Chapter 2
Maximizing the Success of Initial Parathyroid Surgery

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Introduction

Parathyroid surgery has changed significantly over the past two decades. An operation that once required a large incision, exploration of all four glands, postoperative drainage, and inpatient management and was frequently associated with serious complications has largely been replaced by safe, minimally invasive, single-gland procedures that can be performed on an outpatient basis. This revolution has been facilitated by a number of factors. Improvements in the understanding of the complex relationships between parathyroid, renal, and bone physiology and routine annual evaluation of serum calcium levels have changed the classic presentation of hyperparathyroidism (HPT), allowing the disease to be diagnosed earlier and giving rise to a predominantly asymptomatic patient phenotype [1]. Advancements in preoperative imaging modalities make it possible to identify the single hyperfunctional gland in many cases, allowing targeted surgery with the assistance of adjuncts such as intraoperative ultrasound and endoscopic visualization [2]. Biochemical cure can be confirmed with intraoperative parathyroid hormone (IOPTH) assays, eliminating the need for four-gland exploration in most instances and reducing the risk of hypoparathyroidism [3].

Despite these advances, parathyroid surgery remains an endeavor fraught with potential pitfalls. The biochemical diagnosis may be uncertain or even incorrect in some patients. Preoperative imaging studies, required for targeted minimally invasive procedures, may be nonlocalizing, discordant, or misleading. Parathyroidectomy is unique in that locating the diseased organ(s) may be difficult, and grossly differentiating normal from abnormal tissue may challenge even the most experienced

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surgeons. Once identified, the amount of abnormal parathyroid tissue to be excised or preserved is somewhat subjective yet has a profound impact on the surgical outcome. Determining when to terminate the operation is also dependent on the experience of the surgeon, as there is no absolute operative finding or IOPTH threshold that guarantees a cure. This chapter addresses these challenges and describes specific steps to maximize the success of initial parathyroid surgery, in the hopes of avoiding the need for reoperation.

Preoperative Factors

Diagnostic Dilemmas

Establishing the diagnosis of HPT is the most important preoperative step in successful parathyroid surgery. While the diagnosis is usually straightforward in patients with high serum calcium and parathyroid hormone (PTH) levels, there are times when the diagnosis is less clear. Hypercalcemia is generally first discovered on a routine chemistry panel. Often, this prompts later assessment of an isolated PTH level, which may be "normal." This scenario is misleading because while serum calcium levels change relatively slowly over hours or days, the half-life of the PTH molecule is much shorter, only 3–5 min [4, 5]. Additionally, small changes in the serum calcium values may lead to relatively larger changes in the PTH level [6]. Because of these factors, the serum calcium and PTH levels should be obtained simultaneously to provide a clear picture of their relationship.

There are three occasions in which the calcium/PTH relationship may be confounding. The first of these is the scenario in which the serum calcium is elevated but the PTH level is within the normal range, generally around 40–60 pg/mL [7]. The PTH should be suppressed to very low levels in patients with non-parathyroid-mediated hypercalcemia [8]. These patients, as well as patients with concurrent high-normal calcium and high-normal PTH levels [9], are said to have "inappropriately normal" PTH levels, indicating that at least one parathyroid gland is not completely suppressed by the elevated calcium level and is therefore autonomously functioning.

Another atypical phenotype, normocalcemic hyperparathyroidism, has also been described. This condition is characterized by consistent elevations in the PTH level despite normal serum and ionized calcium levels after other causes of secondary HPT have been excluded [10]. Though this condition and its potential morbidity are still incompletely understood, approximately one quarter of patients with this condition may progress to overt hypercalcemic HPT [11]. Long-term observation is warranted in many of these patients, although surgery may be offered in selected patients, particularly if they develop symptoms of classical hyperparathyroidism or have positive imaging findings [10–12].

