Revision Parathyroidectomy

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Goals

The objective of this chapter is to discuss the evaluation of recurrent and persistent hyperparathyroidism, including definition, etiology, diagnosis, indications for reoperation, preoperative planning, localization studies, and operative strategies.

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient setting. As a result of excessive and autonomous parathyroid hormone production, the majority of cases are sporadic, with approximately 80–85% of patients presenting with a single-adenoma, multiglandular hyperplasia in 10–15%, double adenoma in 2–5%, and parathyroid cancer in <1%.

PHPT is biochemically diagnosed, and a surgical cure rate can be achieved in up to 95–97% of cases in nonfamilial, nonmalignant cases. Postoperatively, patients are considered cured if they maintain normal calcium levels 6 months after parathyroidectomy. However, 1–10% of patients may develop persistent or recurrent disease after initial operation, having been reported as high as 30% in some series [1–6]. If hyperparathyroidism does not resolve postoperatively or recurs within a 6-month period the patient is considered to have persistent disease. If a patient has a presumed postoperative cure and hyperparathyroidism recurs after 6 months, the patient is considered to have recurrent disease. Persistent PHPT is more common than recurrent, and is usually the result of a missed adenoma by a less than experienced surgeon.

Etiology

The reasons for recurrent or persistent disease can be associated with multiple factors, including failure to find abnormal adenoma, inadequate surgical resection, and inaccurate diagnosis (failure to find, failure to treat, failure to diagnose). In addition, studies have demonstrated that a surgeon's experience can have a major impact on operative success rate [2, 7–9]. Moreover, the risk of recurrent or persistent disease is increased in patients with multigland disease, familiar syndromes, and parathyroid carcinoma [7].

Missed Adenoma

The majority of patients reviewed in literature for reoperative hyperparathyroidism were discovered to have a missed adenoma as the most com-

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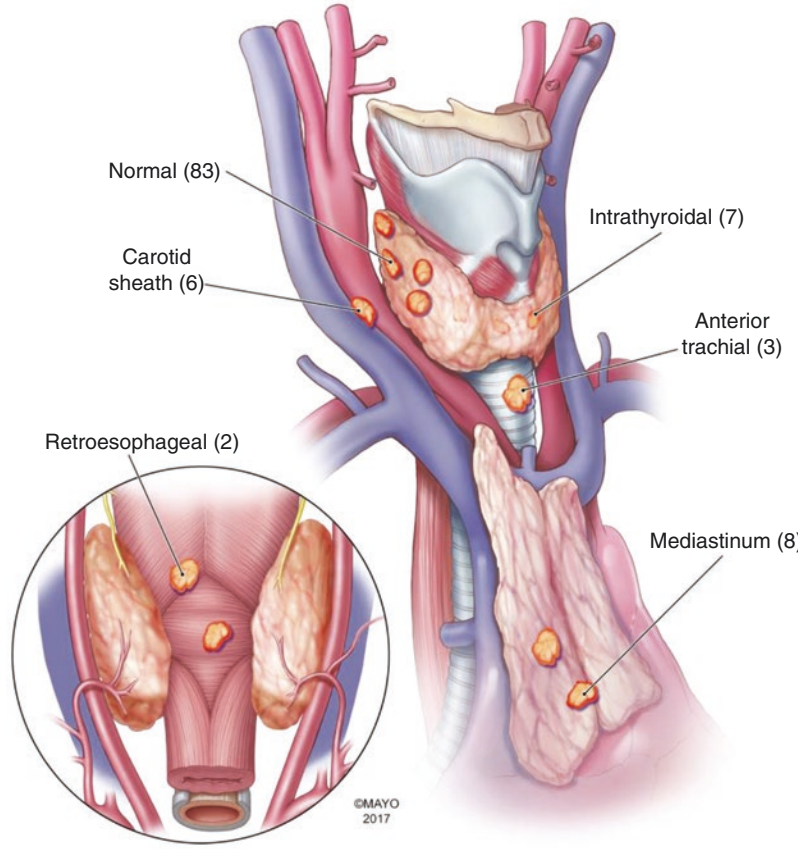

Fig. 23.1 Preoperative parathyroid surgeries at Mayo. Number and anatomic location of abnormal glands removed at preoperative parathyroid surgery (Thompson [1], image modified)

mon reason for both persistent and recurrent diseases [9, 10]. During reoperation, the majority of adenomas have been found in their expected anatomic location, with the inferior parathyroid gland contributing to more variability [1, 9, 11]. If a parathyroid is not in the expected location, it is considered ectopic. Ectopic adenomas vary by location and contribute to persistent or recurrent PHPT in reoperative cases [1, 2, 7, 8] (Fig. 23.1). Most common ectopic locations are the thymus (17–26%) and paraesophageal regions (28%), followed by mediastinum (27%), intrathyroidal (4–10%), pterygopalatine fossa (2–9%), and within the carotid sheath (3.6–9%) [1, 7, 9, 12, 13]. Uncommon locations include the aortopulmonary window (5%), and anterior to the trachea [7].

