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Surgical Techniques and Adjuncts in Hyperparathyroidism

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Introduction

Parathyroid surgery has evolved significantly since its inception and is associated with many pivotal discoveries that have advanced the field. From the discovery of parathyroid glands to the intraoperative measurement of parathyroid hormone this endocrinopathy continues to produce new and innovative techniques to optimize patient outcomes. This chapter describes the historical highlights that have facilitated our current practices in parathyroid surgery, the surgical approaches that have been developed including the role of intraoperative parathyroid hormone (ioPTH) measurements, and additional intraoperative adjuncts that have been developed to maximize surgical cure and minimize patient morbidity.

Historical Aspects of Parathyroid Surgery

The first description of parathyroid glands is credited to Sir Richard Owen in 1862 [1]. His excitement over the "rare opportunity" to dissect an Indian rhinoceros following her death was justified when he later described "a small compact yellow glandular body attached to the thyroid" that would later be found to have profound physiologic impact [2]. The first human parathyroid was reported in 1887 by Ivan Sandstrom, a medical student from Uppsala, Sweden [3]. He noted these small glands in a number of animals, and then went on to describe the glands in variable anatomic locations in over 50 human cadaveric dissections. Sandstrom was the first to coin the term "glandulae parathyroideae" because of their proximity to the thyroid gland [4]. Eugene Gley, a French pathologist, was one of the first to have insight into the function of parathyroid glands. In 1891, he published his observations on the development of tetany in animals following parathyroidectomy. Functional studies continued throughout the early twentieth century with McCallum and Voegtlin describing the relationship between hypocalcaemia and tetany, inferring a relationship to parathyroid function [5]. These two, along with Halstead, were among the first to use calcium and PTH extract as a treatment for tetany [6]. This was confirmed by Collip in 1925 when he was able to show that purified PTH extract was able to reverse tetany in patients with hypocalcemia following parathyroidectomy [7]. Jakob Erdheim, in 1907, explored the role of parathyroid glands when he noted them to be enlarged in patients with severe bone

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disease (osteitis fibrosa cystica); however he inferred incorrectly that the increased size was a consequence rather than a cause of bony destruction [8]. In 1915 Friedrich Schlagenhaufer proposed what would ultimately be accurate that enlarged hyperfunctional parathyroid glands were the cause of the bone destruction and that resection of the offending gland could offer surgical cure [4].

The first recorded parathyroidectomy was in 1925, performed by Felix Mandl, on a tram car driver named Albert Gahne. Unfortunately, the patient was a victim to the initial theories on the cause of enlarged parathyroid glands and was treated with parathyroid replacement prior to changing paths and undergoing a parathyroidectomy. Mandl removed a 2 cm gland that, in hindsight, was likely a parathyroid carcinoma. The patient developed recurrent hypercalcemia 6 years later and passed away after attempting a second surgery [9]. Probably the most famous hyperparathyroid patient was Captain Charles Martell, who was originally diagnosed in 1926 with von Recklinghausen bone disease and hypercalcemia felt to be secondary to hyperparathyroidism. He underwent seven surgeries attempting to locate the offending gland, but the first six were unsuccessful and unfortunately removed the several normal parathyroid glands. His seventh surgery in 1932 was performed by Edward Churchill and Oliver Cope where they removed a 2.5 cm mediastinal parathyroid gland. Sadly, Martell continued to struggle with nephrolithiasis and passed away 6 weeks after surgery from laryngospasm following kidney stone removal [10, 11]. The irony is that the struggle to isolate and remove the hyperfunctional gland(s) is an obstacle in treatment that we still face today. Despite many advances, recurrent or persistent parathyroid disease is often attributed to undiagnosed double adenomas or hyperplasia.

The importance of identifying and removing hyperfunctioning glands is demonstrated in patients like Captain Martell. The challenge becomes localizing and removing the gland or glands and ensuring that there is no residual hyperfunctioning tissue. The morphological determination of an abnormal gland was left to the discretion of the surgeon with the interpretation of “abnormal” being based on the size of the gland and its appearance in comparison to other glands (Fig. 20.1). Intraoperatively an enlarged gland may be interpreted as abnormal based on size criteria; however this does not always correlate with hyperfunctioning tissue [12]. Pathologically there is also variability in distinguishing an adenoma from parathyroid hyperplasia which decreases the accuracy of frozen section as an intraoperative adjunct. This difficulty in intraoperative diagnosis likely led to the wide variability in the incidence of multigland disease described in the twentieth century (3–65%) [13].

