Minimally Invasive Radioguided Parathyroidectomy

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Abstract The surgical management of hyperparathyroidism has evolved over the last 20 years, transitioning from routine bilateral neck exploration to, frequently, a minimally invasive approach. Adjuncts which have made this transition possible include advancements in imaging techniques which allow the pre-operative localization of adenomatous glands, the rapid parathyroid hormone assay and the use of 99-m technetium sestamibi injections the day of surgery to allow for gamma probe detection of abnormal glands. The gamma probe can help with gland localization, which can be particularly useful in a re-operative field or with glands in ectopic locations. It is also helpful in confirming that excised tissue is abnormal parathyroid tissue, alleviating the need for frozen sections during surgery. In this chapter we discuss and review radioguided minimally invasive parathyroidectomy.

Keywords Hyperparathyroidism · Minimally invasive parathyroidectomy · Radioguided parathyroidectomy · Gamma probe · Endocrine surgery · Patient selection · Troubleshooting · Postoperative care · Contraindications

Introduction

Parathyroid surgery has evolved significantly over the last twenty-five years. Bilateral neck exploration (BNE) with excision of abnormal appearing glands was once the gold standard, but in the present day this has largely been replaced by a minimally invasive approach for the majority of patients with primary hyperparathyroidism. This transition in surgical approach is the result in improved imaging techniques, rapid parathyroid hormone (PTH) assays and the understanding of focused uptake of technetium 99-m sestamibi within the parathyroid gland. High-resolution ultrasonography, technetium 99-m sestamibi scanning, and CT scanning with parathyroid protocols have all allowed for pre-operative localization of abnormal parathyroid glands to aid in surgical planning, and better identify those patients whom are candidates for minimally invasive parathyroidectomy. Rapid PTH assays have been used to provide intra-operative feedback regarding appropriate decline in serum PTH levels, indicative of the resection of all hyperfunctioning parathyroid tissue. Finally, along with the use of technetium 99-m sestamibi for pre-operative imaging for localization, an additional dose can be given just before surgery which allows for intra-operative detection of the gamma rays emitted by the technetium 99-m sestamibi taken up within the mitochondria of the pathologic parathyroid glands; this particular technique is referred to as radioguided minimally invasive parathyroidectomy [1].

While the surgical management for secondary, tertiary and hyperplasia still remain BNE with subtotal parathyroidectomy versus four gland parathyroidectomy $\pm$ autotransplant, the above technical advances are still of benefit [2–4]. Radioguidance during resection for these patient populations help guide dissection, shorten operative times, and confirm parathyroid etiology of resected tissue without

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the need for frozen sections [3, 5–7]. As it can help detect supernumerary glands, alerting the surgeon that resection is not yet complete, ioPTH monitoring is still advised.

Patient Selection

While initially thought to be limited to only well-localized parathyroid adenomas, the applications for radioguidance in parathyroid surgery are now widespread [5, 6, 8, 9•, 10, 11•, 12, 13].

In approaching patients with previous neck surgery or with persistent disease after previously attempted parathyroidectomy, the use of the gamma probe can be very helpful [10, 14]. As scar tissue will often distort the normal tissue planes of dissection, the gamma probe can direct the surgeon to the offending gland, allowing for minimal dissection. By decreasing the degree of dissection in a scarred field, risk of injury to surrounding anatomic structures (i.e., recurrent laryngeal nerve) is minimized. Whenever possible, the previous operative reports should still be obtained to provide the surgeon with as much information as possible about the extent of the previous operation.

Patients with negative sestamibi scans can still benefit from a radioguided minimally invasive parathyroidectomy [5]. The negative scan is likely due to multi-gland hyperplasia, or smaller diseased glands. This results in a smaller area of concentrated gamma emission, which is less likely to be seen on imaging. However, during surgery the increased gamma emission from the diseased tissue is sufficient for the gamma probe to detect and direct the surgeon towards the gland with equivalent cure rates compared those patients with positive scans. In general, these glands in negative scan patients have lower ex vivo counts compared to patients with positive scans, but all meet the >20 % rule [5]. While the hyperplastic glands tend to have lower ex vivo counts than adenomatous glands, there can also be a significant amount of overlap between both groups [6]. Because of this, the ex vivo count cannot reliably differentiate an adenomatous gland from a hyperplastic gland, and ioPTH measurements are still needed [3].

