphate levels are often low and mild hypermagnesemia may be present.[67] 24-h urine calcium and Ca/creatinine clearance rate (CCCR) may be helpful for distinguishing FHH and pHPT. The most appropriate evaluation is CCCR. A CCCR <0.01 suggests the diagnosis of FHH. Although CCCR<0.01 in 70–80% of FHHs, CCCR<0.01 can be detected in almost 20% of pHPTs. About 10% of FHH is CCCR >0.02. For the definitive diagnosis of FHH, genetic testing is recommended in patients with a low CCCR and a family history.[66] Especially between the CCCR 0.01–0.02, the number of patients who have difficulty in distinguishing between FHH and pHPT is high. In the studies conducted in recent years, it is noteworthy that the debate on this issue has increased. When CCCR<0.02, the probability of FHH is high, and it is recommended to consider genetic testing in these patients.[68]

Li et al.[69] stated that clinical evaluation is sufficient in patients with CCCR<0.01 to exclude FHH, and genetic testing is required in only 1% of patients. In addition, according to the high volume study by Moore et al.[70] CCCR was determined <0.01 in 19%, 0.01–0.02 in 43.7%, >0.02 in 37.3% of pHPT patients. The authors claimed that the use of CCCR screening for FHH was limited as 63% of patients with confirmed pHPT were <0.02.

Hypercalcemia and increased PTH may occur in patients receiving lithium and thiazide therapy. For the differential diagnosis, treatment should be discontinued in these patients and the Ca test should be repeated a month or two later. Urine Ca measurement is unlikely to be accurate in patients using thiazide and lithium. It is associated with decreased urinary Ca excretion in Vitamin D deficiency or chronic renal failure.[66] Lithium therapy stimulates parathyroid growth along with serum PTH increase.[71] It should also be taken into account that lithium-related HPT may develop with lithium treatment for 10 years or longer.[72,73]

It should not be forgotten that excessive Vitamin D intake, excess Vitamin A, estrogen therapy, antiestrogen therapy or androgens, aminophylline or theophylline, ganciclovir, recombinant growth hormone therapy in patients with AIDS may cause hypercalcemia.[64]

Physiological secondary HPT may occur in cases such as stage 3–5 chronic kidney disease, vit D deficiency, Ca malabsorption, renal hypercalciuria, bisphosphonate, and denosumab use to compensate for calcium intake deficiency. In this case, Ca is low or normal, and if Ca is low, there is no problem in the differential diagnosis. However, if Ca is normal, all of these conditions should be excluded when diagnosing normocalcemic HPT.[64,66]

In long-term secondary HPT such as malabsorption syndromes (e.g., active celiac disease, large bowel resection, and gastric bypass surgery) or uncontrolled renal failure, chronic stimulation of the parathyroid glands may result in the parathyroid glands becoming autonomous and pathological secondary HPT or tertiary HPT may develop. In this case, high PTH and hypercalcemia occur and these should be considered in the differential diagnosis.[64,66]

Verification of Persistence or Recurrence

The biochemical diagnosis of perHPT and recHPT is the same as the initial pHPT diagnosis. Specifically, it is characterized by hypercalcemia with elevated or insufficiently suppressed PTH.[74]

In the post-operative follow-up after successful parathyroidectomy, elevated PTH levels can be detected in patients with nomocalcemia. In a review of 33 studies, the maximum mean prevalence of normocalcemic elevated PTH (NCePTH) was 23.5% and ranged from 3 to 46%. NCePTH is not indicative of persistent disease. NCePTH may be multifactorial.[75]

To predict postoperative NCePTH in studies which multivariance analysis was performed; lower 25(OH)vitD, higher pre-operative PTH value, lower creatinine clearance, lack of vit D supplementation, greater adenoma weight, older age, and higher 10 min ioPTH level were determined as independent risk factors.[76-78]

Especially, hungry bone syndrome, Vitamin D deficiency and decreased glomerular filtration rate are important in physiological variations of NCePTH.[75] In the review, in which studies on NCePTH were evaluated, it was emphasized that although NCePTH does not seem to be associated with recHPT, this possibility should not be ignored.[75] However, some studies have reported that NCePTH may be associated with recHPT and is higher than those with postoperative normal PTH, and recurrent hypercalcemia rates of up to 19% associated with NCeHPT have been reported.[11,79]

In some studies, it was associated with early postoperative NCePTH recurrence, while in some studies it was associated

with NCePTH recurrence at 6 months.[11,57-59]

In addition, NCePTH appears to be associated with a higher incidence of cardiovascular disease.[75]

NCePTH may be a dynamic, reversible, and transient clinical entity after parathyroidectomy. However, these patients should be monitored, potential causes of PTH increase should be investigated and treatment should be attempted.[80]

These patients may be considered for follow-up for cardiovascular disease and possible recurrent disease.