Multiple Adenomas

The incidence of multiple adenomas ranges from 2 to 12% in various studies [14]. Failure to identify multiple adenomas on preoperative imaging may lead to focused unilateral exploration instead of the warranted bilateral exploration, which can lead to inadequate tissue resection and postoperative hyperparathyroidism (HPT). In addition, the recurrence rate of HPT is higher among patients with double adenoma compared to single adenoma [6], suggesting the possibility of early asymmetric hyperplasia. The use of intraoperative PTH with preoperative ultrasound and sestamibi may assist in detecting double adenomas and ensuring that adequate resection is performed [14].

Moreover, supernumerary glands have been detected in up to 13% of random autopsies, and can occur in a small subset of cases, especially in patients with MEN syndromes and up to 30% of patients with renal hyperparathyroidism [15, 16]. If not detected on preoperative imaging this can lead to operative failure especially in the presence of hyperplasia or cancer.

Parathyroid Hyperplasia

Parathyroid hyperplasia occurs in approximately 15% of patients with PHPT; however, it is responsible for approximately 38% of reoperations [7, 12]. This suggests incomplete resection at the initial operation with continued growth of the remaining hyperplasic tissue. Failure is therefore attributed to inadequate tissue resection of tissue and failure to diagnose multigland hyperplasia preoperatively or intraoperatively. The usual treatment involves bilateral exploration with subtotal or total parathyroidectomy with autotransplantation.

Parathyroid Carcinoma

Rare causes of recurrent or persistent disease include parathyroid carcinoma, which accounts for 0.4–4% of PHPT cases [17, 18]. The majority of recurrent disease is within the neck; however, metastases to lungs and bones do occur [19]. Suspicion of parathyroid carcinoma should be considered preoperatively by a thorough history and physical examination, including excessively high preoperative calcium and PTH levels, a palpable mass, and positive family history of parathyroid carcinoma. However, the majority of patients with parathyroid cancer are not diagnosed preoperatively [18]. When parathyroid carcinoma is recognized, most authors recommend en bloc resection (parathyroid, thyroid, RLN, and lymph nodes), although up to 78% of patients were treated with simple parathyroidectomy in one study [18]. Overall, given the high local recurrence rate, recognition of parathyroid carcinoma is imperative. Parathyroid carcinoma requires en bloc resection of the tumor along with other involved structures as indicated.

Local Recurrence

Local recurrence of disease can be seen in the context of malignant disease or benign parathyromatosis. The most common is recurrence due to hypertrophy or hyperplasia of small benign nodules of parathyroid tissue at previous resection sites due to tumor spillage. It is imperative to ensure delicate handling of the parathyroid gland and avoid capsular rupture [20].

Incorrect Diagnosis

Operating for the incorrect diagnosis is another cause for failure [2]. One commonly reported reason is benign familial hypocalciuric hypercalcemia (FHH) [21]. This hereditary disease should be suspected in patients with inappropriately normal PTH concentration in the presence of mild hypercalcemia, and a positive family history. These patients have had lifelong hypercalcemia. It is important to distinguish FHH from PHPT because FHH does not require parathyroidectomy. Testing for the calcium-sensing receptor mutation is diagnostic. Other causes for incorrect diagnosis include the use of lithium or thiazide diuretics.

Preoperative Diagnosis and Planning

When patients present for evaluation of persistent or recurrent hyperparathyroidism, it is imperative to review the patient's old records and reestablish the initial diagnosis. Patients should have a thorough history, physical examination, and repeat biochemical confirmation, including serum calcium, PTH, creatinine, and 24-h urine to rule out FHH. Once the diagnosis has been established, the indications for reoperation should be guided by the current NIH guidelines [22]. Reoperative success is reduced as compared to first-time

operation with both increased morbidity and cost. Therefore, the risks associated with reoperation have to be weighed. These risks include higher incidence of recurrent laryngeal nerve injury, permanent hypoparathyroidism, and increased rates of failure to cure [7, 13, 23, 24].

