20 Parathyroid Surgery 2020

Janice L. Pasieka

Confucius said *study the past if you would define the future*. To envision what parathyroid surgery will look like in 2020, one needs to understand just how far we have evolved since the parathyroid gland was first identified in an Indian Rhinoceros by Richard Owen in 1850. Ivor Sandstrom, a Swedish medical student, went on to describe the *glandulae parathyroideae* in humans in 1880. A decade later Eugene Gley began to elucidate the importance of the parathyroid glands in calcium homeostasis when he recognized the loss of parathyroid gland caused tetany in dogs. In 1903, Max Askanazy noted the association of enlarged parathyroid glands with von Recklinghausen bone disease (osteitis fibrosa cystica). Many thought the parathyroid enlargement was compensatory, and initially, patients with osteitis fibrosa cystica were treated with parathyroid extract and/or grafts. In 1915, Friedrich Schlagenhaufer suggested that the enlarged parathyroid tumors were the primary cause of the bone disease and recommended surgical excision. It was 10 years later, in 1925, that Felix Mandl performed the first parathyroidectomy in Vienna, excising an enlarged parathyroid gland in a patient suffering from bone disease. The patient's calcium dropped significantly postoperatively and the bone disease, overtime, improved. Unfortunately the disease reoccurred 6 years later. Around the same time in North America, surgeons also embarked on neck explorations for what was later termed "hyperparathyroidism" (HPT). In their 1929 article Barr et al described the condition of osteitis fibrosa cystica associated with muscle weakness, renal stones, high serum calcium, and elevated urinary calcium caused by a solitary parathyroid adenoma. As experience mounted, surgeons soon learned that not all patients had solitary adenomas and recognized the need to explore all four parathyroid glands to rule out the 19 % of patients with multi-gland disease. A bilateral neck exploration (BNE) became the standard surgical approach for this disease. The strategy of a unilateral exploration (ULE) was first suggested by Roth et al. in 1975 and subsequently championed by Tibblin et al. in the early 1980s. The principle of a ULE was the removal of one abnormal gland and identification of a normal gland on the ipsilateral side. Developed long before accurate preoperative imaging, the choice of which side to start the operation was arbitrary. It was not until the development of preoperative imaging did this more limited approach gain acceptance. Minimally invasive surgical techniques in general surgery lead many surgical pioneers to experiment within the realm of endocrine surgery. More directed approaches for parathyroid pathology were explored with the development of various surgical adjuncts.

J.L. Pasieka, MD, FRCSC, FACS (✉)
Department of Surgery,
North Tower,
1403 29th Street NW, T2N 2T9
Calgary, Alberta, Canada
e-mail: janice.pasieka@albertahealthservices.ca

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This chapter describes the evolution of the diagnosis of HPT and the developments in preoperative imaging and surgical adjuncts that have expanded the surgical armamentarium that surgeons utilize today. By reflecting on the past, I hope to be able to speculate on what surgery for HPT will look like in 2020.

Diagnosis

Historically, patients presented with the clinical manifestations of long-standing HPT and end-organ damage such as osteitis fibrosa cystica, nephrolithiasis, and muscle atrophy. Other symptoms such as pancreatitis, peptic ulcer disease, and metal disturbances were added to the growing list of symptoms associated with HPT. Fuller Albright can be credited for studying and documenting the clinical manifestation of HPT in the initial decades of this disease. The ability to measure PTH was not developed until the late 1960s. Widespread use of serum channel autoanalyzers in the 1970s allowed for earlier detection of this disease. Approximately 70–80 % of patients diagnosed with HPT today have none of the classical manifestations of the disease. Compared to the initial presentation of this disease, only 20–30 % of patients today have nephrolithiasis, overt skeletal disease is rare, but osteoporosis is increasing and acute pancreatitis and hypercalcemic crisis are uncommon. However, many studies have demonstrated that HPT patients suffer from vague nonspecific symptoms that are difficult to quantify yet appear to improve following parathyroidectomy. Thus over time, HPT has evolved from a clinical diagnosis with end-organ damage to a biochemical one with vague symptomatology. So much so that HPT can be detected before calcium levels are elevated, so call normocalcemic HPT. With earlier detection, it has been demonstrated the patients operated on between after 1995 had a smaller gland weights and lower preoperative serum calcium levels compared to those operated on between before 1995. This trend of earlier detection could potentially lead to a decreased sensitivity in preoperative imaging and increased rate of failed explorations.

Imaging

In 1983, Ferlin et al. described for the first time a novel method of localizing parathyroid adenomas utilizing two different radioisotopes, technetium-99 and thalium-201. This was based on the concept that technetium was taken up by the thyroid alone, and thallium by both thyroid and parathyroid glands. Double-isotope subtraction scans were labor intense and had a much lower sensitivity of localizing the diseased parathyroid gland compared to an experienced endocrine surgeon. The development of technetium-99m sestamibi (Tc-99m MIBI) in 1989 increased both the use and the sensitivity of nuclear imaging. Tc-99m MIBI is taken up by both thyroid and parathyroid tissue but washes out faster from the thyroid gland. Anatomical detail is enhanced with the addition of single-photon emission computed tomography/computed tomography (SPECT/CT). Although this technique can localize single-gland disease 80 % of the time, unfortunately the sensitivity of Tc-99m MIBI remains poor in multi-gland disease with a sensitivity of only 63 %.