Familial hypocalciuric hypercalcemia (FHH) may also present a diagnostic dilemma. This rare autosomal dominant disorder is due to abnormalities in the calcium-sensing receptor (*CASR*) gene. The resultant abnormal calcium-sensing receptors expressed on parathyroid and renal cells have reduced sensitivity to calcium levels, resulting in mild hypercalcemia with normal to slightly elevated PTH levels and normal phosphate levels [13]. Preoperative screening with a 24 h urinary calcium measurement to determine the calcium/creatinine clearance ratio (CCCR) helps differentiate most patients with primary HPT (PHPT) from those with FHH. The urinary calcium level is normal to elevated in patients with PHPT, while it is low to low normal in those with FHH. The urine volume should be over 1000 mL for a 24 h period for the specimen to be considered adequate for interpretation. Additionally, the CCCR is greater than 0.02 in patients with PHPT and typically less than 0.01 in FHH. The diagnosis becomes less clear when the CCCR is between 0.01 and 0.02, so patients with a CCCR in this range may benefit from *CASR* mutational analysis to clearly establish the diagnosis [14, 15]. Securing the diagnosis is critical, as patients with FHH will not benefit from surgical intervention [16].

In addition to assessing serum calcium and PTH levels, other laboratory values may be of importance in securing the diagnosis, evaluating for confounding factors, and assessing for the presence of secondary hyperparathyroidism. An ionized calcium should be obtained. Both the ionized calcium and serum calcium are usually elevated in PHPT, but in some cases of PHPT, the ionized calcium will be elevated even though the serum calcium is normal [17]. Renal function (creatinine and glomerular filtration rate) and 25-OH vitamin D should be measured to evaluate for causes of secondary HPT. An albumin level helps determine the reliability of the serum calcium measurement and permits calculation of a corrected calcium level if the albumin is abnormal. Alkaline phosphatase is a useful marker of bone turnover, and assessment of serum phosphorous is valuable in patients with renal hyperparathyroidism or when the diagnosis of PHPT is unclear. Finally, temporarily halting medications associated with PTH elevations, such as lithium, bisphosphonates, and thiazide diuretics, may assist in securing the diagnosis [10].

Surgical Candidacy

Once the diagnosis of PHPT is confirmed, a decision must be made as to whether or not the patient needs an operation. Patients with symptomatic PHPT [18], severe renal hyperparathyroidism [19], and persistent tertiary hyperparathyroidism [20] should be referred for surgery if there are no contradictory medical comorbidities. Guidelines exist to help manage the majority of patients with PHPT who now present with “asymptomatic” disease [18, 21]. Some of these patients may be candidates for observation or medical therapy, but regardless of their symptoms (or lack thereof), every patient diagnosed with PHPT should be offered the option of surgical consultation, since surgery presents the only opportunity to cure the disease [21].

Preoperative Localization

Preoperative localization is a fundamental component of minimally invasive focused parathyroid surgery, but these studies must be applied appropriately and interpreted thoughtfully to maximize their clinical utility. The diagnosis of PHPT is biochemical, not radiologic, and the purpose of preoperative localization is only to plan and guide the operation [21]. Therefore, preoperative localization studies should only be obtained after confirming the diagnosis with laboratory testing and after deciding to proceed with surgery. Conversely, it is the patient and their disease that determine surgical candidacy, and surgical consultation should not be withheld if localization studies are negative.

Localization studies are most often performed with imaging modalities such as technetium-99 m (^{99m}Tc)-sestamibi (sestamibi) [22] and high-resolution ultrasound (US) [23]. More recently, four-dimensional computed tomography (CT) scanning has been employed, especially where sestamibi scanning has yielded suboptimal results [24, 25]. The quality of preoperative imaging, particularly sestamibi, is volume and technique dependent, with busy centers producing the most reliable results [26]. However, surgeons are encouraged to personally review all imaging findings and be aware of potential imaging pitfalls. We will discuss the two most common imaging studies obtained when considering focused surgery for primary hyperparathyroidism.

Sestamibi

^{99m}Tc-sestamibi is a radiopharmaceutical agent that is preferentially taken up by cells with high mitochondrial activity, such as the thyroid and parathyroid glands [27]. It is retained longer by hyperfunctional parathyroid tissue than by the thyroid, and therefore a dual-phase study after a washout period may reveal a parathyroid adenoma. The timing of the second study acquisition is important, with optimal results obtained after a 2 h period [28]. Images obtained after this time interval risk missing the lesion [29], so surgeons should pay close attention to when the second phase of the scan was performed if the study is negative. Occasionally the sestamibi will rapidly wash out of a parathyroid adenoma, resulting in a negative scan even at 2 h [30]. In either of these situations, careful scrutiny of the early-phase image may reveal subtle asymmetry in the height of the thyroid lobes, which may point toward the location of an adenoma (Fig. 2.1) [31].

