Chapter 6
Surgical Techniques and Pearls: The Unsuccessful Reoperation

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Introduction

Even in the most skilled of hands, a small percentage of patients will not be cured after reoperative parathyroid surgery. Reoperative parathyroid surgery can be dangerous even for the most experienced surgeons and is associated with higher complication rates. Damage to the recurrent laryngeal nerve (RLN), hypoparathyroidism, and persistent hyperparathyroidism are the common complications associated with reoperative parathyroid surgery [1]. Reoperative parathyroid surgery is often indicated for persistent primary hyperparathyroidism and recurrent primary hyperparathyroidism. Persistent primary hyperparathyroidism is defined as a failure of serum calcium and parathyroid hormone (PTH) normalization after a parathyroidectomy operation. Recurrent primary hyperparathyroidism occurs when serum calcium and PTH levels are initially normal but become elevated 6 months after surgery [2]. This is common in patients who have undergone a subtotal parathyroidectomy without correction of the underlying abnormality, such as renal disease. This represents a separate entity and will not be considered an unsuccessful operation.

Unsuccessful reoperative parathyroid surgery can result from the misdiagnosis of hyperparathyroidism, the failure to identify affected parathyroid glands radiographically or surgically, incomplete or inappropriate use/interpretation of intraoperative PTH measurements, and lack of adequate postsurgical follow-up. Lack of surgical experience and surgery performed at low-volume surgical centers have shown to have increased rates of unsuccessful repeat surgery [3]. This chapter aims to review common causes of reoperative parathyroid surgery failure with hopes to improve surgical outcomes in this difficult patient population.

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Misdiagnosis

Obtaining the correct diagnosis of primary hyperparathyroidism is crucial to successful reoperative parathyroid surgery. Given the increased morbidity associated with re-exploration, the threshold for surgery in remedial operations should be more stringent than for patients undergoing primary surgery. Several diagnoses must be ruled out prior to proceeding with repeat surgery to avoid poor surgical outcomes. Endocrine disorders can mimic primary hyperthyroidism, and a careful preoperative workup is necessary to prevent unsuccessful reoperations or unnecessary operations. In one study, 144 patients who had had previous parathyroid surgery requiring reoperation were evaluated with hopes of improving success rates in parathyroid reoperations. Successful reoperation was defined by prolonged reversal of hypercalcemia. The most common cause of recurrent hyperparathyroidism in their cohort was multiple endocrine neoplasia type 1 (MEN1). Failure of adequate preoperative family history can lead to the failed diagnosis of this disorder, resulting in persistent or recurrent hyperparathyroidism. MEN1 is associated with multiglandular, ectopic, and supernumerary disease. The presence of the syndrome is often not evident at the time of primary operation but can be revealed in prolonged follow-up [4]. The optimal surgical treatment for MEN1 is frequently under debate, but typically involves either total or subtotal parathyroidectomy. Persistent hyperparathyroidism is more frequent after subtotal parathyroidectomy than after total parathyroidectomy with autologous graft of parathyroid tissue. Recurrent hyperparathyroidism has a similar frequency in the two surgical strategies. Genetic testing should be performed on all young patients diagnosed with hyperparathyroidism [5]. In one study, outcomes for 130 consecutive remedial parathyroid explorations were reviewed, resulting in seven failed reoperations due to persistent disease. Four of these patients had multi-gland hyperplasia, one was diagnosed with multiple endocrine neoplasia type 2A (MEN 2A), and one had an occult supernumerary gland after four gland excisions [6].

Not only can unsuccessful parathyroid surgery be secondary to misdiagnosis of primary hyperparathyroidism, certain diseases can mimic normocalcemia in postoperative patients leading to the false belief that the patient has been cured. Similarly, a surgical cure can be incorrectly considered unsuccessful and lead to unnecessary reoperations if not monitored closely. When using surgical adjuncts such as intraoperative PTH (ioPTH) assays as criteria for intraoperative success, it is important to be aware of factors that can falsely alter the measurement. For example, in one large study, younger patients were found to have lower preoperative serum calcium, PTH levels, and ioPTH levels than older patients [7]. Metabolic disorders and poor renal function may falsely elevate the ioPTH. Vitamin D is a known inhibitor of PTH secretion and cause of secondary hyperparathyroidism. These patients may experience deceptive normocalcemia and elevated PTH after parathyroidectomy and have also been shown to have larger adenoma size [8]. These findings may play a role in failure of reoperative parathyroid surgery and support postoperative Vitamin D supplementation in this population [7, 9, 10].

