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Focused Approach to Parathyroidectomy

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Abstract Minimally invasive parathyroidectomy is performed after preoperative parathyroid localization—usually with high-quality sestamibi scans and/or ultrasonography—often under cervical block anesthesia during which a limited exploration is performed. The rapid intraoperative parathyroid hormone assay is then employed to confirm an adequate resection and cure of primary hyperparathyroidism. This article discusses imaging, anesthesia, results, and the surgical management of patients undergoing minimally invasive parathyroidectomy.

Introduction

Approximately 85% of patients with primary hyperparathyroidism (pHPT) harbor a single adenoma and are cured by excision of the incident gland. Thus, with accurate preoperative localization, targeted surgery using unilateral neck exploration under regional or local anesthesia has been developed and evaluated over the past decade and has become the standard of care in an ever-increasing number of specialized centers. Unilateral surgery for pHPT was advocated in 1975, and the side to be explored was chosen based on palpation, esophageal imaging, venography, or arteriography [1]. If both an enlarged and normal gland were found on the initial side, then contralateral cervical exploration was obviated. Other authors advocated a similar approach, arguing that bilateral exploration increased the risk, cost, and morbidity of surgery for pHPT [2]. The Lund University surgeons advocated unilateral parathyroidectomy, which they defined as removal of both an adenoma and a normal gland from one side [3]. The excised tissue was studied microscopically during surgery with oil-red-O, and the decision to stop the operation at this stage was based on demonstration of a reduction in intracytoplasmic fat droplets in the excised adenomatous parathyroid tissue. Both techniques would fail, however, in the setting of a double adenoma on the contralateral side and if the essentially “random” choice of which side to explore was incorrect. Today, minimally invasive parathyroidectomy (MIP) is performed after preoperative parathyroid localization, usually with high-quality sestamibi scans and/or ultrasonography, often under cervical block anesthesia during which a limited exploration is performed, and the rapid intraoperative parathyroid hormone assay is employed to confirm an adequate resection [4].

The indications for MIP are the same as those for traditional cervical exploration, i.e., symptomatic patients or those with asymptomatic pHPT fulfilling the criteria established by the recent National Institutes of Health (NIH) consensus meeting [5]. In addition, we believe that there is a large population of patients with subtle or overt neurocognitive impairment who also benefit from parathyroidectomy [6–8]. Minimally invasive techniques are rarely employed when preoperative localization of the parathyroid tumor has not been performed, when localization is negative, or when it is consistent with multiglandular enlargement. The role of MIP in the setting of familial HPT (i.e., multiple endocrine neoplasia type 1 [MEN1], MEN2A, the hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHPT), and HPT occurring in patients with an underlying mutation in the calcium sensing receptor (CASR) gene is

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evolving [9]. A conventional cervical exploration should be performed in most of these cases, although MIP may prove to have a limited role in specific instances of familial HPT. For instance, in HPT associated with MEN2A, HPT-JT, and FIHPT where uniglandular uptake is noted on preoperative imaging, MIP may be considered [9]. In rare cases when parathyroid carcinoma is diagnosed or suspected preoperatively, the patient should undergo radical resection at the initial operation [10].

Preoperative imaging

The development and refinement of parathyroid imaging has been essential for the development of MIP techniques. Several noninvasive preoperative localization methods are available, including sestamibi-technetium 99 m scintigraphy, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and thallium-201-technetium Tc 99 m pertechnetate scanning. There is consensus that the single best study is sestamibi imaging, especially when sestamibi scans are imaged with single photon emission computed tomography (SPECT), which generates three-dimensional localization (Fig. 1) [11–13]. In 1989, it was first reported that a new agent, technetium-99 m, which was being used for cardiac imaging, also was avidly taken up by parathyroid tissue [14]. Parathyroid cells have a large number of mitochondria, which take up sestamibi/Tc 99 m [5]. Sestamibi, a monovalent lipophilic cation, diffuses passively across cell membranes, concentrates in mitochondria, and accumulates in adenomatous parathyroid tissue because of increased blood supply, higher metabolic activity, and an absence of p-glycoprotein on the cell membrane [16]. Sestamibi imaging can be performed preoperatively to plan a MIP or on the morning of operation, in combination with the use of a gamma probe in the operating room to guide the surgeon during the operation [17]. A meta-analysis of the sensitivity and specificity of sestamibi scanning in 6,331 cases gave values of 90.7% and 98.8%, respectively, and suggested that 87% of the patients with sporadic pHPT would be candidates for unilateral exploration [18]. The sensitivity of sestamibi is limited in multi-glandular disease. In a large study, scintigraphy localized at least one gland in all patients, but only 62% of the total number of hyperplastic glands [19]. SPECT, which allows localization of structures in the anterior/posterior plane, is particularly helpful in detecting smaller lesions and adenomas located behind the thyroid gland. The overall sensitivity for localizing adenomas smaller than 500 mg varies significantly, from 53% to 92% [20, 21]. A major limitation of sestamibi scans is related to the coexistence of thyroid nodules or other metabolically active tissues (e.g., lymph nodes, thyroid nodules, and metastatic thyroid cancer) that can mimic parathyroid adenomas by causing false positive results on sestamibi scans. This limitation can be overcome in part by using the double-tracer subtraction technique of sestamibi, in which both thyroid and parathyroid nodular abnormalities can be diagnosed simultaneously, or in combination with a neck ultrasound to preoperatively distinguish between thyroid lesions and parathyroid enlargement [22]. Sestamibi scans are now being performed with simultaneous CT imaging, yielding correlative functional and anatomic localization.