Patients with multi-gland hyperplasia, sporadic or familial, may have negative sestamibi imaging prior surgery, but still demonstrate gamma emission of >20 % of background at time of radioguided parathyroidectomy [2, 6]. For those patients with known familial hyperparathyroidism, who generally have multi-gland disease, studies have shown that the gamma probe was able to locate all the abnormal glands, comparable to the patients with sporadic hyperparathyroidism [2]. In both familial and sporadic multi-gland hyperplasia, patients may have a dominant parathyroid gland which with the gamma probe and on imaging can appear to be a single adenoma. For this reason it is important to still use ioPTH monitoring [3].

Patients with both secondary and tertiary hyperparathyroidism demonstrate sestamibi uptake at time of surgery regardless of any pre-operative scan findings. As these patients require complete excision of all parathyroid tissue, intra-operative adjuncts which can help facilitate localization of ectopic or supernumerary glands are invaluable [4, 6]. For these patients, another benefit of the intra-operative gamma probe is the ability to localize hyperplastic autotransplanted parathyroid tissue, which had not been previously marked with either clips or permanent sutures [7, 9•, 15]. While this can help identify unmarked autotransplanted glands, it is still preferable to have the glands marked at time of original surgery. Patients with persistent disease will also need a pre-operative sestamibi scan to ensure the area of recurrence or persistence is due to the autotransplanted graft, and not a supernumerary gland located in either the neck or mediastinum [15].

When pre-operative imaging suggests the presence of a mediastinal gland, radioguided parathyroidectomy can still be planned [16–18]. Based on the pre-operative imaging, surgeons can determine based on gland location which anatomic approach will be best to access the gland of interest. A gland located in the superior mediastinum can often be reached with a traditional cervical incision, while those located more anterior and inferiorly will often require an approach through the chest [18]. In the past, this approach required a morbid median sternotomy for those lower glands; however, today video assisted thoracoscopic surgery (VATS) is most commonly employed to reach these particular glands [16, 17]. A laparoscopic gamma probe is used with traditional thoracoscopic equipment to find the gland within the mediastinum. With this approach, the background is generally measured at the periphery of the lung. Ex vivo counts of >20 % are still indicative of pathologic parathyroid tissue. ioPTH monitoring is still advised, as additional glands may be present. Should PTH levels fail to drop, the surgeon should be prepared and ready to explore the neck at the same setting [16, 18].

99-m technetium sestamibi injections are safe and effective in the pediatric population [19]. Pre-operative localization with sestamibi scanning was helpful in identifying abnormal glands both in normal and ectopic locations, similar to the adult population. Intra-operative use was also successful when the injections are timed appropriately. One marked difference from the adult population is that the recommended dose of 99-m technetium sestamibi is much smaller, at only 1–2 mCi.

Thyroid tissue is also known to take up 99-m technetium sestamibi, due to the mitochondrial content. Normal thyroid tissue will have a quick wash-out of the technetium, allowing for differentiation between thyroid and parathyroid tissue on scan images [3]. However, pathology of the thyroid gland tends to hold the technetium for longer, and

on the later scan images may continue to show uptake in the thyroid. This can make the images less reliable for parathyroid adenoma localization. It was initially thought that this would prevent radioguided parathyroidectomy from being possible. As surgeons continued to gain experience with this technique, it became apparent that radioguidance can be safely used when thyroid pathology is also present [11•]. However, again it is imperative that other adjuncts are used.

Given the increasing incidence of obesity in America, it is to be expected that a significant portion of patients with hyperparathyroidism will be obese. A retrospective of all patients undergoing parathyroidectomy grouped patients based on BMI [20]. They found no difference in the ability of the sestamibi scan to correctly localize the parathyroid adenoma. Interestingly, the morbidly obese patients were found to have heavier gland weights, and tended to have higher ex vivo counts. No difference in complication rates were noted between the morbidly obese patients and the non-morbidly obese patients.

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism, characterized by significantly higher PTH levels, calcium levels >14 mg/dL and a palpable neck mass. Pre-operative suspicion of the diagnosis is imperative to ensure en bloc surgical excision is performed at the first operation, as it is one of the primary means of appropriate oncologic treatment. Use of radioguidance can be beneficial in these cases, especially if patients are requiring re-operation for recurrence [21].

Contra-Indications

The applications for this technique are widespread, with few contra-indications. The main patient populations which cannot safely undergo radioguided parathyroidectomy are pregnant patients, and patients with 99-m sestamibi technetium dose limitations [8]. If patients have had a sestamibi injection in the last three days, surgery is usually delayed to allow for complete washout prior re-dosing with 10 mCi the morning of surgery.