James Walton, in 1931, was one of the first to advocate for wide exploration for all parathyroid glands, arguing that if glands were not identified in the common locations less common locations should also be explored (retroesophageal, thymic, carotid sheath, etc.) [14]. The trend over the next 60 years was to perform a bilateral neck exploration (BNE) in order to assess each parathyroid gland and resect all abnormal glands. Over time it became clear that the majority of patients with primary HPT had a single-gland disease, so is the late 1970s Tibblin proposed the concept of a unilateral exploration if one normal and one abnormal gland were found on the first side of the neck explored [15]. Although this approach laid the groundwork for a limited exploration, it was not universally excepted until decades later with the introduction of ioPTH measurements and improved preoperative localization.

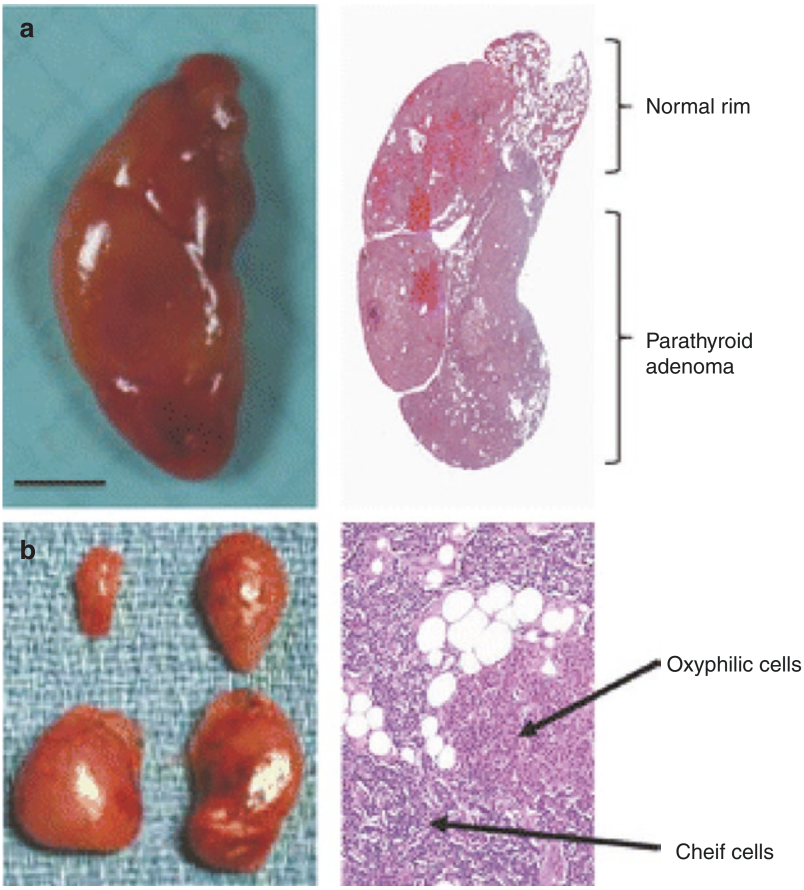

Fig. 20.1 Gross macroscopic photo of a parathyroid adenoma (**a**) and four-gland hyperplasia (**b**). (**a**, right) Microscopic section of parathyroid adenoma and a normal rim. In many cases, but not all, histopathological sections in parathyroid hyperplasia show nodules containing chief and oxyphilic cells (right in (**b**)). Photos are shown owing to courtesy of pathologist Dr. Christofer Juhlin, Karolinska Institutet, Sweden [78]

Evolution of Preoperative Imaging and ioPTH

The functional use of radionucleotide imaging with technetium-99m-sestamibi in the early 1990s revolutionized parathyroid surgery by providing a method of localizing hyperfunctioning glands preoperatively [16]. Patients were injected with Tc-sestamibi and then had cervicothoracic imaging at 15 min and 3 h. A parathyroid adenoma was identified by persistent focal uptake on late imaging that was separate from the thyroid gland (Fig. 20.2). This is thought to be secondary to the radionucleotide being retained in the mitochondria-rich adenoma. Initial studies showed up to 90% accuracy in localizing hyperfunctioning glands, but follow-up studies show more variable accuracy ranging from 70 to 90% [17]. However, it was established as a valuable imaging modality that would come to facilitate minimally invasive parathyroidectomies despite the recognition that patients with hyperplasia or double adenomas may be at higher risk for non- or inaccurate localization [18].