Ultrasound is effective, noninvasive, and inexpensive, but its limitations include both operator dependency and being limited to application in the neck because it cannot image mediastinal adenomas. The normal parathyroid gland is generally too small to be visualized sonographically, whereas the parathyroid enlargement seen in pHPT is often identified as a homogeneously hypoechoic, extrathyroidal, ovoid mass (Fig. 2). Parathyroid adenomas are typically vascular, and an arterial branch can often be

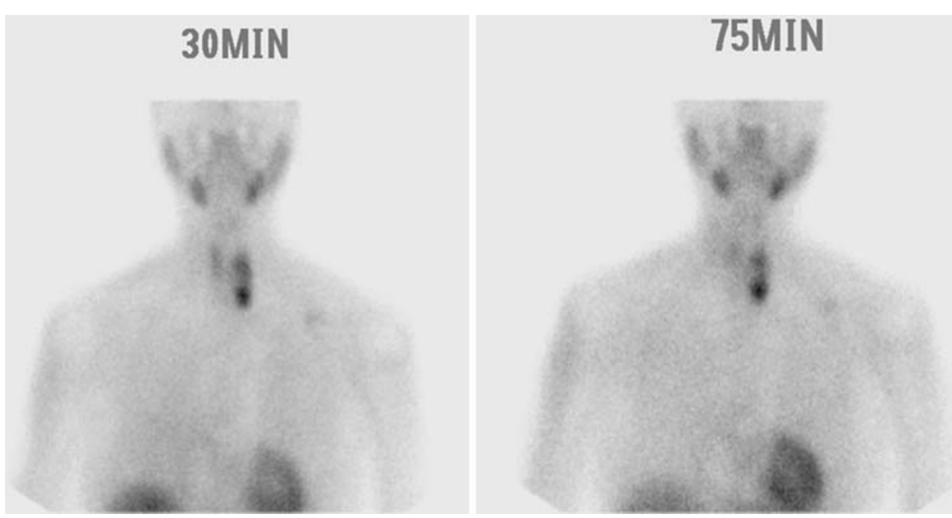

Fig. 1 Sestamibi single photon emission computed tomography (SPECT) imaging in a 69-year-old woman with primary hyperparathyroidism (pHPT) displaying uptake in the left lower position after 30 and 75 min washout, respectively

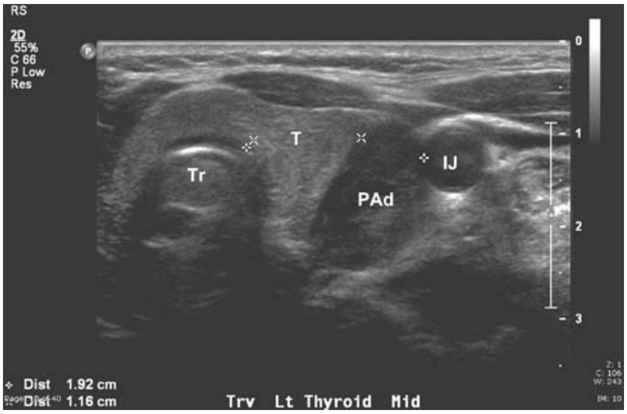

Fig. 2 Corresponding cervical ultrasound from the patient shown in Fig. 1, showing a large hypoechoic cystic parathyroid adenoma (PAd). The left thyroid (T), trachea (Tr), and left internal jugular vein (IJ) are indicated

followed to the superior or inferior pole of the lesion [23, 24]. An additional advantage with ultrasound is the ability to perform fine needle aspiration with rapid PTH measurements of the aspirates, especially in patients undergoing re-exploration [11, 25]. By itself, ultrasound has approximately a 50%–75% true-positive rate, with generally better rates for larger glands [23, 24]. However, when combined with sestamibi, the true-positive rate approaches 90%, with few false positives [26].