Operative Preparation

After the clinical diagnosis of hyperparathyroidism has been determined via history, physical exam, and serum calcium and PTH measurements, operative planning can commence. In preparation for surgery, patients usually undergo some form of localization study. Options for localization include ultrasound, technetium 99-m sestamibi scan, and CT scan with parathyroid protocol. Imaging quality can vary greatly from institution to institution, so it

is imperative to be knowledgeable of which modality will provide the needed anatomical information at your particular institution. Lastly, if the patient has had previous parathyroidectomy or neck surgery, the operative reports should be reviewed whenever possible. Information from these reports will afford the new surgeon with the details of the previous exploration, tissue removed and anatomic findings, all of which will be helpful in preparation for parathyroidectomy.

Localization studies do not have to be positive to be able to offer a radioguided minimally invasive approach [5]. The patient must be appropriately counseled prior surgery so that they understand that if the offending gland is not found in the anticipated location, a greater degree of dissection will be required, just as would be required if ioPTH levels do not drop appropriately. It is imperative that the operative surgeon reviews these images themselves, and not rely on the read provided by the radiologist. An experienced surgeon will more often call a sestamibi study positive, and have greater accuracy than the radiologist [22•]. This may be due to the surgeon's familiarity of the operative findings given a particular scan appearance, and this experience overtime reinforces the surgeon's ability to determine gland location on the scans. The surgeon's willingness to call a scan positive also reflects the fact that the scan is merely providing a starting point for the surgeon, and should the gland not be found in the initially expected location, exploration continues until it is found and cure confirmed with ioPTH levels. It cannot be stressed enough that localization studies are only for operative planning by the surgeon, and do not contribute to the diagnosis of hyperparathyroidism. The diagnosis of hyperparathyroidism is a clinical one, and negative localization studies should not delay referral for surgery.

The day of surgery, the patient is scheduled for an injection of 99-m technetium sestamibi. Dosing of the sestamibi varies by protocol, but is generally between 1 and 25 mCi [1, 6, 23]. This intravenous injection is given via an upper extremity IV, with the exception of those patients with forearm graft hyperplasia. As an injection in the affected upper extremity results in very high background levels, often the contralateral limb, or more frequently a lower extremity must be used [15]. Ideal injection timing is an hour and a half prior surgery, but a window of 30 min–3 h is generally accepted. If more than six hours have elapsed, the gamma probe is less helpful.

To ensure system efficiency, prior notification to the laboratory that rapid PTH assays will be used during the surgery will hopefully avoid any delays in the running of the assay, and the reporting of results. Depending on the location of the operating room in relation to the rapid PTH assay machine, a designated “runner” may be required to ensure samples reach the lab in a timely fashion. The

laboratory technician should also be aware that the operative team will be expecting immediate notification of the assay results to guide operative decision making.

Surgical Technique

Anesthesia options for radioguided parathyroidectomy range from local to general with either a laryngeal mask or an endotracheal tube. Patients with significant medical comorbidities can safely and comfortably undergo minimally invasive radioguided parathyroidectomy with a cervical block and monitored anesthesia care [24, 25]. In regards to the use of general anesthesia, there was initially concern regarding the use of propofol during parathyroid surgery due to potential interference or alteration of PTH detection with the given assays. However, *in vivo* studies showed no difference between the use of propofol and other anesthetic agents as far as PTH level accuracy [26].

Once adequate anesthesia is established, a PTH level is drawn via a peripheral IV and sent to establish the baseline level. After this is done, surgeon performed ultrasound can be performed which allows confirmation of gland location, and possible modification of incision placement should a lateral approach be planned. The patient is then positioned, prepped and draped in usual fashion.

Prior incision, background counts are obtained over the thyroid isthmus. These counts will be used as a reference point to compare both *in vivo* and *ex vivo* measurements during the procedure.

Incision placement is generally just below the level of the cricoid cartilage in the midline, and is 1–3 cm in length. Through a midline incision a bilateral exploration can be performed, with minimal extension of the incision if needed. Alternatively, a lateral approach can be used in instances where a superior gland is well localized. The incision is then placed directly over the gland. Surgeon-performed ultrasound prior the start of the procedure is necessary in these instances to mark out the appropriate incision location.

For purposes of our description, a traditional midline approach will be taken. After the skin incision is made, dissection is carried down through the platysma. Subplatysmal flaps are not necessary, but can be performed if it is the surgeon's preference. The strap muscles are then divided vertically in midline. The gamma probe is then directed in the wound to measure the sides of the neck or the four quadrants of the neck. The direction of highest count levels is taken to guide further dissection. In patients with positive localization studies, these measures help confirm the imaging results.