In the 1960s Rosalyn Yalow and Solomon Berson developed a radioimmunoassay that could be used to measure substances within the body, including parathyroid hormone. This technique was refined over time, but was a cornerstone in the development of PTH assays and set the stage for intraoperative PTH measurements

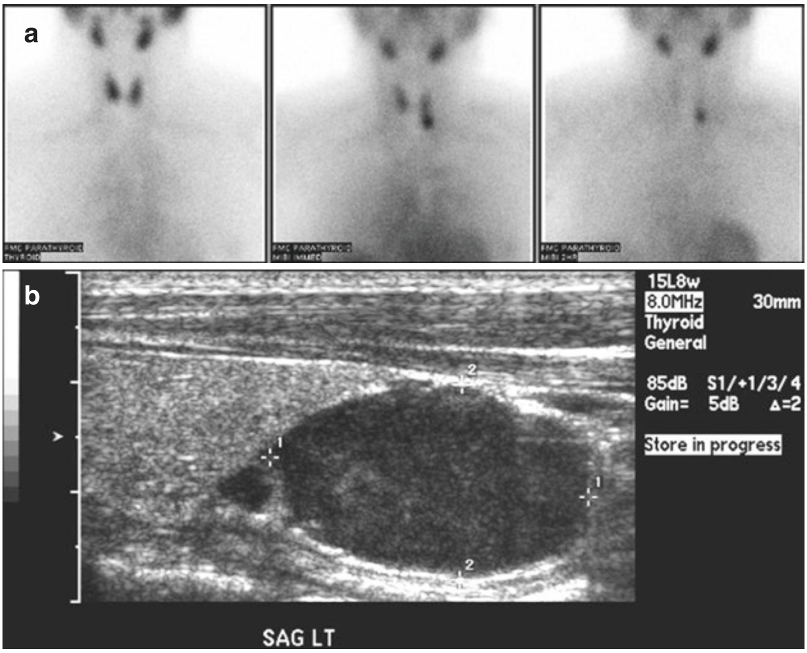

Fig. 20.2 Preoperative imaging in primary hyperparathyroidism. (**a**) Sestamibi with SPECT displaying focal retention in the left lower position seen on delayed 2 hour images. (**b**) Corresponding cervical ultrasound from the same patient showing a large hypoechoic parathyroid adenoma

which would help to restructure parathyroid surgery. Berson passed away suddenly in 1972, but Yalow went on to accept the Nobel Prize in Medicine in 1977 for their combined work on radioimmunoassays [19]. As serum PTH measurements became more readily accessible in the 1980s the assay evolved to be able to rapidly yield a result. This facilitated the intraoperative use of PTH testing. George Irvin was one of the first to publish on this in the early 1990s and showed that an intraoperative drop in PTH reflected the appropriate removal of hyperfunctioning parathyroid tissue [20]. Intraoperative PTH measurements developed quickly as an adjunct to parathyroid surgery and were found to be most useful in patients with preoperative imaging that suggested single-gland disease.

Preoperative localization studies in conjunction with ioPTH facilitated an increasingly less invasive approach to parathyroidectomy by providing additional confidence that all hyperfunctioning gland(s) were resected, thus allowing the era of minimally invasive parathyroidectomy (MIP) to evolve. A MIP is defined by either (1) a unilateral neck exploration (UNE) that identifies both parathyroid glands on one side of the neck or (2) a focused image-directed parathyroidectomy that locates a single gland on preoperative imaging and removes it without identifying any additional glands. There are multiple studies suggesting that the cure rate for primary hyperparathyroidism is similar between BNEs and MIPs when intraoperative PTH monitoring (ioPTH) is used [12, 21]. In addition there are potential benefits to MIP with some evidence to support shorter operative time [22], shorter hospital stays [23], and decreased risk of temporary hypocalcemia [24]. However, the caveat is that during a unilateral exploration if no abnormal glands are identified on the ipsilateral side or the ioPTH fails to drop appropriately the procedure is converted to a BNE which occurs in up to 40% of attempted unilateral explorations [21].