Computed tomography and MRI scans both provide cross-sectional imaging and are useful for imaging parathroid tumors in the mediastinum, tracheoesophageal groove, and behind the esophagus. Further, MRI does not involve the use of radiation, and parathyroid adenomas may appear very intense on T2-weighted images. Computed tomography is less expensive, and many studies have shown the two techniques to be of equivalent sensitivity. Computed tomography has a sensitivity of 70% and a specificity of nearly 100%. In contrast to unexplored patients, those that require remedial cervical exploration often require extensive preoperative imaging.

A subset of patients who require re-exploration will have negative, discordant, or unconvincing noninvasive localization studies. Current guidelines recommend that these patients undergo invasive localization procedures in the form of selective parathyroid venous sampling (SVS) with measurements of PTH. Rapid PTH measurement is now being used in the angiography suite, because results are rapidly available on site, and interventional radiologists can obtain additional samples from a region in which a subtle but potentially significant PTH gradient is detected [27]. In a recent study SVS had a sensitivity of 83.3% for the correct localization of a parathyroid adenoma or hyperplastic parathyroid glands, whereas false positive or indeterminate results of SVS were found in 6% and 2%, respectively, of the patients [28].

Anesthesia

The majority of parathyroidectomies are done under general anesthesia using either an endotracheal tube (ETT) or a laryngeal mask airway (LMA). For a number of reasons, we prefer local and regional block anesthesia with monitored anesthesia care (MAC). The regional block is performed by the surgeon in the operating room, and intravenous supplementation is administered by the anesthesia staff (Fig. 3). In most patients, 1% lidocaine containing 1:100,000 epinephrine is used and supplemented during the operation as required. Care is always taken to aspirate before delivering the anesthetic to avoid intravascular administration. We have found that by also infiltrating along the anterior border of the sternocleidomastoid muscle, as well as a local field block, excellent analgesia is obtained in virtually every case (Fig. 4). The total cumulative volume of lidocaine administered is typically 18–25 ml. Intravenous sedation is used to minimize patient anxiety while maintaining an awake, conscious patient who can phonate. Propofol was thought to possibly interfere with the PTH assay, but a recent randomized trial has shown that the PTH assay can be employed during propofol sedation [30].

Regional anesthesia avoids complications associated with general anesthesia, including endotracheal intubation, which has been reported to cause vocal cord changes in up to 5% of patients [31]. Furthermore, exploring a conscious patient permits intraoperative assessment of the superior and recurrent laryngeal nerve functions because the patient can vocalize throughout the procedure.

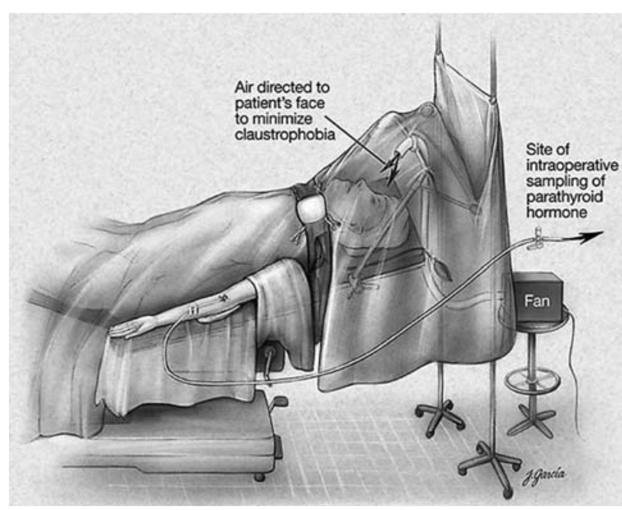

Fig. 3 The patient has a large-bore peripheral intravenous line inserted, which is used for medication and fluid administration, as well as sampling for parathormone (PTH) levels. The patient is awake, and a fan is used to blow room air gently toward his or her face to minimize the sensation of claustrophobia. (From [29] with permission. Copyright ©2002, Lippincott Williams & Wilkins