High-resolution ultrasound (US) has become more commonly utilized for preoperative imaging. It provides excellent anatomical detail, is noninvasive, and is inexpensive. It also has the ability to detect concomitant thyroid nodules that must be addressed prior to surgical exploration. Although operative dependent, US has been shown to have an accuracy of 70–80 % for solitary disease, much less for multi-gland disease (35 %). As a result many centers use the combination of US and Tc-99m MIBI, increasing the accuracy in solitary disease to >94 %.

Other techniques such as axial imaging with CT and MRI have been shown to be useful in the re-operative setting. Four-dimensional CT imaging (4DCT), with the additional dimension being time, has improved on the other imaging modalities. In a study of 75 patients, 4DCT had a greater sensitivity for localization of the parathyroid adenoma (88 %) compared to MIBI (65 %) and US (57 %). However, the same group has recently analyzed this technique and found it did not appear to shorten operative time or failure rates.

As such the clinical benefit of 4DCT in first-time HPT patients must be weighed against the increased cost and increased radiation exposure to the patient.

Despite the increased technological advances in preoperative imaging, multi-gland disease remains a challenge. Surgical exploration still is the best localizing modality when done by an experienced endocrine surgeon. What is important to remember is that none of the imaging modalities are diagnostic. The indication for any preoperative imaging modality is for surgical planning only. Patients in whom imaging failed to localize disease are still surgical candidates and the majority will be cure with a BNE.

Surgical Technique

Given that the definition of minimally invasive parathyroidectomy (MIP) is "any surgical access to a selected single gland," it can be said that the first parathyroidectomy was a focused, "MIP" operation. When it became apparent early in the surgical experience that up to 20 % of patients had multi-gland disease, BNE became the standard operation for HPT. With the majority of patients having solitary adenomas, in 1975, Roth et al. first proposed that a unilateral approach would be adequate for the majority of patients as long as the surgeon recognized one abnormal and one normal parathyroid gland on the same side. Unilateral exploration met with early resistance given that 50 % of the time, the surgeon had to convert to a BNE because selection of the operative side was arbitrary. Once preoperative imaging became more reliable, surgeons started to see the benefit of a more focused approach to this disease. In a randomized control trial, Bergenfelz et al. demonstrated that ULE patients had lower incidence of postoperative hypocalcemia and shorter operative time with the same cure rate (97 %) compared to a BNE.

With the development of intraoperative PTH (iPTH) came the move from purely morphologically based operations (BNE, ULE) to utilizing this adjunct to indicate when all abnormally functioning parathyroid tissue was removed. Others experimented with another adjunct borrowed from the sentinel node experience in breast and melanoma. Utilizing a gamma probe to find and measure the radioactivity of excised tissue, several surgeons found that this technique allowed for a focused approach without the need for iPTH or frozen section to confirm parathyroid tissue.

With the development of better preoperative imaging and surgical adjuncts that demonstrated when all autonomously functioning parathyroid tissue was removed, the era of MIP was born. The focused open approach to a single gland demonstrated several advantages over a BNE. An anterior cervical approach allowed for regional anesthesia in selected patients, shorter incisions, and decreased morbidity while maintaining an excellent cure rate of 95–97 %. Advances in surgical endoscopic techniques allowed for the development of a variety of MIP surgical approaches. Miccoli introduced the video-assisted technique, Henry introduced the endoscopic approach, and various "scarless" approaches from the axilla or anterior chest with the use of gasless techniques or robotic surgery have been described. In a review of the literature, currently robotic techniques for parathyroid surgery appear to be reasonable for mediastinal tumors, but there is lack of data to support an advantage over an open cervical approach for the majority of patients. Natural orifice surgery has been applied to thyroid surgery, so it is conceivable that parathyroidectomy maybe be next. The wisdom of development of such a procedure has been questioned.

What Will Parathyroid Surgery Look Like in 2020?

Parathyroid surgery in 2020 will likely have geographic diversity. Not all health-care systems will be able to afford the emerging technology presently driving the changes in the surgical approach to HPT. The utilization of preoperative imaging must remain cost-effective, safe for the patient, and easily accessible. Ultrasound and/or Tc-99m MIBI scan will likely continue to play a key role in the preoperative planning of patients that are suitable for MIP. Three-dimensional virtual imaging will likely become more mainstream in the surgical world in developed nations by 2020. It is only a matter of time before Tc-99m MIBI scans can be superimposed on a 3D virtual model. This will allow the surgeon to plan the ideal operative approach and conceivably allow for simulator training preoperatively.