Surgical Approaches

Bilateral Neck Exploration

After the recognition that one or more parathyroid glands could be hyperfunctioning and that they could be in variable positions in the neck, BNE was adopted as the surgical approach of choice in the twentieth century. Performed through an approximately 3 cm cervical neck incision, all four glands are assessed prior to resecting the abnormal gland(s). The determination of an "abnormal gland" is made by the surgeon by means of increased size (greater than 50 mg) or atypical gland characteristics. Frozen section has limited value in differentiating hyperplastic from normal parathyroid tissue [25]. As such the BNE relies on the surgeon's experience and expertise to accurately diagnosis single- versus multi-gland disease.

The goal of a BNE was to excise 1–3.5 glands depending on whether an adenoma, double-adenoma, or four-gland hyperplasia was present. Now that a number of adjuncts including preoperative imaging and ioPTH are commonly utilized, the indications for BNE as the initial planned procedure have narrowed to focus on patients that are at higher risk for multi-gland disease. This includes patients that fail to localize on preoperative imaging and patients with preexisting conditions such as multiple endocrine neoplasia (MEN) 1, MEN 2a, familial primary hyperparathyroidism, and lithium-associated parathyroid disease. The risk of multi-gland disease ranges from 24% in patients that do not localize on imaging to 100% in patients with MEN 1 [26, 27]. For sporadic HPT, BNE in experienced hands has a durable cure rate of 98% without the utilization of preoperative localization or ioPTH measurements. In centers where these modalities are not readily available, BNE remains the most cost-effective operation.

In North America, many BNEs are performed following intraoperative failure to unilaterally localize an abnormal gland or if the ioPTH fails to drop appropriately. In this setting, ioPTH is often used in conjunction with bilateral exploration. However, if BNE is the initial planned procedure there is little reported benefit for using ioPTH intraoperatively as the cure rates are similar without it [28]. Early criticism of BNE involved the potential increased risk of complications with extended dissection, such as hypocalcemia or recurrent laryngeal nerve injury [29]. However, several studies have shown complication rates between BNE and MIP to be similar, especially when performed by an experienced endocrine surgeon [30, 31].

Minimally Invasive Parathyroidectomy (Unilateral and Image Directed)

A UNE involves the identification of one abnormal and one normal parathyroid gland on the ipsilateral side of the neck. Failure to meet these criteria necessitates the need for conversion to a BNE. Initially these operations were performed without the advantages of preoperative imaging or ioPTH measurements, and can still be done utilizing only the morphological assessment of the glands in experienced hands with excellent results. Initially conversion to a BNE occurred 50% of the time, yet despite this the success rate for a UNE was 97% [32]. Modern-day series still require conversion to a BNE up to 40% of the time because of either failure for the ioPTH to drop appropriately or failure to meet unilateral criteria [21, 33].

An image-directed MIP, as the name implies, is the removal of a single abnormal parathyroid gland seen preoperatively of imaging. Since there is no assessment of any of the other parathyroid glands to aid in the discovery of multi-gland disease, ioPTH is recommended for this approach [34]. Either of these techniques is typically performed through a slightly smaller incision and can be done with regional anesthetic. Traditionally this has been done using an open approach; however, video assisted or robotic are being popularized in some high-volume centers [35]. The basis for success of the MIP is that it is performed on patients with sporadic primary hyperparathyroidism that have preoperative imaging to suggest single-gland disease. If the sensitivity of preoperative imaging modalities was higher, there could be an argument made for performing MIP without ioPTH. However, despite significant advances in the accuracy of sestamibi, ultrasound, single-photon emission CT (SPECT), or 4-D CT, there is still a 10–15% margin of error for detecting multi-gland disease [36, 37]. In patients with concordant localization on sestamibi and US, operative success with ioPTH reaches up to 98% with the use of ioPTH changing management in only 2% of cases [34].

There have been many studies comparing the efficacy of BNE with that of MIP in treating HPT, including at least four randomized trials (Table 20.1). When ioPTH is used with MIP, the cure rate is greater than 95% up to 5 years postoperatively. There have been arguments for each approach for decreasing operative times, cost, and associated complications; however there is no conclusive evidence suggesting a significant difference [38]. Currently the majority of endocrine surgeons favor MIP as an initial approach for sporadic HPT in appropriately selected patients, but several groups have developed techniques using BNE or additional adjuncts that have similar outcomes.