Failure to formulate a well-rounded differential diagnosis and accurately diagnose causes of hypercalcemia and/or hyperparathyroidism can lead to poor outcomes and failure of repeat surgical operations for this population of patients. The differential diagnosis includes hypercalcemia of malignancy, which can falsely elevate calcium and PTH levels. Measurement of an intact PTH (iPTH) level can aid in the differentiation of these diseases; iPTH is generally low in hypercalcemia of malignancy. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disorder that is imperative to diagnose correctly as parathyroidectomy is not indicated for this disorder. An abnormal calcium-sensing receptor characterizes this disease, leading to hypercalcemia, normal or high PTH, and low urinary calcium excretion. The calcium/creatinine clearance is typically <0.01 in FHH [11]. Other important causes of hypercalcemia that the surgeon should be familiar with include exogenous calcium, medications (thiazides and lithium), granulomatous diseases, and metabolic diseases [12].

Failure to Identify Affected Glands Radiographically

Numerous studies have emphasized the need for accurate imaging prior to considering parathyroid surgery. The intraoperative features used to identify parathyroid adenomas such as color, shape, and tactile perception of gland may be much more difficult to appreciate because of fibrosis within the tissues from the previous procedure. For these reasons, most surgeons agree that preoperative imaging studies are an essential component of the workup prior to reoperative parathyroid surgery [13]. Preoperative localization can reduce complication rates and shorten operating time by directing the surgeon to the sites of abnormal glands. The lack of appropriate diagnosis radiographically can lead to unsuccessful reoperative parathyroid surgery.