Once the diagnosis and indication for reoperation have been established, it is important to review prior operative notes to determine the extent of surgery, how many parathyroid glands were identified and removed, if the recurrent laryngeal nerve (RLN) was visualized, and the intraoperative PTH values if available. If the operative report is unclear, attempts should be made to contact the operative surgeon. Also, the pathology report and slides need to be reviewed to verify the histopathology. Evaluation of concordance with previous localization studies is very helpful.

Given the increased risk of injury to the recurrent laryngeal nerve with reoperation, preoperative vocal cord check should be performed in all cases considered for reoperation. Studies have shown that patients with recurrent laryngeal nerve palsy have reconstitution of function in the majority of cases at 6 months, and up to 2 years [25]. Therefore, in a patient with a known vocal cord palsy from prior surgery, up to 6 months should be allowed for recovery before considering reoperation. Additional injury to the contralateral recurrent laryngeal nerve can result in greater morbidity, including the need for tracheostomy. The status of RLN may, therefore, impact the decision-making process and should be weighed heavily.

Localization Studies

Multiple studies have shown that preoperative localization improves outcomes, reduces morbidity, decreases operative time, and is essential when treating recurrent or persistent hyperparathyroidism [12, 26]. Increased failure rates can be seen in patients with non-localizing studies [27]. In general, localization studies can be divided into two categories: noninvasive and invasive. Noninvasive studies should be done before considering invasive studies. Typically, at least two or more concordant imaging studies should be obtained prior to proceeding with a reoperation [5]. Currently, the optimal imaging modality or combinations thereof have not been established [28].

Noninvasive Localization

Sestamibi Scintigraphy

Sestamibi parathyroid scintigraphy has been established as cost effective, reliable, and the first choice for localization of abnormal parathyroid tissue [29, 30]. It utilizes technetium-99m-methoxyisobutylisonitrile (99mTc sestamibi), which is absorbed and retained longer by the parathyroid tissue than thyroid [31]. Studies have demonstrated 64–88% sensitivity for detecting a single adenoma and 98.9% specificity [31–33]. However, 99mTc sestamibi has been associated with false-negative rates up to 25%, which is more common in patients with multigland disease, small adenomas, nodular thyroid disease, and normocalcemia [31]. At our institution, we utilize I123 in addition to sestamibi, performing a subtraction scan along with SPECT and planar imaging, providing better accuracy (Figs. 23.2 and 23.3).

Ultrasound

Ultrasonography is a relatively inexpensive, noninvasive, readily available localization tool with good sensitivity when done by experienced operators, and can be used in reoperative cases to localize a parathyroid adenoma (Fig. 23.4) [1]. The sensitivity of ultrasound for detecting a single adenoma ranges from 61 to 92% of patients [32]. The sensitivity can be increased with concurrent fine-needle aspiration for cytology and washout PTH levels. Studies have shown that a combination of neck ultrasound and 99mTC sestamibi increases sensitivity to greater than 90% for localizing an adenoma [32]. However, ultrasound is limited because it is operator dependent, with a sensitivity range of 33–92%, and has reduced success in detecting ectopic adenomas,

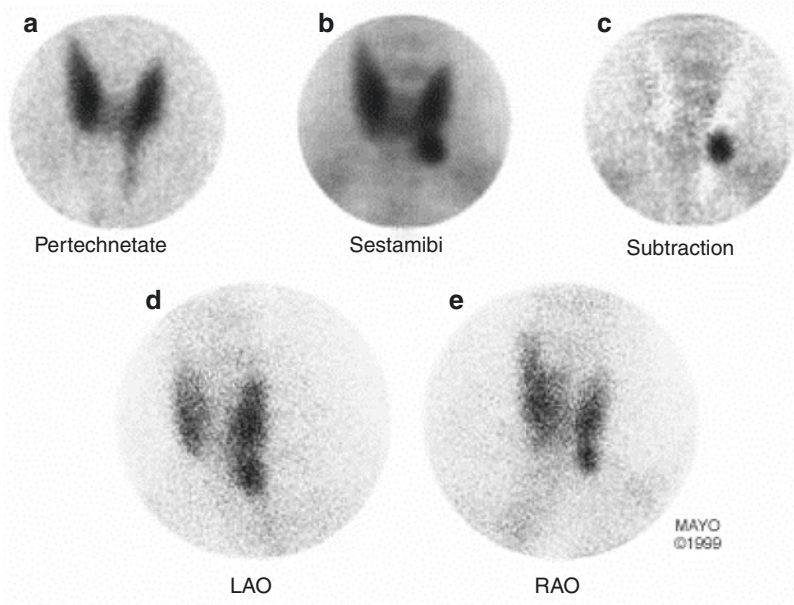

Fig. 23.2 Sestamibi scan demonstrating left inferior parathyroid gland adenoma on subtraction view (**c**). The left and right oblique images are concordant with a left inferior adenoma