Table 20.1 Randomized and retrospective series comparing focused neck exploration and bilateral neck exploration

Series	Study type	Outcome
Westerdahl and Bergenfelz (2007) [21]	Randomized	=Cure rate at 5 years
Bergenfelz et al. (2002) [80]	Randomized	=Cure rate; increased cost and operative time in FNE; increased postoperative hypocalcemia with BNE
Slepavicius et al. (2008) [81]	Randomized	=OR time and cure rate; increased cost with FNE; increased postoperative hypocalcemia with BNE
Aarum et al. (2007) [82]	Randomized	=Cure rate; =complication rate; increased cost with FNE
Grant et al. (2005) [83]	Retrospective	=Cure rate; =complication rate
Udelsman et al. (2011) [84]	Retrospective	Increased cure rate and lower complication rate with FNE

Note that studies do not compare all similar outcome measures

Abbreviations: = equivalent, *OR* operating room, *FNE* Focused neck exploration, *BNE* Bilateral neck exploration [38]

Adjuncts

Intraoperative PTH

Yalow was credited with the development of the first serum PTH assay; however the technique continued to be refined and in 1987 Nussbaum published on a rapid immune-radiometric assay that would eventually be used to measure PTH intraoperatively [39]. The attractive feature of circulating PTH is a half-life of only 3–5 min, whereas the hypercalcemia does not normalize for several hours. This allows almost real-time detection of a drop in systemic PTH levels following the resection of all autonomously hyperfunctioning parathyroid gland(s), while the normal gland remains suppressed. An appropriate hormone decrease indicates that additional exploration to look for additional abnormal glands is not necessary, which can lead to a shorter operation and less disruption to normal parathyroid glands [40]. The group at the University of Miami developed criteria for determining when all hyperfunctional tissue had been removed based on serial measurements of PTH prior to and following excision of the affected gland. PTH levels are measured prior to incision, prior to gland excision, and at 5 and 10 min post-gland excision. An intraoperative drop in PTH of greater than 50% from highest value of either the pre-incision or pre-excision value to the 10-min value provides the most accurate estimation of postoperative normocalcemia [41]. Although this is the most widely accepted criteria several other groups have proposed that, in addition to a greater than 50% drop, the PTH returns to within normal limits in order to more accurately discriminate against multi-gland disease [42].

Intraoperative PTH does require interpretation by the surgeon and thoughtfulness about unexpected trends. Additionally, it requires a facility prepared to process rapid PTH assays and an operative team available and educated in collecting samples. Its popularity grew rapidly in the United States, but given the variability of resources throughout the world it is not universally considered the standard of care.

Parathyroid Localization

There are other adjuncts that are used to confirm parathyroid tissue, visualize parathyroid glands, and assist in gland localization and functional status. Confirmation of parathyroid tissue is important when determining which tissue to resect, which to leave in vivo, and which to autotransplant. Although used more frequently prior to the advent of ioPTH, two described techniques that are still used in specific circumstances are frozen section and tissue aspirate. Frozen section has had two roles: (1) to confirm that tissue is parathyroid gland and (2) to attempt to differentiate adenomas from hyperplastic parathyroid tissue. The first of these is still used to differentiate parathyroid tissue from lymph nodes, cervical fat, thymus, or thyroid nodules. This has been validated and has shown accuracy up to 99.2% in determining parathyroid tissues [34, 43]. Frozen section to differentiate adenoma from hyperplasia has shown a high degree of inaccuracy in a number of studies [44, 45]. The general consensus is that if there is question about the diagnosis of single- versus multi-gland disease a BNE should be performed and subjectively abnormal glands should be removed regardless of histology [34]. Gland aspiration on the other hand has proven to be an accurate and cost-effective method to identify parathyroid tissue in institution with the infrastructure to perform ioPTH. A small-gage needle is inserted into the tissue and the aspirate is suspended in 1 mL of normal saline. The sample is sent for rapid PTH testing and if the value is greater than 1500 pg/mL there is a 100% sensitivity and specificity for parathyroid tissue [46].