NCePTH should not be considered as a persistent disease. Unnecessary tests should not be performed as if it is a persistent disease. This may be an important negative factor that will increase both patient stress and cost.

Post-operative Ca Normalization

After curative parathyroidectomy, normocalcemia occurs in the majority of patients within 48–72 h postoperatively. Delayed Ca normalization may occur in approximately 10% of patients. In the majority of these patients, Ca returns to normal within 1–2 weeks. If PTH is normal, the failure of Ca to return to normal in the early period should not be considered as persistent disease and the Ca level should be monitored in these patients.[81,82]

Surgical Indications for perHPT and recHPT

Surgery is recommended when patients with pHPT meet any of the recommendations in the guidelines for surgery and there are no surgical contraindications.[66]

Surgical indications for perHPT and recHPT are not different from the surgical indications for pHPT. These patients have undergone unsuccessful parathyroid surgery compared to patients who will undergo primary surgery and are at increased potential risk due to the secondary procedure.[74] Parathyroidectomy is an option for all patients, with the agreement of the patient and physician, and in the absence of any contraindications.[66]

The fact that primary surgery has been performed on an asymptomatic patient who does not have any specific recommendations in the guidelines does not mean that there is a need or indication for routine reoperation if perHPT has developed. The risk of complications secondary to reoperation is markedly high, with up to 10% permanent RLN paralysis and up to 20% permanent hypoparathyroidism reported. Asymptomatic mild hypercalcemia is better than permanent hypocalcemia and permanent RLN paralysis. Therefore, reoperative surgery is not required for every patient.[25] The threshold for reoperative surgery should be higher than for the initial surgery. For this, the severity of the disease should be evaluated quantitatively. Baseline assessment of the degree of hypercalcemia (such as serum calcium >3.00 mmol/L [12.0 mg/dL]) may be complemented by assessment of renal function (especially glomerular filtration rate), renal imaging (abdominal ultrasound or CT for nephrolithiasis or nephrocalcinosis)/nephrocalcinosis), somatic symptoms (musculoskeletal aches and pains), bone health assessment (by dual-energy X-ray absorptiometry), and cardiovascular risk assessment.[74]

When deciding on surgery for reoperative parathyroidectomy, factors such as whether the patient is symptomatic, whether there is target organ involvement, whether he meets the criteria recommended for surgery in asymptomatic patients, whether successful surgery will improve clinical outcomes, whether parathyroidectomy is curative, and the risk/benefit balance should be considered. While surgery should be considered in patients with significant ongoing symptoms, significantly elevated Ca, patients with nephrolithiasis, and patients with ongoing bone loss, non-operative treatment can be considered for patients who are mildly asymptomatic and have no systemic findings.

Timing of Secondary Surgery

Especially in perHPT, the decision for surgery should not be made hastily. If an adenoma is not found in the first operation, early reexploration can sometimes be performed in the first 48–72 hours. Pre-operative imaging methods should be performed again in these patients. In general, the initial imaging methods are of low quality in these patients, and high quality imaging methods should be performed in an experienced center. The pathological gland must be precisely localized.[50]

Early reoperation is rare in patients with PerHPT. In these patients, there should be no doubt about the diagnosis and perHPT, and high PTH and hypercalcemia should persist. Time is usually needed for the evaluation of patients. In patients with adequate decline in post-operative PTH, it may take time for hypercalcemia to turn into normocalcemia, as discussed above. Early intervention should not be applied to these patients.