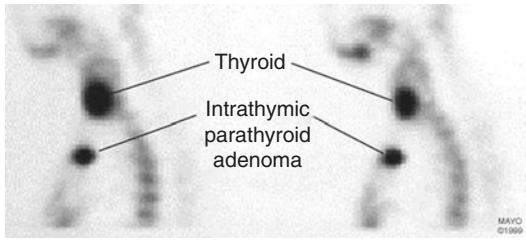

Fig. 23.3 Sestamibi with sagittal SEPCT shows an intrathymic left inferior parathyroid adenoma in the anterior mediastinum

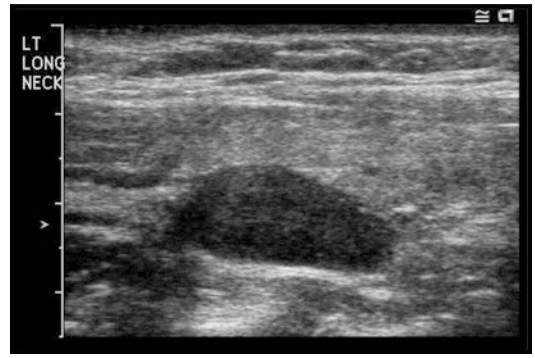

Fig. 23.4 Neck ultrasound demonstrating single parathyroid adenoma

especially in the presence of thyroid nodules and those within the mediastinum [32, 34].

Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) can be a useful adjunct to sestamibi, especially in detecting ectopic adenomas. Both modalities can be combined for increased sensitivity [31, 35]. In patients undergoing reoperation, sensitivity can be improved from 79.5 to 87% for adenoma detection [31]. In addition, SPECT provides higher resolution images and additional tomography aids in mapping the relationship of the abnormal parathyroid to the surrounding structures, including trachea, esophagus, thyroid, thymus, and carotid artery. However, SPECT imaging can still fall short with multiglandular disease [31].

Four-Dimensional Computed Tomography

4D CT can be helpful when there are equivocal or negative conventional imaging findings [36]. One study looked at 45 patients undergoing reoperative parathyroidectomy and found that 4D CT had an 88% sensitivity compared to 54% with sestamibi [37]. The main disadvantage of this test is the increased radiation exposure and contrast load.

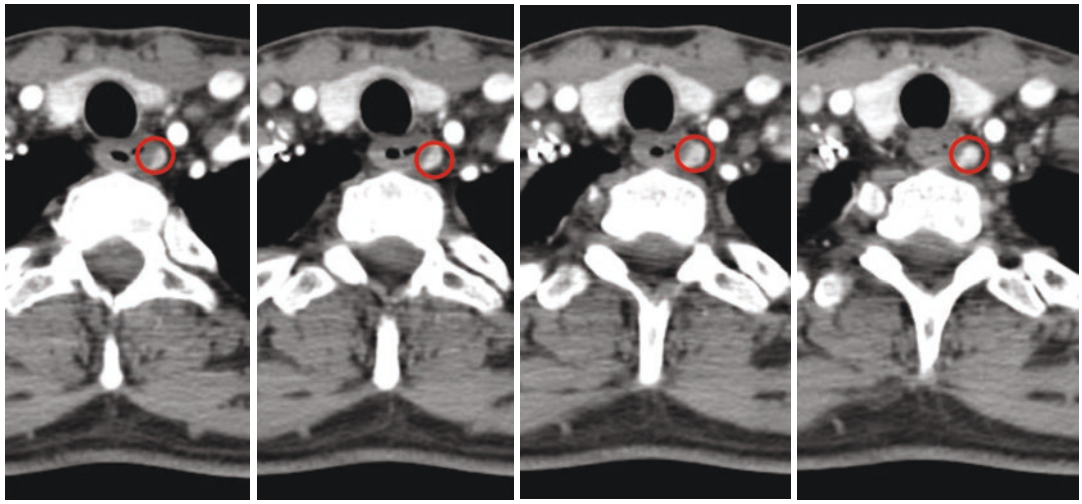

Fig. 23.5 CT scan demonstrating a left parathyroid adenoma along the left posterolateral border of the cervical esophagus (arterial phase, 2 mm slices, adenoma measured 8 × 4 × 14 mm)

Computed Tomography

Computed tomography has been shown to be helpful in identifying ectopic adenomas (Fig. 23.5), particularly in the mediastinum, with an overall sensitivity from 46 to 87%.