Recent advances in preoperative localization have led to substantial improved outcomes after remedial surgery. Chen et al. evaluated 254 patients with hyperparathyroidism and found that the positive predictive values for sestamibi scanning, radioguided surgery, and ioPTH testing were 81%, 88%, and 99.5%, respectively [14]. Yen et al. proposed that ultrasonography and sestamibi scans should be performed before all reoperative parathyroid operations [15]. Shen et al. found that the sensitivities of preoperative localization studies were as follows: technetium Tc 99m sestamibi scan, 77%; magnetic resonance imaging, 77%; selective venous catheterization (SVC) for intact parathyroid hormone, 77%; thallium-technetium scan, 68%; ultrasonography (US), 57%; and computed tomography (CT), 42%. The highest false-positive results were found in MRI, and the highest false-negative results were seen in US. Coexisting thyroid disease can often be a confounding variable in both nuclear imaging and high-resolution ultrasound; interpretation of these exams by experienced radiologist and surgeons is of paramount importance. MRI, thallium-technetium, and technetium sestamibi scans were more sensitive for ectopically located tumors than tumors found in normal positions. They concluded that patients who require a reoperation should receive preoperative localization with the combination of noninvasive imaging methods including US, MRI, CT and sestamibi scans; when used together, they correctly identified abnormal glands in 87% of cases. After a failed primary parathyroidectomy, artifacts from surgical clips placed in the neck often limit the diagnostic quality of CT, although it can be useful for evaluation of altered anatomy [16]. Previous studies have demonstrated limited success in locating mediastinal, retrotracheal, retroesophageal, or small adenomas [2]. If radiographic localization remains equivocal after the previous modalities have been performed, then invasive SVC is recommended. This combination of invasive and noninvasive studies identified abnormal glands in 95% of cases [2, 13]. In one large prospective trial performed at the National Institutes of Health (NIH), the results of preoperative imaging protocols and surgical re-exploration in a series of patients with missed parathyroid adenomas after failed initial procedures for primary hyperparathyroidism were evaluated. The highest false-positive results were seen in ultrasonography, likely due to the identification of lymph nodes within the neck. The study concluded that the single best noninvasive imaging study was the sestamibi scan. Sestamibi with 99mTc is the most commonly used radiotracer for imaging of the parathyroid glands. Sestamibi is taken up by both the thyroid and the parathyroid glands, but hyperactive parathyroid tissue retains the radiotracer longer than normal thyroid tissue on delayed images [16]. As a single test, the sestamibi scan has the advantage of relatively low cost, very good sensitivity, and high specificity. Coexisting thyroid disease such as multinodular goiter, autoimmune thyroiditis, and well-differentiated thyroid cancers can be confounding factors decreasing the identification accuracy of technetium sestamibi. Previous studies have described the accuracy of sestamibi scanning in identifying single adenomas to be approximately 99% [17]. Single-photon emission computed tomography (SPECT) can help to differentiate parathyroid activity from overlying thyroid and has been shown to increase sensitivity of scintigraphic parathyroid imaging [16]. The aforementioned study and several others have concluded the optimal combination would be ultrasound (better intrathyroidal evaluation than sestamibi) and sestamibi (improved mediastinal evaluation) [18, 19]. With regard to invasive studies, venous sampling showed a higher rate of true-positive results versus angiography and should be considered when noninvasive studies are inconclusive, as they are expensive and dependent on the skill of the interventional radiologist [13]. Selective venous sampling has been shown to correctly identify the side of affected gland in >89% of cases [20]. Ultrasound-guided parathyroid FNA provides an alternative technique for identification of abnormal glands, in particular intrathyroidal glands. The addition of on-site PTH analysis aids the ultrasonographer by providing real-time feedback and improves accuracy [6]. Although it has been stated that one should not perform remedial parathyroid surgery unless two preoperative imaging studies are both positive and concordant, many accept a positive sestamibi alone as adequate imaging [6]. Interestingly, investigations have shown that surgeon-performed cervical ultrasonography improved the localization of abnormal parathyroid glands preoperatively [21]. Although ultrasound and scintigraphy are established studies for preoperative localization of parathyroid adenomas, four-dimensional computed tomography (4D-CT) has been increasingly adopted and is routinely used at many hospitals [22]. These images provide anatomical and functional information by incorporating perfusion characteristics of hyperfunctioning glands. One recent study compared scintigraphy to 4D-CT in 40 patients and found that the CT correctly localized 76% of parathyroid lesions in 80% of patients and scintigraphy correctly localized 43% of lesions in 48% of patients. Both modalities missed 20% of lesions. Importantly, in patients with prior failed parathyroidectomies, 4D-CT correctly identified lesions in all five patients, and scintigraphy missed two lesions. The smallest lesion detected by 4D-CT was 4 mm and 10 mm for scintigraphy. 4D-CT exposes the patient to significantly higher doses of ionizing radiation [23]. Four phases may not be necessary; Noureldine et al. found that two-phase and four-phase CT provide an equivalent diagnostic accuracy in localizing hyperfunctional parathyroid glands. The reduced radiation exposure to the patient may make two-phase acquisitions a more acceptable alternative for preoperative localization [24]. To improve unsuccessful reoperative parathyroid surgery, continued research in the radiographic diagnosis of parathyroid lesions is warranted.