Secondary surgery should be performed after a minimum of 3 months postoperatively, as the surgical area is greatly affected by the inflammatory scar from the first surgery for a few months after the 1st week. It should be noted that parathyroid implantation or parathyromatosis is the one of the most difficult surgical situation similar to oncological neck surgery, such as cervicocentral lymph node dissection.[83]

Evaluation of the Clinical History

In patients whose diagnosis is confirmed and surgery is indicated, family history and personal history should be

evaluated in detail, especially in terms of the possibility of a familial disease. All patients who are thought to be from a syndromic proband should undergo formal genetic testing for multiple endocrine neoplasia 1 and 2A syndromes, HPT-jaw tumor syndrome, and genetic counseling should be given. Careful family screening should be performed in these patients.[24]

Evaluation of Pre-operative, Intraoperative, and Post-operative Data

Localization studies of these patients before the first operation should be carefully re-examined. Operation notes, if any, operation drawings, intraoperative PTH results, pathological results and post-operative biochemical results should be reviewed. The surgical report of an experienced parathyroid surgeon performing the initial surgery is more important compared to the information that can be obtained in the evaluation of an inexperienced surgeon. However, if an inexperienced surgeon performs the first operation, the pathology report is more important than the operation report.

The type of surgery performed (lateral or central approach, focused surgery, unilateral exploration, and bilateral neck exploration), which parathyroid glands were identified, which parathyroids were removed, whether biopsy was taken from the parathyroids seen, and whether the left parathyroids were marked with clips or sutures should be evaluated in the surgical report. It should be evaluated how many parathyroid glands are removed in the pathology report, whether these glands are normal or pathological, and whether the glands from which biopsy was taken are parathyroid. If necessary, the remaining tissues from the previous pathological examination can be reevaluated. It may be useful to evaluate preoperative localization studies and intraoperative findings together. These reports may contribute to estimating the number of normally vascularized parathyroid glands in the surgical area, the overlooked parathyroid gland and its probable location, depending on whether there is a pathological gland removed, whether there is a normal parathyroid gland removed or not. In fact, the possibility of perHPT to be a single or multiple gland pathology and the possible location of the lesions that are overlooked by the surgeon can be determined. If no parathyroid gland(s) were excised at the initial surgery, or if only normal parathyroid glands were removed, the patient's pathology is likely to be a solitary adenoma. Particular attention should be paid to which glands are identified in the operative note, which are removed, and what the pathology is in each excised specimen. If the tissue defined as a normal parathyroid gland in the operating site by the first surgeon does not have histological confirmation, it should be considered that this defined tissue may not be a parathyroid gland.[24,84]

These data can help predict the quadrant where the pathological lesion is most likely to be found, increasing the probability of success and reducing the risk of hypoparathyroidism. This analysis can also predict where the most dense scar tissue may be, and may contribute to the development of a strategy to reoperate from the area with the least scar tissue. If capsule rupture is suspected at previous surgery, the possibility of parathyromatosis should also be considered.[74]

Preoperative Vocal Cord Examination

In perHPT and recHPT, vocal cord examination with flexible laryngoscopy should be performed in every patient preoperatively.[74,83]

Vocal cord paralysis (VCP) due to initial parathyroidectomy may be symptomatic or asymptomatic. Examination of all patients rather than only symptomatic patients doubles the rate of VCP. If the patient has preoperative VCP, it will have a significant impact on the surgical plan. If VCP is on the side on which reoperation is planned, perhaps the patient is exposed to little or no additional risk of adverse effects on the voice with reoperation. However, if surgery is going to be performed on the opposite side of the paralytic cord, the functional, mobile single vocal cord will be at risk. In this case, the indication for surgery should be reconsidered. If surgery is indicated, the patient is at risk of postoperative bilateral VCP that may require tracheotomy. This possibility should be discussed widely with the patient, and full and written informed consent should be obtained.[74,83]

Localization Studies (Non-invasive and Invasive)

Localization studies with pre-operative imaging methods should be performed in patients with PerHPT and recHPT in all patients with a confirmed diagnosis and surgical indication.[74]

The specificity and negative predictive value of imaging methods are not clinically relevant, as imaging methods have no place in confirming or excluding the diagnosis. The sensitivity and positive predictive value of these tests are clinically important features.[85] In these patients, imaging performed before the first surgery can give important clues. If the initial scans are positive for adenoma and even if the adenoma was missed at the first surgery, the patient should undergo new imaging. Because there may be changes in the position of the lesion due to surgery. Multiple imaging modalities should be applied in combination in these patients. The role of imaging in perHPT and recHPT is both to accurately identify and localize a parathyroid lesion (or lesions) and to identify postoperative changes

from previous parathyroid explorations that may affect a subsequent surgery.[85]