Magnetic Resonance Imaging

The role of magnetic resonance imaging (MRI) is very similar to that of a CT scan. Magnetic resonance has a reported sensitivity and positive predictive value of 79.9% and 84.7%, respectively. Moreover, addition of MRI to sestamibi and ultrasound has been shown to increase sensitivity to 91.5% [38]. The drawbacks of MRI include higher cost, patient tolerance, and availability.

Invasive Localization

Invasive localization studies are indicated when noninvasive studies have failed to reveal the pathology. Since there is increased risk associated with an invasive procedure, these should be reserved for select patients who have biochemically confirmed hyperparathyroidism with equivocal or negative imaging studies that clearly need reoperation. Selective venous sampling is the most commonly utilized invasive study. However, with advent of new imaging modalities and improvement in radiology techniques, this is indicated far less frequently. Selective venous sampling of cervical and mediastinal veins can help focus the extent of dissection when a gradient is identified in relation to the value in a peripheral vein.

Selective Venous Sampling

This modality is the most common invasive technique utilized for localizing parathyroid glands; however, it is time consuming and expensive [39]. It requires catheterization of perithyroidal and mediastinal veins under fluoroscopic guidance with subsequent measurement of PTH hormone levels. These levels are then analyzed and compared to the contralateral neck and mediastinal samples as well as a peripheral sample to determine the region involved. More recently, interventionalist can obtain samples from smaller venous branches to increase sensitivity, with the sampling method referred to as "super selective" venous sampling (sSVS) [39]. The adenoma will typically be localized in an area with twice the

PTH values compared to peripheral levels. In a single-institutional study, sensitivity and positive predictive values of 86% and 93%, respectively, were achieved using sSVS [39]. Prior surgery and subsequent venous remodeling, however, can negatively impact the results [39].

Nonoperative Ablation Therapies

Angiographic Embolization

Angiographic catheter ablation has been reported for some mediastinal glands with reasonable outcomes and cure rates of up to 60% [40]. It is especially useful in patients with previously failed neck surgery and the risk of increased operative morbidity. The technique involves insertion of catheter in the feeding artery branch and chemically ablating the adenoma. Contrast media and ethanol have been reported [40]. Peripheral nerve symptoms, bradycardia, and renal failure have been seen. In addition, there is a risk of possible embolic complications [40].

Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) has been reported as a treatment modality in patients with both primary and secondary hyperparathyroidism, either with remnant or graft-dependent tissue or in those at high surgical risk [41]. Following washout confirmation, the therapy involves insertion of an ultrasound-guided needle and injection of 95% ethanol into the target parathyroid tissue. Additional treatment sessions can be performed as needed [41, 42]. Complications of REI include pain, hematoma, transient laryngeal nerve palsy, as well as permanent palsy [42, 43]. The overall success has been reported anywhere from 35 to 80% [42]. Ethanol injection has been associated with fibrosis and can negatively impact subsequent reoperations if ever indicated [43]. This approach should only be used in select cases.

Operative Management

Reoperation for persistent or recurrent hyperparathyroidism can be successful in 89–95% of cases with proper preoperative localization studies and a focused approach [12, 44]. It is important to plan the reoperation based on localization studies, previous surgical dissection, and knowledge of parathyroid embryology. The operative approach is tailored according to the location of disease, neck versus mediastinum, and the pathology, solitary versus multigland. Intraoperative laryngeal nerve monitoring is recommended in hopes of reducing the risk of RLN injury. Patients should only be considered for reoperation when NIH guidelines are met or the patient has symptomatic disease (kidney stones, fragility fractures, pancreatitis, hypercalcemic crisis).