Methylene Blue and Indocyanine Green

There are a number of other techniques that have been proposed with varying success to aid in the identification of parathyroid glands intraoperatively. These include but are not limited to the use of methylene blue and indocyanine green fluorescence with near-infrared fluorescence. Methylene blue was introduced in 1971 as an agent that collected in the parathyroid glands following intravenous administration. It localized to both normal and abnormal parathyroid glands, so it was originally proposed as a method of identifying and preserving tissue rather than identifying hyperfunctional tissue [47]. Over time, as the technique was refined, it showed some efficacy in staining only abnormal glands and had some potential to reduce operative duration [48]. However, use of the dye was associated with the risk of significant toxicities including cardiovascular instability and severe neurologic complications. As well, it is contraindicated during pregnancy and in patients taking serotonin reuptake inhibitors [49]. Recently, there have been some studies using lower dose methylene blue, 0.5 mg/kg rather than the traditional 7.5 mg/kg, that have a lower toxicity profile and showed potential when combined with the use of near-infrared fluorescent light in identifying parathyroid adenoma [50]. Despite some advances, the use of methylene blue for parathyroid identification is not used widely.

Indocyanine green (ICG) fluorescence imaging is an emerging technique. It has a potential dual purpose of assisting in parathyroid gland identification, but also assessing gland perfusion and as such viability. After adequate neck exposure, 5 mg of the dye is injected intravenously and near-infrared fluorescence imaging is used to visualize the glands. Many of the studies have used ICG fluorescence in conjunction with thyroidectomy rather than during parathyroid surgery, but the accuracy of detecting glands was up to 84% [51]. The ability to visualize at least one well-perfused gland with ICG fluorescence correlated with normal postoperative PTH levels [52]. This technique may not be relevant for patients with single-gland disease undergoing MIP, but has potential relevance in patients with multi-gland disease undergoing a subtotal parathyroidectomy.

The quality of parathyroid glands to take up various intravenous dyes can assist with localization after adequate exposure; however, techniques to localize hyperfunctional parathyroid tissue prior to exposure increase the potential for MIP. Several adjuncts have gained popularity including intraoperative ultrasound, jugular venous sampling, and radio-guided adenoma localization. Ultrasound is known to be an effective tool for localizing parathyroid adenomas especially when combined with sestamibi preoperatively [53, 54]. It has the advantage of being inexpensive, having no risk of radiation, or being noninvasive to the patient. However, it is user dependent and its accuracy and ability to detect parathyroid glands are reliant on the user's experience and technique. As well, patient size, gland size, and additional thyroid or neck pathology can limit the ability to locate glands. On ultrasound, parathyroid glands appear as solid, well-circumscribed, hypoechoic masses (Fig. 20.2). When in classic positions abnormal glands are usually easily detectable, but barriers to locating them include ectopic positions (retrotracheal, retro-esophageal, mediastinal), multi-gland disease, and previous surgery [55, 56]. The majority of ultrasound for parathyroid disease is performed preoperatively; however intraoperative ultrasound plays a role in real-time localization and has been shown to be beneficial especially in the reoperative setting and when other preoperative imaging has been discordant [57, 58].

Internal Jugular Venous Sampling

Differential internal jugular venous sampling (JVS) is another effective technique to lateralize the side of the neck that a hyperfunctioning parathyroid gland is located. It can be used preoperatively or intraoperatively and is indicative of gland localization when the PTH level on one side is greater than 10% of the contralateral side. The accuracy of localization is reported as up to 81% overall and in patients with negative preoperative sestamibi accuracy can be up to 65% [59–61]. Risk factors for non-lateralization include multi-gland disease, and ectopic location of parathyroid glands outside of the neck and in the reoperative setting. Overall, JVS is a simple and effective method of lateralizing parathyroid pathology and can increase the ability of the surgeon to perform an MIP.