Surgical success can be increased with pre-operative imaging methods in reoperative parathyroid surgery, and success rates close to primary surgery can be achieved in experienced centers.[86]

Ultrasonography (USG)

USG should be applied as the first-line imaging modality in perHPT and recHPT. Parathyroid adenoma missed by the previous USG specialist can be detected at second imaging.[74]

Although USG is a highly operator-dependent modality, it is an inexpensive, accessible, and radiation-free modality. Thyroid lesions can also be evaluated together with a suspected parathyroid lesion. If necessary, it allows FNAB to be performed from both the suspected parathyroid and the thyroid glands. USG often fails to localize adenomatous glands or localize ectopically located glands in obese patients.[87]

Sensitivity of USG is significantly lower in multi-gland disease, which is higher in patients requiring reoperation.[88]

In patients with perHPT and recHPT who underwent parathyroidectomy, the sensitivity of USG varies between 38 and 72% and its positive predictive value ranges between 70 and 93%, and it is lower than patients with pHPT who will undergo the first surgery.[86,89-92]

In a meta-analysis, the pooled sensitivity for localizing abnormal parathyroid glands in patients with de novo pHPT was 76%, PPV 93%.[93]

Scintigraphy

Sestamibi scintigraphy is a frequently used method for imaging abnormal parathyroid glands and is one of the first-line imaging methods in perHPT and recHPT. The most commonly used protocol includes the dual-phase method using sestamibi labeled with 99mTc. This technique is combined with single-photon emission computed tomography (SPECT) and hybrid imaging with both SPECT and computed tomography (SPECT/CT) to increase sensitivity by providing additional anatomical imaging. To evaluate ectopic parathyroids, imaging should be taken below the aortic arch.[87]

There are limited data on SPECT and SPECT/CT with dual phase method in patients with perHPT and rec HPT.[85]

Kluijfhout et al.[89] reported sensitivity with sestamibi scintigraphy combined with SPECT/CT as 74% and PPV as 86% before reoperative parathyroidectomy for perHPT.

In another study, the highest PPV among non-invasive imaging methods in patients with perHPT and recHPT was reported with sestamibi combined with SPECT (96%), and PPV was reported to be 100% in mediastinal parathyroid adenomas.[94]

Patients with the previous exploration may have impaired anatomy, altered perfusion of the remaining glands, and impaired 99mTc uptake, all of which reduce the accuracy of sestamibi scintigraphy in the reoperative setting.[87] Especially in patients with secondary perHPT and recHPT, the rate of proper localization of residual hyperactive glands with sestamibi scintigraphy combined with SPECT is significantly lower than in the initial imaging performed in patients with pHPT.[95]

In a multicenter study by Frey et al.[96], they found that secondary sestamibi scintigraphy (with planary or SPECT/CT) in patients with perHPT allowed imaging of new pathological glands in 50% of patients, secondary imaging confirmed surgical failure in 12% of patients, emphasizing that a second scintigraphy should be performed regardless of the initial imaging results.

Shin et al.[97] performed SPECT or SPECT/CT scintigraphic imaging with a combination of sestamibi and iodine-123 in patients with primary, secondary, and tertiary HPT who underwent reoperative parathyroidectomy for perHPT and recHPT. They reported the sensitivity as 74% with SPECT and 86% with SPECT/CT. The main limitations of scintigraphy are the relatively long time required for imaging and exposure to radiation.

The success of scintigraphic imaging, especially in localizing small parathyroid glands or multi-gland disease, and its anatomical resolution are quite limited. An experienced and high-volume specialist (radiologist or nuclear medicine specialist) is required for correct interpretation.[87]

The combination of USG and sestamibi scintigraphy (Planary or SPECT) before reoperative parathyroidectomy increases the localization of the pathological gland.[94,98]

Four-dimensional (4-D) CT

4D-CT consists of multiphase CT, which often uses non-contrast, arterial and delayed (venous) phases to detect changes in enhancement over time. Parathyroid adenomas show lower attenuation than normal thyroid tissue on non-contrast images, peak increase in arterial phase, and washout in delayed phase.[87]

4D-CT is an effective method for localizing the pathological gland, and the pooled sensitivity in reoperative cases is 81% (95% CI, 64%–98%).[99] The sensitivity of 4D-CT is significantly higher than both scintigraphy and USG in lateralizing recurrent cases (77.4%, 46%, and 38.5%, respectively).[92]

Kelly et al.[100] found that 4D-CT detected unilateral or bilateral disease with 95.8% accuracy in patients undergoing reexploration. They reported that unlike USG and sestamibi scintigraphy, the accuracy of 4D-CT did not differ significantly between primary and reoperative patients.