Focused Neck Exploration

The most common reason for revision parathyroidectomy is a missed adenoma. If confirmed on preoperative evaluation, the previous neck incision can be used in most cases [9, 10, 12]. Often, the parathyroid glands can be approached through either a central or a lateral neck approach. Utilizing the central approach, the dissection is carried out through the previously operated field with the disadvantage of having to deal with a scarred field. The central approach usually provides the easiest route to the inferior parathyroid glands, especially if intrathymic. The lateral approach is best suited to access the superior parathyroid glands. The lateral approach can be done using the previous cervical incision. Dissection is carried out lateral to the median raphe, between the strap muscles and the anterior border of sternocleidomastoid muscle. The strap muscles are retracted medially and the sternocleidomastoid laterally. The omohyoid muscle can be divided to gain exposure to the carotid sheath, which is retracted laterally to expose to the tracheoesophageal groove (Fig. 23.6a, b). The recurrent laryngeal nerve should be identified prior to gland removal. In case of an undescended parathyroid adenoma, a direct approach can be

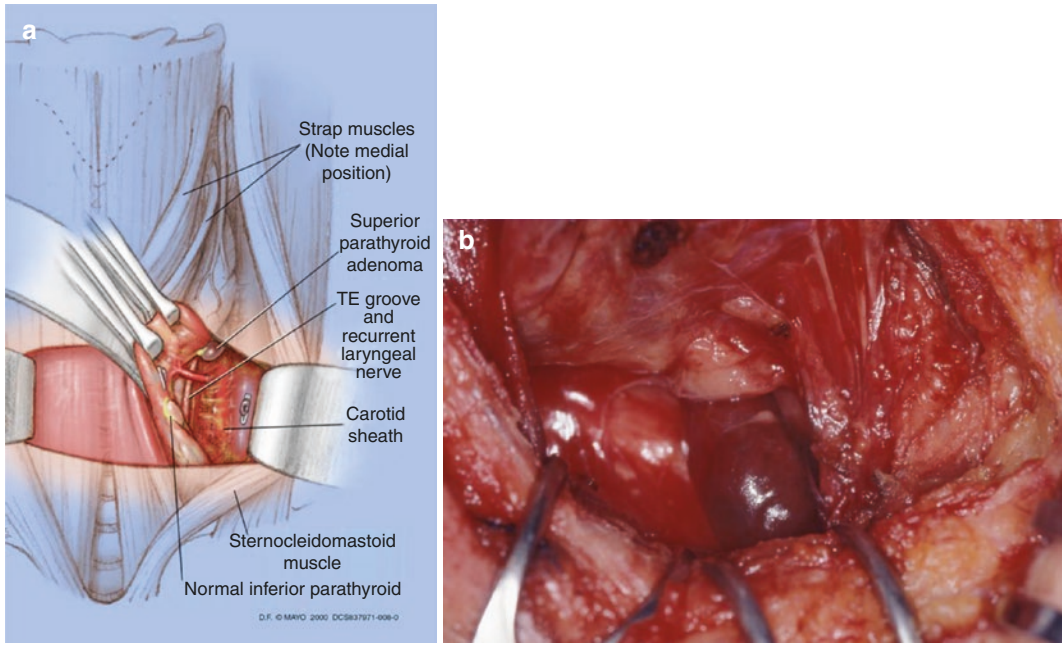

Fig. 23.6 (**a**) Reoperation for a superior parathyroid adenoma. Lateral approach is used using the previous collar incision, developing a plane between the anterior border or sternocleidomastoid and lateral border of strap muscles. (**b**) Lateral approach for a reoperative case showing a superior adenoma located in the tracheoesophageal groove

used (Fig. 23.7). This can be achieved using a transverse incision either over the carotid bifurcation or along the anterior border of sternocleidomastoid. The hypoglossal nerve courses deep to the adenoma and should be carefully avoided during dissection.

Bilateral Neck Exploration

Multigland parathyroid hyperplasia is responsible for hyperparathyroidism in approximately 15% of cases [7, 12]. If preoperative evaluation and workup suggest multiglandular disease, the goal with reoperation is to remove most of the residual disease. The surgical options include bilateral exploration or directed approach with either subtotal or total parathyroidectomy with autotransplantation or cryopreservation. Autotransplantation can be performed subcutaneously in the anterior chest wall or intramuscularly in the forearm brachioradialis muscle. The advantage of the subcutaneous route is that the parathyroid tissue can be removed at bedside the day after surgery if PTH levels indicate normal functioning tissue in the neck.