With the growing number of patients undergoing MIP, utilization of iPTH has increased. Recent advances in the development of a fast iPTH point-of-care assay will allow for faster and simpler means of measuring PTH in the operating room. However, the cost-effectiveness of iPTH has been questioned by some. Intraoperative PTH was found to be advantageous in only 3 % of patients, making BNE, or one could argue a traditional ULE, still the most cost-effective surgical strategy for centers unable to afford this adjunct.

The open focused MIP techniques are more cost-effective than any of the endoscopic or robotic techniques, especially when performed under regional block. Expertise in these more costly endoscopic techniques will likely remain focused in a few centers throughout the world, yet for most, a cervical approach will remain the most commonly performed operation. It is said however, that *history has way of repeating itself*. If true, does that mean we are moving from the era of MIP back to a BNE? Although several authors have reported excellent results with MIP, recently some surgeons have started question whether this technology-driven phenomenon has gone too far. The Achilles' heel for the parathyroid surgeon will always be multi-gland disease. Both iPTH and concordant preoperative imaging have been shown to be inaccurate in multi-gland disease. Siperstein et al in their large prospective study of over 900 patients undergoing BNE found that the combination of localizing studies and iPTH failed to identify multi-gland disease in 16 % of patients. They questioned whether long-term follow-up of these patients will demonstrate a greater recurrence than reported to date. Large prospective databases, with long-term follow-up, are starting to notice a greater recurrence rate in patients undergoing MIP versus a BNE. Schneider et al. analyzed more than 1,000 cases and found overall that there was no difference in the recurrence rate between MIP and BNE (2.5 vs. 1.9 %). Yet when considering the period beyond 8 years alone, there was an 8 % recurrence rate in MIP-treated patients compared to zero in the BNE. This has led one of the MIP staunchest advocate to abandon MIP and return to BNE. Furthermore, there is an ongoing body of literature reporting an increased rate of elevated PTH levels postoperatively in patients considered cured. Elevated PTH with concomitant normal serum calcium has been found to occur between 11 and 44 % of postoperative patients. Although this can occur following a bilateral exploration (36 %), focused approaches have demonstrated a higher incidence of this phenomenon (64 %). A recent 10-year follow-up of MIP patients with persistently elevated PTH demonstrated a 5 % recurrence rate. It is therefore conceivable that many of the 16 % of patients that Siperstein et al. found with multi-gland disease on further exploration will ultimately recur if followed long enough. The clinical relevance of this anomaly is unclear. Let us not forget, however, that the first parathyroidectomy patient recurred 6 years later. Hopefully by 2020 we will have elucidated the clinical significance of this finding with more long-term prospective follow-up studies.

Finally, nonsurgical techniques for HPT are under investigation. Surgery for other slow-growing tumors such as hepatocelluar carcinoma and neuroendocrine tumors has changed over the past decade with the development of ablative techniques such as radiofrequency ablation (RFA) and ethanol injections. Although most of these techniques have been for unresectable disease, the technology does exist and can be adapted to the neck region. Both ethanol and RFA have been utilized for locoregional control in thyroid cancer patients. Injury to the RLN was seen in those treated with RFA in the central compartment, yet it is likely just a matter of time before smaller probes are developed allowing for more precise application. Ethanol injection for HPT was initially reported by the Mayo Clinic group in 1998. In this study, 12/36 patient treated were eucalcemic on follow-up, demonstrating the feasibility of this technique. Little has been written since that report until recently. In 2011 Chen et al. reported their results of percutaneous ethanol injection in persistent or recurrent secondary HPT. Forty-five of the 49 patients have a clinically significant decrease in their PTH. Kovatcheva et al. reported a pilot study utilizing high-intensity focused ultrasound on four patients with HPT. Three patients normalized their calcium and two had normalization of their PTH at follow-up. It is therefore conceivable that nonoperative, percutaneous techniques for ablation of parathyroid adenoma will be part of the surgical strategies offered to patients in the future. It is therefore important that endocrine surgeons be part of this developing technology.

The history of parathyroid surgery illustrates how surgical pioneers, along with technical advances, have changed the surgical paradigm for this disease. We started with removal on one gland, only to find a BNE was needed to ensure long-term cure. More recently, with the development of better imaging and iPTH, we have moved towards a more focused approach to this disease. George Santayana said, *those who do not learn from history are doomed to repeat it.* I would therefore like to dedicate this chapter to my surgical mentors, Norman W Thompson and Bertil Hamberger, two endocrine surgical leaders who taught me the sound principles of parathyroid surgery in the era of BNE. It is those principles that have allowed me to recognize that these technological advances and adjuncts are only tools, and not substitutes, for diligent surgical exploration. Surgery for parathyroid disease will continue to evolve well beyond 2020. However, it is paramount that the next generation of endocrine surgeons has within their armamentarium an ability to safely and effectively perform a BNE and to properly select patients for a less invasive approach.

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