Radio-Guided Parathyroid Localization

Radio-guided parathyroid localization uses the same principle as sestamibi scanning, in that technetium 99-m is injected into the patient and collected in mitochondria of hyperfunctioning parathyroid glands. When used for localization intraoperatively the patients are injected 1–2 h preoperatively and a handheld gamma probe is used to narrow the location of the adenoma, similar to localization in a sentinel lymph node biopsy. There are several applications for this technique: (1) to guide the location of incision, (2) to localize glands in classic and ectopic position, (3) to confirm activity in resected glands, and (4) to assess residual activity in the surgical bed. In 1999, the "20% rule" was proposed, stating that any resected tissue measuring greater than 20% of the background count, in the setting of a positive sestamibi scan, was the result of a parathyroid adenoma [62]. This provided a guideline for practitioners to use radio-guided localization to perform MIP with confidence that the hyperfunctioning gland had been removed. Other advantages to using radio guidance included verification that the correct glands have been removed and assistance in localization in difficult cases such as reoperative surgery or ectopic glands [63, 64]. As well, there is evidence that it is effective in multi-gland disease, in secondary and tertiary hyperparathyroidism, and in patients with negative preoperative sestamibi imaging [63, 65]. However, thyroid pathology, especially goiters, has been shown to decrease its accuracy [66, 67]. Contraindications to the use of radio guidance include pregnancy and allergy to the radioactive tracer. In one study by Chen et al. (2005) radio-guided localization had an accuracy of 83% for localizing a single hyperfunctioning gland, which alone was inferior to ioPTH (accuracy 98%) [17]. However, their combined use allows for the enhanced gland localization with radio guidance and greater accuracy with the use of ioPTH.

Additional techniques are evolving that use the principles of radio-guided localization such as a portable mini-gamma camera to take intraoperative images [68] or low-dose radio-guided localization using 37 MBq of technetium 99-m rather than the standard 600 MBq [66]. Radio-guided parathyroidectomy has been shown to be effective when used as part of an MIP combined with ioPTH or with BNE; however, there is no convincing evidence that its accuracy is adequate when used on its own. Although the use of radio guidance techniques has been growing over the last 20 years, it is still not universally utilized. Critics of the method report difficultly with the timing of administering the radio tracer, malfunctioning of the equipment, and unnecessary additional cost when most endocrine surgeons can find the glands without its use [69].

Recurrent Laryngeal Nerve Monitoring

Recurrent laryngeal nerve (RLN) monitoring has been described extensively in the thyroid surgery literature but has a much smaller role in parathyroid surgery. It is a technique that uses nerve stimulation to evaluate vocal cord function in an effort to prevent intraoperative nerve injury. However, despite extensive observation, there is no definitive evidence that intraoperative nerve monitoring decreases the risk of postoperative temporary or permanent vocal cord paralysis during thyroidectomy [70]. A proportion of surgeons do not routinely identify the RLN during parathyroidectomy and, only rarely, would be dissecting along its insertion into the larynx. So, although there is little literature evaluating nerve monitoring in parathyroid surgery given the low rate of nerve injury (<1%) there is little predicted benefit [71].

Clinical Pearls and Conclusion

Parathyroid surgery has had an exciting and, at times, controversial evolution over the last century. The development and ongoing refinement of surgical adjuncts continue to push parathyroid surgeons to achieve success rates far superior to other functional tumors. The significant population of people that suffer from HPT facilitate the creation of a large body of literature to evaluate and refine our approach to the surgical treatment. BNE remains the cornerstone for surgical management, and all endocrine surgeons must be familiar and facile in performing this operation safely and effectively. The development of MIP with ioPTH has been one of the largest contributions to treatment in the last 20 years. It has provided a consistent method of evaluating in vivo parathyroid function and can be applied to primary, secondary, tertiary, and reoperative disease.

Less invasive surgical exploration with similar success of normocalcemia postoperatively has helped to enhance recovery and improve patient care. Whether MIP has the same robust long-term cure as a BNE is currently debated among experts [72–77]. Appropriate patient selection is more than ever required in the era of MIP, as persistent disease is a surgical failure and should remain less than 3%. Efficiency, expense, and resources, in addition to optimizing patient outcome, need to be considered when selecting adjuncts for parathyroid surgery and understandably these factors will vary between institutions, countries, and surgeons. Ultimately if there is any question intraoperatively about residual disease or failure of adjuncts to determine pathology, the approach is converted to a BNE. An experienced endocrine surgeon understands the pathophysiology for parathyroid disease and should be able to develop an approach using the adjuncts available to them in their healthcare environment that will maximize surgical cure. This may not be the same worldwide, but each surgeon and institution will balance their resources and experience to provide the best care for patients.

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