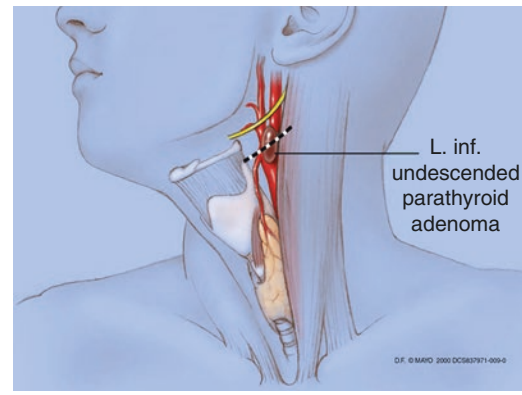

Fig. 23.7 Shows an undescended parathyroid adenoma anterior to the carotid bifurcation

Mediastinal Disease

The rate of mediastinal adenomas accounts for up to 27% of reoperative cases [7, 9, 12, 13]. In most instances, these represent inferior parathy-

roid glands that have descended into the chest during the embryologic development. In one series, they evaluated 38 patients that underwent revision parathyroidectomy via median sternotomy for parathyroid adenomas [45]. In those patients 47% of the adenomas were located in the thymus, in 21% it was found in the anterior mediastinum, 24% para-aortic, and 5% pericardial [45]. The approach to mediastinal disease can be based on the relationship to the aortic arch. When the adenoma is located above the aortic arch, it can generally be approach through the previous collar incision. If it is located below the aortic arch and deep in the mediastinum, a median sternotomy either total or partial may be required [1, 3, 9, 12]. More recently, minimally invasive techniques for ectopic mediastinal parathyroidectomy have been reported. The techniques utilized include video and robotic assisted thoracoscopy, the transcervical approach with a Cooper retractor, and mediastinoscopy [46]. A retrospective review showed comparable outcomes between minimally invasive and open techniques, but with significantly shorter hospital stays for minimally invasive approaches [46].

Intraoperative Adjuncts

There are multiple intraoperative adjuncts that can be utilized to help locate the adenoma. These adjuncts include methylene blue injection, intraoperative ultrasound, IOPTH, radioguided sestamibi scanning, bilateral jugular venous sampling, and frozen section. However, the majority of patients should have preoperative localization with two or more concordant studies before proceeding with reoperation, thus avoiding the need for some of these techniques. Intravenous methylene blue injection has been reported as an adjunct to localize parathyroid glands intraoperatively [47]. However, it has untoward side effects, including neurotoxic sequelae, pseudocyanosis, pseudohypoxia, and temporary urine discoloration [47]. The efficacy of this adjunct in the context of other techniques has not been proven [47]. However, we do find that the most useful adjuncts are intraoperative PTH and frozen section. Frozen section is useful when there is uncertainty regarding tissue removal. If intraoperative frozen section is not available, intraoperative specimen FNA with washout IOPTH has been reported as a possible alternative.

Autotransplantation and Cryopreservation

One of the most common complications after a parathyroidectomy is hypocalcemia, and in most instances this is a transient phenomenon; however a small subset of patients develop permanent hypocalcemia and require long-term calcium and vitamin D supplementation [48]. The decision has to be made intraoperatively if autotransplantation should be carried out. If a patient had a total parathyroidectomy or if there is a question of remaining parathyroid tissue, autotransplantation should be performed. Autotransplanted parathyroid tissue is successful in reestablishing meaningful function in approximately 80% of cases when performed at the time of re-exploration.

Cryopreservation should be considered in reoperative cases with the goal of providing a treatment option for patients experiencing permanent hypocalcemia after reoperation [49, 50]. However, the practice of cryopreservation has been decreasing as compared to the past, and is selectively practiced. In general it is considered costly and time consuming, with limited success [49, 51]. Cryopreserved parathyroid grafts can regain functionality in anywhere from 8 to 83% of reported cases [51, 52]. The success of function is dependent on multiple factors, including cryopreservation, thawing, and autotransplantation techniques [49, 51]. In one study, of all the patients who had cryopreserved tissue, only 1% required delayed autotransplantation. Thus, given the low utility of cryopreserved tissue and the variable success of delayed autotransplant, cryopreservation should be considered on a case-by-case basis as well as institutional availability. Subcutaneous autotransplantation is our preferred option (Fig. 23.8).