Another pitfall in sestamibi interpretation involves determining the vertical location of a hyperfunctioning gland and distinguishing an inferior adenoma from a superior one that has descended low in the neck. These overly descended superior adenomas may be mistaken for inferior gland adenomas on two-dimensional planar imaging (Fig. 2.2) [32]. Surgeons may miss these adenomas, which are always posterior to the coronal plane of the recurrent laryngeal nerve, if the dissection is not continued deep enough in a paraesophageal or retroesophageal plane. Additionally, surgeons acting on misleading information from the planar imaging may remove the

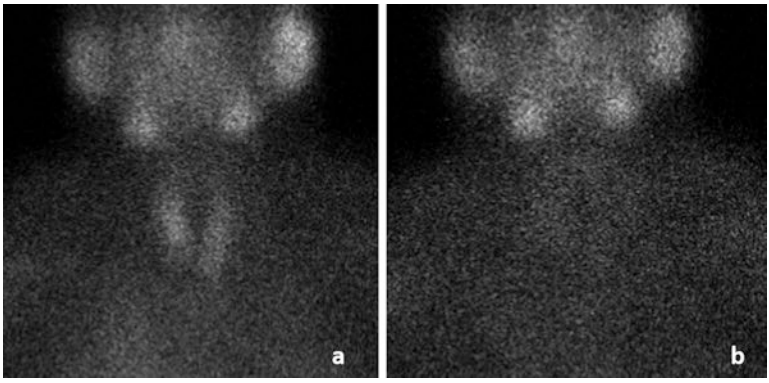

Fig. 2.1 Early (**a**) and late (**b**) planar two-dimensional ^{99m}Tc-sestamibi scan showing complete washout on the late-phase image. Careful evaluation of the early-phase image shows asymmetric inferior extension of the left thyroid, suggesting the presence of a left inferior parathyroid adenoma, which was confirmed at surgery

normal inferior gland. If the inferior gland appears normal, it should be preserved, and the surgeon should dissect deeper into the neck to identify the overly descended superior adenoma. This condition may be more readily predicted by adding single photon emission computed tomography (SPECT) coupled with computed tomography (CT) to the preoperative imaging regimen, which gives more precise anatomic localization of these deep adenomas (Fig. 2.3) [33].

Ultrasound

Ultrasound, which is also frequently employed to localize anatomically abnormal parathyroid glands, offers a number of advantages, particularly when performed by the operating surgeon [34]. It is quick and noninvasive, avoids radiation, and permits differentiation between thyroid nodules, lymph nodes, and parathyroid lesions (Fig. 2.4) [2, 35]. Surgeon-performed ultrasound in the operating room immediately before incision allows the surgeon to triangulate the location of the adenoma relative to the surrounding structures, facilitating the subsequent dissection. Though the overall sensitivity of ultrasound for detecting parathyroid lesions is only 76% [36], experienced parathyroid surgeons know that there is often information to be gleaned in even "negative" studies.

Ultrasound reports, especially when they reportedly fail to definitively identify a parathyroid adenoma, deserve careful scrutiny to ensure that a parathyroid lesion is not mistaken for a "posterior" hypoechoic thyroid nodule. There will often be a rim of normal thyroid tissue along the deep surface of a posterior thyroid nodule, which will be absent when the hypoechoic lesion "just posterior to the thyroid capsule" is in fact the parathyroid adenoma. Biopsy of these posterior thyroid "nodules" may be reported as "suspicious for follicular neoplasm." Even in this context, the lesion may still represent a parathyroid adenoma, which is difficult to distinguish from