The accuracy of 4D-CT in MGD is variable. It is reported that it can predict multi-gland disease 80-88% accurately in reoperative cases.[101,102] However, the sensitivity is lower in MGD than in solitary gland disease, and 57–75% of the lesions missed in 4D-CT are multi-gland disease.[92,103]

Incompatible pre-operative first-stage imaging or inability to localize the parathyroid gland is among the risk factors for reoperation. The sensitivity of 4D-CT is 73% and PPV 87% in patients in whom USG and scintigraphy are incompatible.[104]

In patients with negative USG and scintigraphy, the sensitivity of 4D-CT was reported to be 89% and PPV 74%, and it was revealed that the rate of unilateral exploration or focused surgery and success of surgery were increased compared to those who did not undergo 4D-CT.[105]

Multiple gland disease, parathyroid glands smaller than 10 mm, inferiorly located parathyroid glands, or patients with concomitant thyroid pathology are features associated with discordant imaging on 4D-CT.[106] In addition, the important disadvantages of 4D-CT are the use of ionizing radiation, iodinated contrast, and the need for an experienced radiologist to interpret the method correctly.[87]

4D-CT has many strength that make it well suited for reoperative surgery. Due to its very high spatial resolution, it provides critical information that can guide surgical reexploration by identifying important anatomical landmarks and structures surrounding diseased glands. It requires short imaging times and can localize ectopic adenomas. 4D-CT is an accurate and informative modality in perHPT and recHPT due to its many features.[87]

Dynamic 4D Magnetic Resonance Imaging (Dynamic 4D-MRI Imaging)

MRI is a modality that can sometimes be used in the case of negative or incompatible primary imaging modalities, or in pre-operative localization in perHPT and recHPT. The sensitivity of conventional MRI is similar to that of USG and MIBI. Today, dynamic 4D-MRI methods similar to dynamic CT are used as the second stage examination.[89,107]

Dynamic 4D-MRI is a high spatial and temporal resolution T1-weighted sequence with multi-phase (4-phase) contrast with fat suppression. Like 4D-CT, dynamic MRI uses the hypervascular behavior of parathyroid adenomas to provide quantitative perfusion parameters that allow discrimination between pathological parathyroid glands, lymph nodes, and thyroid tissue. On dynamic MRI, parathyroid adenomas exhibit significantly faster arterial enhancement and higher wash-in and higher washout properties compared to lymph nodes and thyroid tissue. Multiparametric MR perfusion can separate parathyroid adenoma from thyroid tissue and lymph node with 96% accuracy.[108]

Becker et al.[109] reported that 4D dynamic MRI can accurately localize single gland disease 92% and multi-gland disease 74%, which is superior to 4D-CT studies.

The number of studies on dynamic MRI before secondary interventions is limited. Kluijfhout et al.[89] determined that the sensitivity and PPV of conventional MRI in patients undergoing reoperative parathyroid surgery were 82% and 85%, respectively, and the sensitivity and PPV increased to 90% with dynamic MRI.

In another study, it was revealed that while the sensitivity was 63% with conventional MRI before reoperative surgery, it increased to 93% with dynamic MRI angiography.[89] MRI does not contain ionizing radiation and its sensitivity does not decrease in the presence of concomitant thyroid pathology.[89] However, dynamic 4D-MRI is more costly, difficult to access, and time consuming than 4D-CT, and may not be suitable as a first-line imaging modality. Despite the high sensitivity of dynamic MRI to localize reoperative lesions, more research is needed before definitively determining the role of MRI in patients with perHPT or recHPT.[87]

Today, it can be used in cases where it can be preferred instead of 4D-CT in patients who need to avoid radiation.