Once the gland is visualized, the gamma probe can be used to measure *in vivo* counts. To ensure the targeted

tissue is truly demonstrating elevated counts, measurements should be taken with the probe held at various different angles over the tissue in question. An *in vivo* background ratio of >150 % is strongly suggestive of a parathyroid adenoma, whereas hyperplastic glands may not be quite as high, but are greater than background levels [3, 6, 27••]. The surgeon then isolates the vascular pedicle, controls and divides it. *Ex vivo* counts of excised tissue are measured by placing the excised tissue on the tip of the probe, which is directed towards the ceiling (away from the patient). A >20 % of background levels are expected if the tissue represents pathologic parathyroid tissue. Fat, lymph nodes, benign thyroid and benign parathyroid tissue will be significantly lower [28, 29].

PTH levels are then drawn at 5, 10, and 15 min post excision, and evaluated based on the institutional guidelines for ioPTH monitoring. The generally accepted criteria is based on the work of Dr. Irvin which determined a drop of >50 % of baseline at the 5, 10 or 15 min post excision value is indicative of achieving normocalcemia post-operatively [30, 31•]. These measurements determine the appropriate drop in hormone production, and confirm the completeness of excision. Some groups advocate the use of the gamma probe alone during radioguided parathyroid surgery, stating that ioPTH monitoring is redundant [1, 29]. However, many others have shown that ioPTH is the most reliable adjunct during minimally invasive parathyroidectomy, and plays a critical role in assessing completion of excision during radioguided parathyroidectomy [8, 11••, 27••].

Once all pathologic tissue has been removed, meticulous hemostasis is established, and the incision is closed in standard fashion. We recommend leaving the incision sterile and the patient under anesthesia until the ioPTH results indicate cure. Should the ioPTH levels fail to drop, the incision can be re-opened and exploration continued.

Multiple studies have looked at the various adjuncts used for parathyroid surgery—sestamibi scanning, ioPTH monitoring and radioguidance with a gamma probe [8, 11••, 27••, 32, 33]. Pre-operative sestamibi scanning had a reported sensitivity ranging from 69 to 85 %, the gamma probe was reported to have a sensitivity of 82–98 %, and ioPTH monitoring had a sensitivity of 85–100 %. ioPTH monitoring was consistently found to be the most reliable adjunct during parathyroidectomy reinforcing its critical role in parathyroid surgery.

Trouble-Shooting

If the gamma probe is not carefully held, increased background can be detected from the heart, carotid artery or the salivary glands. When using the probe to guide dissection, try to keep the tip pointed posteriorly, and avoid shallow

angles which may inadvertently pick up emissions from the previously mentioned structures. If tissue in question is truly a positive read, it should continue to have high counts regardless of the probe angle over it.

For maximum utility of the gamma probe, long delays between injection and surgery must be avoided. Gamma emissions slowly decay with time, and wash-out from the parathyroid glands occurs as more time elapses [28]. While some delays may be unavoidable due to emergencies, in general good system level co-ordination between the operating room, nuclear medicine, patient transportation and operative team is imperative to ensure patients have optimal operative timing.

Post Operative Care

The majority of cases can be performed on an outpatient basis. Ice packs over the neck incision are a helpful tool to minimize tissue swelling and provide a degree of local pain control. While we routinely send patients home with a small amount of oral narcotics (hydrocodone), most generally do fine with over-the-counter analgesics. To minimize problems with hypocalcemia post-operatively, patients can be sent home with routine oral calcium supplementation, as well as instructions to take additional doses as needed for any symptoms of hypocalcemia (numbness, tingling, muscle cramping). If patients experience difficulties with symptomatic hypocalcemia in the post-operative period that are not improved with continued oral calcium supplementation, they are started on calcitriol in addition to the oral calcium and instructed to stop proton pump inhibitors if they are on them. The supplements are then weaned based on symptoms in the following weeks. Patients return for a post-operative visit at 1 week after surgery. PTH and serum calcium are measured at this time, and again at 6 months.

Conclusions

Radioguided parathyroidectomy is a great tool for the parathyroid surgeon, and augments the abilities of pre-operative imaging and intra-operative PTH monitoring in performance of minimally invasive parathyroidectomy. It can be invaluable in the re-operative field, in assisting with guiding dissection in cases of a “missing” ectopic gland, in mediastinal exploration, and in identifying hyperplastic parathyroid autograft if location was not marked at time of original surgery. It avoids frozen section for confirmation of parathyroid tissue. However, like any tool, it needs to be routinely used to ensure correct interpretation of the data, as well as surgeon performance based on that data. In order

to become facile in the technique, we recommend routine use for all parathyroid surgery to ensure both surgeon familiarity as well as ability to take advantage of the gamma probe when cases turn out to be more difficult than initially anticipated [10]. Finally, this technology is safe for both patient and operating room staff [34].

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