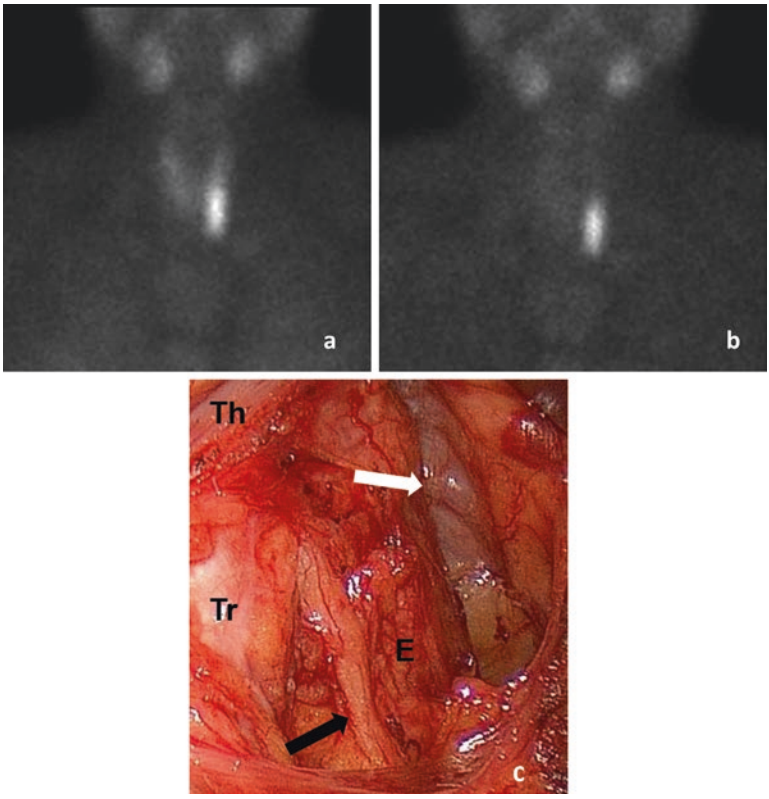

Fig. 2.2 Early (**a**) and late (**b**) planar two-dimensional ^{99m}Tc-sestamibi scan showing a suspected left inferior parathyroid adenoma. (**c**) An ectopic, overly descended superior parathyroid adenoma (*white arrow*) was identified at surgery, deep to the recurrent laryngeal nerve (*black arrow*) and esophagus (E). *Th* thyroid, *Tr* trachea

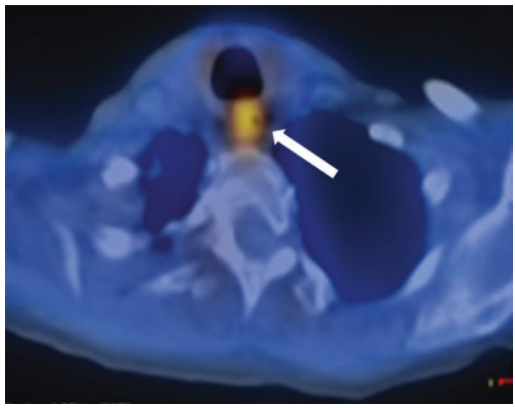

Fig. 2.3 Single photon emission computed tomography/computed tomography (SPECT/CT) image showing a retrotracheal parathyroid adenoma (*arrow*)

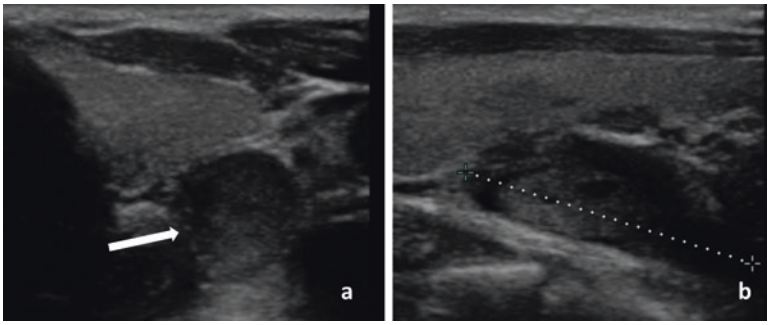

Fig. 2.4 Transverse (**a**) and longitudinal (**b**) ultrasound images showing a left inferior parathyroid adenoma. Parathyroid adenomas are generally rounded or ovoid on transverse view (**a**, *arrow*) and ovoid with a polar vascular supply on longitudinal imaging (**b**, *dotted line*). This distinguishes them from lymph nodes, which are more rounded and have a central hilar vascular supply

thyroid tissue on cytopathology [37]. If there is suspicion that a "thyroid" nodule might actually be a parathyroid adenoma, then a washout of the aspirate may be sent for PTH analysis. While this is rarely necessary and generally reserved for reoperative cases, aspiration of parathyroid tissue usually reveals an unequivocally high PTH level in the thousands, while aspiration of thyroid or lymph node tissue typically results in levels below 100 pg/mL [38]. Truly negative ultrasound studies also may offer helpful information and hint to the surgeon that the adenoma may be small, deep, or ectopic, or that multigland disease may be present [39, 40].