Positron Emission Tomography (PET) and PET/CT

PET is an advanced nuclear medicine imaging method that provides functional and metabolic information with high quality imaging. PET/CT is combined with CT images for improved anatomical localizations. PET imaging has improved sensitivity and spatial resolution over SPECT imaging. PET can allow detection of very small pathological glands, providing better accuracy and clearer images with faster acquisition compared to SPECT. Similarly, 18F-fluorocholine (18F-FCH) PET/CT has higher spatial resolution, lower radiation load (2.8 mSv), and shorter total run time (38 mSv) than SPECT/CT (11.8 mSv, total run time 120 min).[87,110]

While previous studies have suggested 11C-methionine as a promising agent in PET imaging for patients with primary HPT, more recent studies have focused on choline for its increased accuracy. 11C-choline and FCH have been reported to be useful in imaging parathyroid hyperplasia and adenomas. 11C requires an in situ cyclotron as it has a half-life of only 20 min. Therefore, FCH is a more practical PET tracer for potential commercial use.[110]

In a meta-analysis comparing the diagnostic relevance of 18F-Florocholin and 11C-methionine, the sensitivity of fluorocholine was higher (92% vs. 80%, p<0.01), and its PPV (94% vs. 95%, p=0.99) was similar.[111]

In a meta-analysis in which 18 FCH-PET studies were evaluated, for each patient sensitivity was 95% (95% CI: 92–97%), PPV was 97% (95% CI: 95–98%), and detection rate was 91% (95% CI: 87–94%), pooled sensitivity for each lesion was 92% (95% CI: 88–96), and PPV was 92% (95% CI: 89–95).[112]

In another systemic review including eleven studies, the pooled detection rate on FCH-PET/CT was 97% per patient and 94% per lesion.[113]

The number of studies on FCH-PET in patients with perHPT and recHPT is still limited. Positive 11C-choline PET findings were detected in 33 out of 43 patients whose scintigraphy and 4D-CT images were negative. About 72% of 25 operated patients were reoperative cases, and surgical cure was achieved in 20 cases (80%). The sensitivity of 11C-cholin PET/CT was 64%, and its PPV was 72%. There were 20% false positives due to normal parathyroid, lymph node and 1 recurrent laryngeal nerve neuroma.[114]

Latge et al.[115] investigated the efficacy of FCH-PET/CT and 4D-CT in 43 patients with perHPT and recHPT, finding the sensitivity as 95% and 70%, detection rate as 88% and 63%, respectively, and FCH-PET/CT was found to be superior. There was no increase in sensitivity and detection rate when the two techniques were combined. Investigators recommended FCH-PET/CT in patients with perHPT and rec HPT and reported that 4D-CT could be performed in the presence of suspicious lesions in this examination.

Grimaldi et al.[116] reported that all pathological lesions were localized with FCH-PET/CT in 6 patients with perHPT and recHPT.

In a study in which 29 patients with perHPT and recHPT were evaluated, the sensitivity of FCH-PET and 4D-CT for each lesion was 96% and 75%, PPV 77% and 80%, sensitivity for each patient 85% and 63%, respectively. The authors emphasized that while FCH-PET/CT is a promising method in patients to be reoperated, 4D-CT is also a confirmatory imaging method.[117]

Christakis et al.[118] found that in addition to detecting ectopic and difficult parathyroid lesions, FCH-PET/CT in patients with perHPT and recHPT in whom conventional imaging was negative, the arterial phase of CT made a significant contribution to the differentiation of true positive lesions and false positive (such as lymph nodes) lesions.

Evangelista et al.[119], in a systemic review of 23 studies involving 1112 patients, compared FCH-PET plus CT or MRI imaging with conventional anatomical and functional methods in the literature. They found FCH-PET/CT more accurate than (USG) and 99mTc-sestamibi SPECT. PET/MRI seemed more accurate than MRI alone in detecting benign parathyroid lesions. Therefore, the authors stated that FCH-PET/CT may be a reliable tool in HPT for both primary and secondary surgery.