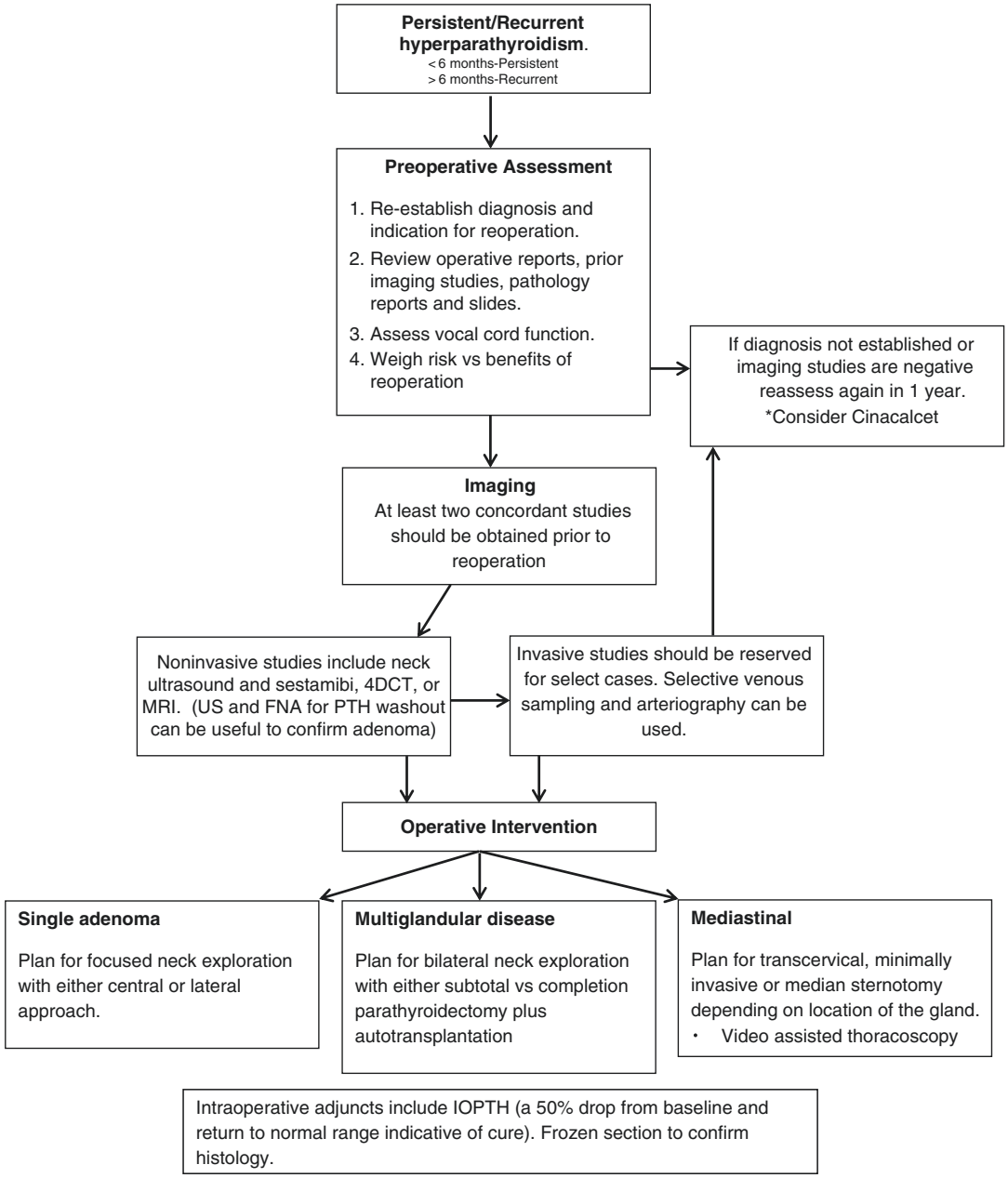

Fig. 23.8 Approach to patients with recurrent or persistent hyperparathyroidism

Conclusion

Persistent and recurrent hyperparathyroidism can occur after initial parathyroidectomy. The best practise is to avoid reoperation by optimizing the success of the initial operation. Reoperation is associated with increased morbidity and cost, and the decision to reoperate should be made by analyzing the patient's risk/benefit ratio. The patient record should be thoroughly reviewed and at least two concordant localizing studies should be obtained prior to proceeding with reoperation. There are multiple approaches available for reintervention and should be tailored for each patient.

Pearls

1. Most missed glands are in eutopic locations.
2. Avoid first-time failures. Experience is key.
3. Reoperations for PHPT are associated with a lower success rate and greater morbidity than with first-time operations.
4. Reestablish the diagnosis. Rule out FHH, thiazides, and lithium.
5. Weigh benefits of surgery versus risks.
6. Obtain at least two concordant localizing studies.

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