Intraoperative Factors

Preoperative Ultrasound

Performing an ultrasound examination just prior to the start of the operation can be of tremendous value in pinpointing the location of a parathyroid adenoma. Cervical landmarks and tissue relationships change considerably between the upright, supine, and final surgical position [41], and muscle relaxation from the anesthetic may improve the image quality. This examination confirms the location of the adenoma and its relationship to the surrounding structures, which allows focused dissection to the adenoma.

Parathyroid Identification

Successful parathyroid surgery requires a complete command of parathyroid embryology and cervical anatomy, which has been covered in Chap. 1. Parathyroid tissue may be present in ectopic locations in up to 20% of patients [42, 43], and surgeons

must be prepared to explore these sites if a parathyroid gland is not found in its expected position. Ectopic superior glands may be found in paraesophageal, retroesophageal, retropharyngeal, or retrolaryngeal sites or within the carotid sheath or posterior mediastinum [43–45]. They may be overly descended in a deep location or undescended near the hyoid [32]. Ectopic inferior glands are most frequently located in the thymus, thyrothymic ligament, or anterior mediastinum, though they can exist anywhere between the skull base and anterior mediastinum, including the pyriform sinus, submandibular region, and aorticopulmonary window or pericardium [43, 44, 46–48]. Both superior or inferior parathyroid glands may be found within the thyroid parenchyma [45]. Ultrasound may be beneficial in identifying intrathyroidal adenomas [48]. Bilateral venous sampling of the internal jugular veins for IOPTH assessment may help identify which side of the neck harbors the hyperfunctional gland if abnormal parathyroid tissue is not readily identifiable [49]. A difference in the PTH level of more than 5% between the two aspirates has been shown to predict the side of the hyperfunctional tissue [50].

Surgeons must also be able to distinguish parathyroid tissue from surrounding fatty, lymphatic, thymic, and thyroid tissue and be able to discern normal parathyroid glands from abnormal ones. Normal parathyroid glands are typically flat, 3–8 mm long, with an average weight of 40 mg and a light brown to tobacco color [44, 51]. They are usually surrounded by or capped with fat. Parathyroid adenomas and hyperplastic glands are typically larger, more rounded or nodular, and rubbery and have a darker red-brown color. Bloodless dissection is essential in parathyroid surgery, as any bleeding will stain the tissue and make it challenging to differentiate the parathyroid glands from the surrounding tissue.

Confirming Surgical Cure

Bilateral neck exploration (BNE) with visual confirmation of all four parathyroid glands has been the gold standard for parathyroid surgery for nearly 100 years [52, 53]. This procedure, which requires surgeons to compare the appearance of the glands and determine which one(s) to resect based on their gross appearance, has a long-term cure rate greater than 95% in experienced hands [54]. More recently, unilateral and minimally invasive single-gland procedures have been developed that share the same cure rates as BNE [18, 55]. However, since visual assessment of all parathyroid glands is not performed in these more focused approaches, the use of intraoperative adjuncts such as IOPTH monitoring or radioguided surgery using a handheld gamma probe is recommended to ensure complete removal of all hyperfunctional parathyroid tissue [56, 57]. Though radioguided parathyroid surgery has been successfully routinely implemented in some practices [57], other groups have found it cumbersome and unhelpful in many cases and reserve its use for selected reoperative procedures [58]. It is reported to be associated with a 6% long-term recurrence rate, calling into question its value in parathyroid surgery [59].

IOPTH assessment is the most common method of assessing biochemical cure in minimally invasive parathyroid surgery, and multiple algorithms for predicting successful surgery have been proposed [56, 60]. Although the Miami criterion, which predicts postoperative normocalcemia when the IOPTH value decreases ≥50% from the highest of either the pre-incisional or the pre-excision level 10 min after removal of all the hyperfunctional parathyroid tissue [60], is often reported in the literature, many surgeons have adopted a stricter threshold that requires the PTH level to also drop into the normal or low-normal range prior to terminating the operation in patients with PHPT [56, 61]. Additionally, obtaining IOTPH values 5, 10, and sometimes 15 min after adenoma excision allows the degradation trajectory to be trended to ensure that there is no additional hyperfunctional tissue [2].