Intraoperative Failure to Identify Affected Glands

Aberrant parathyroid tissues are more likely to deviate from the typical anatomic positions of normal parathyroid tissue in patients who have previously had neck surgery. An unsuccessful reoperation may be secondary to ectopic parathyroid tissue, hyperplasia, supernumerary glands, or inadequate/partially resected normal parathyroid adenoma which can result in parathyromatosis. An ectopic parathyroid gland may be hidden anywhere from the pericardium up to the nasal septum. A normal superior gland position is defined as the region posterolateral to the superior pole of the thyroid superior and posterior to the course of the RLN. The normal inferior gland position is defined as in the region of the lower pole of the thyroid gland anterior to the RLN and the inferior thyroid artery [13]. Shen et al. evaluated 102 failed parathyroid operations and found that ectopic parathyroid tissue was present in >50% of reoperative cases. Thirty-seven percent of cases resulted from the incomplete resection of multi-gland disease, and 7% were due to the lack of identification of an adenoma in a normal location. Similar to previous studies, the majority of ectopic glands were found in the paraesophageal region (28%), non-thymic mediastinal region, (26%), intrathymic region (24%), and intrathyroidal region (11%), within the carotid sheath (9%), and in high cervical position (2%). Five patients had unsuccessful reoperations, and two of these had multiple supernumerary glands in ectopic positions in the mediastinum. All five had false-positive localization studies [2]. Lesions in the tracheoesophageal groove/posterior superior mediastinum can be considered to be in the normal position of the superior parathyroid gland; therefore, it is not considered a true ectopic site. It is not uncommon for adenomas to be adherent to the undersurface of the RLN in this region. Reluctance to dissect near the nerve can be a major factor in the failure to appreciate superior parathyroid glands in this region. In one prospective study, 222 consecutive patients who underwent re-exploration for hyperparathyroidism at the National Institutes of Health (NIH) were evaluated. The most common site for a missed adenoma was in the tracheoesophageal groove in the posterior superior mediastinum, and the most common ectopic site was the thymus or mediastinum. 13 of the 222 initial reoperations failed the procedure, with six patients requiring another procedure. One patient had diffuse muscular seeding in the strap and sternocleidomastoid muscles (parathyromatosis). Successful extirpation of diseased parathyroid tissue in these cases may require expansion of the resection to include non-parathyroidal adjacent tissues in order to reestablish calcium homeostasis; the trade-off however is that operative morbidity may be increased. The other five patients were re-explored 6 months after the initial procedure. Repeat imaging workup in three patients showed unusual abnormal gland locations in the nasopharynx and aortopulmonary window. Two failed the procedure when intrathyroidal tissue was incorrectly identified as being adenomas on frozen section. Seventeen patients with failed reoperations developed recurrent disease at much later dates (>6 months). Most parathyroid glands were found to regrow at the site of initial surgical resection, and seven had recurrent disease in a single lesion on the contralateral side of earlier abnormal lesion; this entity has been described to be a double adenoma [13]. It must be emphasized that a surgeon who performs a unilateral exploration runs the risk of missing a second adenoma or hyperplastic glands even if ioPTH is used. MEN1 has increased frequency of supernumerary glands and ectopic glands, and embryonic rests can be embedded within fatty tissue surrounding the trachea, esophagus, and carotid artery [5]. Patients with MEN1 frequently present at age less than 40 years as well; so the threshold for consideration of MEN1 should be higher in the younger patient cohort. There is a subset of patients in whom parathyroid glands are not identified during reoperative surgery, potentially leading to an unsuccessful reoperation. In this setting, it is recommended that bilateral explorations be performed to search potential ectopic sites. In addition, if one ectopic parathyroid gland is initially visualized, other possible ectopic sites should be evaluated prior to any removal of parathyroid tissue, such that the existence of single versus multiglandular disease can be more appropriately defined. These sites include the thymus, superior mediastinum, retroesophageal and submandibular regions, carotid sheath, upper cervical region for missing lower gland, and posterior mediastinum for missing upper gland. If all areas are negative, intraoperative ultrasound and bilateral internal jugular vein sampling to determine if an ipsilateral PTH gradient is present should be considered, although ultrasound can be difficult once surgery has started and surgical planes are disrupted. A thyroid lobectomy is an option, with median sternotomy/mediastinoscopy or other thoracic endoscopies reserved for failure to identify the abnormality in all other locations; this could occur coincident to cervical exploration or at a later date considering the overall condition of the patient. If all else fails, ligation of the blood supply to the missing parathyroid gland has been reported, but represents a strategy with limited evidence basis for long-term efficacy [6]. Gamma probe detection of radiolabeled sestamibi has been used to guide cervical dissection in remedial cases. One study experienced successful minimally invasive radioguided parathyroidectomy (MIRP) in reoperative parathyroid surgery using the gamma probe for single adenomas as predicted by sestamibi scan. Current thinking is that minimally invasive surgery when indicated is likely to decrease the risk of nerve injury due to directed technique and less exploration of unnecessary areas while minimizing dissection and can offer a patient avoidance of general anesthesia and perhaps a lower rate of permanent hypoparathyroidism [6, 17].