No distinction was made between imaging protocols, which varied across studies. With the FCH-PET/CT or FCH-PET/MRI acquisition protocols, there are no technical limitations preventing the use of conventional 4D imaging approaches simultaneously in CT and MRI. Therefore, these methods can be combined as needed.[119] In addition, hybrid PET/CT performed with the use of both 18F-FDG and 18F-FCH has been reported to be useful in assessing parathyroid carcinoma in terms of primary disease, metastases, and recurrence.[120] However, it is not uncommon for FCH-PET/CT to fail to detect hyperplastic glands and ectopic adenomas, which are common causes of reoperation.[87]

Today, FCH-PET/CT is expensive and not available everywhere in every center.

Invasive Localization Methods

Invasive examinations can be performed when suspicious, inconsistent results are obtained in noninvasive imaging methods, or in patients where no pathological lesion can be detected. Nowadays, invasive examinations are rarely needed in parallel with the developments in noninvasive imaging methods.

Invasive techniques can cause complications such as hematoma, contrast-enhanced nephropathy, and cerebrovascular infarction. In addition, although contrast-enhanced CT is a noninvasive method, anaphylaxis may occur due to an allergic reaction to iodinated contrast material during contrast-enhanced imaging.[121]

Parathormone Measurement with Bilateral Jugular Vein Sampling

This method is to measure PTH by taking blood from the right and left internal jugular veins from the lowest level of the neck as much as possible under USG for the purpose of lateralization of the pathological gland. A test is considered positive if the PTH is 10% higher on one side than the other. In cases with perHPT or recHPT, it may be considered before or when more complicated techniques such as selective venous sampling (SVS) cannot be performed.[122]

SVS

In SVS, increased PTH levels are tried to obtain by examining PTH levels at the blood taken from the superior vena cava, bilateral brachiocephalic vein, internal jugular vein, vertebral vein, thymic vein, superior, middle, and inferior

thyroid veins from the points where they drain into the internal jugular vein by angiography through a catheter entering the femoral vein.[121]

In a meta-analysis evaluating 12 studies, pooled sensitivity, specificity, and positive likelihood ratio for SVS were found to be 74%, 41%, and 1.55, respectively.[123]

Parathyroid Arteriography

Parathyroid arteriography is both a complementary and an adjunct technique to the SVS. Contrast infusion near the thyrocervical trunk can demonstrate abnormal parathyroid tissue as a hypervascular blush, can guide operative exploration and confirm a gradient revealed by the SVS. Arteriography may be particularly valuable in patients with prior neck surgery where the usual parathyroid venous drainage can be profoundly altered. When a blush is visualized, the false positive rate is approximately 9%.[124,125]

Powell et al.[94] reported that arteriography was the best method to localize the pathological gland before pre-operative parathyroid surgery and the PPV was 92%.

Selective arteriography has been shown to contribute better localization over venous sampling when combined with SVS.[126] This technique is operator dependent and requires high experience.

Fine Needle Aspiration Biopsy with Guidance of Imaging Studies

Suspicious lesions can be confirmed by USG or CT-guided fine-needle aspiration biopsy (FNAB).[127]

It is not a routine recommended procedure before the first operation. It may contribute to the patient before the secondary intervention. It can make an important contribution to the differentiation of intrathyroidal parathyroid adenomas from nodules. USG-guided FNAB can be performed in patients with suspicious lesions on USG and who cannot undergo additional imaging (such as pregnancy) due to the risk of radiation.[128]

PTH washout in FNAB increases the sensitivity of the procedure. Only 31% parathyroid cells could be identified by FNAB cytology.[129]

The FNAB PTH washout study is more reliable than cytology, with a sensitivity of 70–100% and a specificity of 75–100%. Despite these results, the FNAB PTH washout study is still not well standardized.[130]

Conclusion

The only definitive treatment of pHPT is surgery. Surgical failure is the most common complication of this treatment today. perHPT is defined as persistence of hypercalcemia after parathyroidectomy or recurrence of hypercalcemia within the first 6 months, and recurrence of hypercalcemia after a normocalcemic period of more than 6 months is defined as recHPT. In the pre-operative evaluation, the initial diagnosis of pHPT and the diagnosis of perHPT or rec HPT should be confirmed in patients who are evaluated with a pre-diagnosis (suspect) of perHPT and recHPT. Localization studies with preoperative imaging methods should be performed in all patients with perHPT and recHPT with a confirmed diagnosis and surgical indication. Invasive examinations can rarely be performed in patients in whom suspicious, incompatible or pathological lesion cannot be detected in noninvasive imaging methods.

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