Failed Exploration

Parathyroidectomy may be both one of the most rewarding and most challenging surgical endeavors. Despite a high success rate with either four-gland or focused techniques, operative failures persist. If all four parathyroid glands cannot be identified with BNE or if IOTPH levels fail to decline as expected, it is important for surgeons to first verify their findings and "know what they know." If the surgeon has any doubts, suspected parathyroid tissue may sampled away from its polar blood supply to be sent for frozen section confirmation that it is indeed parathyroid tissue and not lymph node, fat, thyroid, or thymus. While frozen section analysis can generally distinguish between parathyroid and non-parathyroid tissue, it is not able to reliably and consistently differentiate a normocellular parathyroid gland from one that is adenomatous or hyperplastic [62, 63]. Aspiration of the excised tissue for IOPTH analysis is also beneficial in confirming the presence of parathyroid tissue and can be performed more quickly than frozen section analysis [63]. Once the identity of the excised tissue is confirmed, a diligent search for the missing, and presumably hyperfunctional, tissue can commence. The preoperative localization studies should be reviewed, and the early- and late-phase sestamibi images, if available in the operating room, should be carefully scrutinized for any hint of additional abnormal foci. Attention should first be turned to the side of the neck where both glands have not yet been found. If more than one gland has not been identified or if IOPTH levels remain elevated after finding all four glands, simultaneous bilateral venous sampling of the internal jugular vein may help guide the dissection.

Each side of the neck should be carefully and fully explored. Identifying the recurrent laryngeal nerve will help guide the depth of dissection for a missing superior or inferior gland. If the inferior glands are missing, the thyrothymic tract and thymus should be explored or excised first. If the superior glands are missing, dissection should initially be directed deeply toward the esophagus or paraspinal musculature. If the missing glands are not found in these typical locations, all sites of potential ectopic tissue in the neck and upper mediastinum should be systematically evaluated. Intrathyroidal parathyroid adenomas have been reported in up to 7%

of cases [64]. Thyroidectomy is discouraged unless there is clear ultrasonographic evidence of a suspicious lesion within the thyroid and thorough exploration for the missing gland has failed. Consent for thyroidectomy should be obtained. If all four glands have been positively identified and the patient remains biochemically hyperparathyroid, then the possibility of supernumerary parathyroid glands should be considered [45]. If no further parathyroid tissue is identified or if the single hyperfunctional gland cannot be located, then the surgeon should consider intraoperative consultation with another experienced surgeon. Surgeons should refrain from removing any grossly or histologically normal parathyroid tissue. This "debulking" provides no benefit to the patient, as these glands are biochemically quiescent, and such an approach predisposes the patient to a risk of permanent hypoparathyroidism if an abnormal gland is removed during a subsequent operation.

If all of these efforts still fail to identify the source of the hyperparathyroidism, then the operation should be terminated, before any undue morbidity occurs. All confirmed normal parathyroid tissue should be marked with a clip or permanent suture away from its blood supply. The surgical findings should be fully documented in the operative report, including which glands were positively identified, which were missing, what was removed, and which areas were explored. Prior to parathyroid surgery, every patient should be counseled about the possibility of a negative exploration and the possible need for additional procedures. This counseling helps temper the patient's expectations of what may be perceived as "routine" or "minor" surgery and may help mitigate their disappointment if surgery is unsuccessful.

Conclusion

Although most patients with primary hyperparathyroidism can anticipate being cured after a single procedure, the sometimes challenging nature of parathyroid disease ensures that operative failures cannot be obviated completely. Surgeons should understand the potential causes of failed parathyroid surgery and be aware of possible pitfalls in the diagnosis and management of surgical parathyroid disease. Armed with a thorough understanding of parathyroid pathology, and with careful preoperative assessment, meticulous operative planning and execution, and thoughtful integration of surgical adjuncts, surgeons are well positioned to maximize the likelihood of successful initial parathyroid surgery.

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