Pitfalls of the Utilization of the Intraoperative Parathyroid Hormone Assay

Intraoperative parathyroid hormone (ioPTH) assay has allowed surgeons to perform minimally invasive parathyroid surgery with success rates comparable to bilateral exploration and can confirm the removal of all hyperfunctioning parathyroid tissue in a relatively short time period, as the half-life of PTH is approximately 5 min [25]. The earliest method for monitoring ioPTH was described in the 1990s by Irvin et al. [26], who recommended a 50% decline from pre-excision PTH levels at 10 min after gland excision. The commonly applied Irvin criterion is reported to correctly predict postoperative calcium levels in 96–98% of patients. However, when these criteria are met intraoperatively yet persistent hyperparathyroidism occurs, one must question the clinical accuracy of the 50% drop criteria in PTH levels. Other investigators have shown presence of multiglandular disease despite a 50% drop in the ioPTH level. However, the PTH baseline reference concentration can be markedly increased by surgical manipulations during preparation of the affected glands, individual variability of the PTH half-life, and modifications in the physiological state of the patient during surgery such as renal failure [27]. Thus, one could misinterpret an apparent 50% decrement as representing an adequate fall in ioPTH and thereby miss occult residual multi-gland disease [13]. One study evaluated 1882 patients and found that a 10 min post-excision ioPTH level that decreased 50% from baseline and is normal or near normal was highly successful, versus relying on 50% decrease alone. 22.4% of patients with multiglandular disease experienced failed operation when using the 50% decrease alone [28]. In the challenging reoperative patient, unsuccessful reoperation may be attributed to failure of accurately evaluating the ioPTH degradation curve. Accordingly, more stringent criteria have been appropriately described for an intraoperative definition of cure in the reoperative scenario. A measurement of a 10 and 20 min value could contribute to the identification of patients eligible for avoidance of further neck exploration in a previously operated neck with higher risk of surgical complications [29]. When used for the discrimination of hyperparathyroidism caused by hyperplasia or multiglandular disease such as in MEN1, ioPTH has shown substantially lower reliability, with a high rate of false-positive values [5]. One retrospective review evaluated 1371 patients undergoing ioPTH monitoring and found that persistent and recurrent disease rate was lowest in the patient with final ioPTH <40 pg/mL [7]. Another study evaluated

1108 individuals with a mean follow-up of 1.8 years and found that patients with final ioPTH levels <40 pg/mL also had lower recurrence rates [30]. Baseline index PTH levels can alert the surgeon to the potential for the presence of multi-gland disease. Baseline levels below 100 pg/ml in patients with hyperparathyroidism often indicate, low volume, single gland disease [31]. The failure to obtain final ioPTH level < 40 pg/mL by surgeons may partially be responsible for an unsuccessful operation, especially in the absence of bilateral exploration. Of all the perioperative adjuncts used during parathyroid surgery, intraoperative PTH testing has the highest sensitivity, positive predictive value, and accuracy. Although important for preoperative evaluation, imaging modalities allow the surgeon to localize the abnormality, but ioPTH evaluation are crucial in assessing results of surgery and emphasize the critical importance of close follow-up after surgery [14].

Incomplete Follow-Up

Postoperative reoperative parathyroid surgical patients must be carefully monitored for surgical complications. Intraoperative PTH values not only provide valuable intraoperative information for the surgeon but can also be used as a guide for follow-up plan. ioPTH levels greater than 40 have been shown to experience higher rates of persistence and recurrence, and recurrence may not be evident until roughly 2 years after surgery or longer. It is therefore imperative to perform close surveillance for patients who meet this criteria to avoid unsuccessful reoperations [7].

Reoperative patients are at higher risk for inadequate postoperative parathyroid function and RLN paralysis. Postoperative hypocalcemia is often temporary; most patients becoming hypocalcemic will improve, while normal residual parathyroid tissue regains function in the first several days after reoperation. A subset of patients, however, will remain hypocalcemic and will require lifelong calcium and vitamin D replacement. A possible cause of unsuccessful reoperative parathyroid surgery defined by postoperative complications is due to incomplete initial workup and/or follow-up. Laryngoscopic evaluation of bilateral RLN function is a critical component of the preoperative evaluation, even if the patient is asymptomatic. The knowledge of a RLN injury is likely to impact the choice of operative approach in the remedial setting. Close monitoring of calcium and PTH levels is critical in a reoperative patient. Long-term follow-up must be especially performed in patients with endocrine disorders (MEN) as they are at higher risk for recurrent hyperparathyroidism [4]. If persistent or recurrent disease is biochemically confirmed, the patient must be carefully reassessed as a new patient. This includes repeat history and physical examination, repeat laryngoscopic evaluation, preoperative imaging (often multimodal), and laboratory values including 24 h urine calcium. Given that the risk of surgical complication increases with each repeat exploration, truly asymptomatic reoperative patients with unsuccessful surgery with borderline laboratory abnormalities may be considered for nonoperative management [25].

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