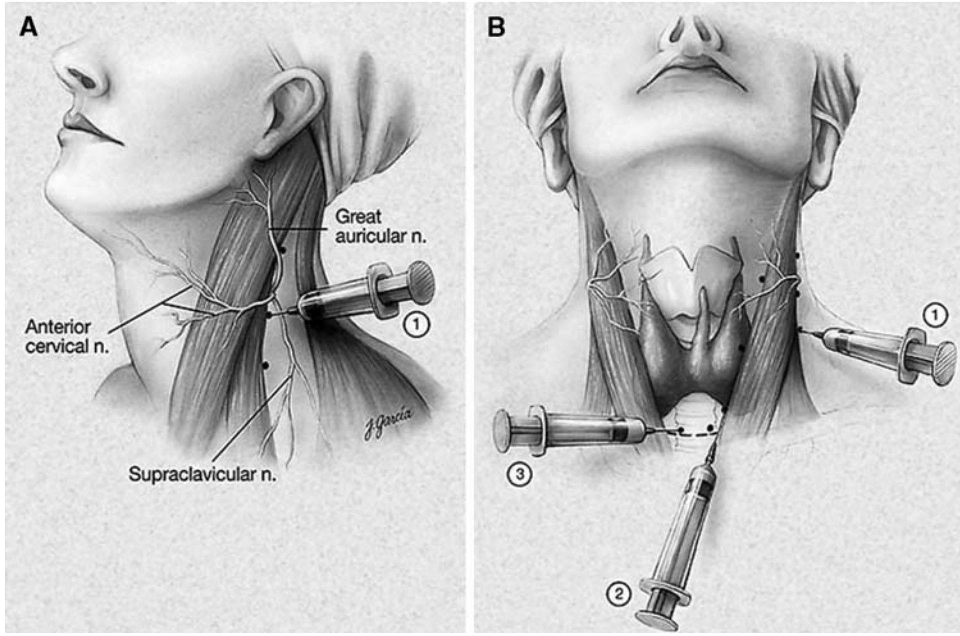

Fig. 4 Cervical block anesthesia. (**A**) A superficial cervical block is administered posterior and deep to the sternocleidomastoid muscle (SCM) (1). (**B**) Local infiltration is also performed along the anterior border of the SCM (2), and a local field block (3) is performed. (From [29], with permission. Copyright © 2002, Lippincott Williams & Wilkins.)

Lo Gerfo has shown that bilateral neck exploration under regional anesthesia can be performed safely and effectively in patients with coexisting thyroid disease and a nonlocalized adenoma. In a series of 236 patients undergoing MIP, 62% had a nonlocalizing sestamibi scan preoperatively or no scan at all, but only 4 required conversion to general anesthesia. Twenty-three percent had a simultaneous procedure performed for thyroid disease, and 85% underwent bilateral neck exploration [32]. We recently reported in 441 consecutive patients that 47 (10.6%) required conversion to general anesthesia [33]. In all instances, conversion was performed in a controlled fashion using neuromuscular blockade, endotracheal intubation, and maintenance of the original surgical field preparation. Sixteen procedures were converted to accomplish simultaneous thyroid resections. An additional 15 were converted because the intraoperative parathyroid hormone level failed to decrease by at least 50% from the baseline after resection of the incident parathyroid tumor and extensive exploration was required. Eight procedures were converted because of technical difficulties related to ensuring adequate protection of the recurrent laryngeal nerve. Five procedures were converted to optimize patient comfort, and two were converted because of the intraoperative recognition of parathyroid carcinoma. One patient experienced a toxic reaction to lidocaine, causing a seizure [33].

Results

The success of MIP has been confirmed by evidence of cure and complication rates that are at least as good as those achieved by conventional bilateral exploration. Specifically, in a series of 656 consecutive parathyroidectomies (of which 401 were performed in the standard fashion and 255 were performed with MIP) between 1990 and 2001, there were no significant differences in complication (3.0% and 1.2%, respectively) or cure rates (97% and 99%, respectively) [34]. Also, MIP was associated with an approximately 50% reduction in operating time (1.3 h for MIP versus 2.4 h for standard operation), a sevenfold reduction in length of hospital stay (0.24 days versus 1.64 days, respectively), and a mean cost savings of $2,693 per procedure, which represents a reduction by nearly one half of total hospital charges.

A prospective randomized controlled trial comparing unilateral to bilateral neck exploration was recently published [35]. In this study of 91 patients, comparison was made between patients assigned to preoperative sestamibi localization and unilateral neck exploration with the rapid PTH assay versus patients assigned to bilateral neck exploration. Patients who underwent unilateral neck exploration had a lower incidence of early postoperative hypocalcemia necessitating calcium supplementation. There were no statistical differences between complication rates, costs, and operative time between the two groups. The study, which was not blinded, was encumbered by a high crossover rate; only 62% of patients assigned to unilateral exploration actually underwent this operation. This may relate to the relatively low sensitivity (71%) of the sestamibi imaging in this population.

Challenging patients

Equivocal imaging

Although the preoperative imaging of patients with pHPT has improved, still approximately 10%–15% of patients present with equivocal or negative imaging results after having undergone sestamibi and/or ultrasonography. We do not routinely perform additional imaging in the previously unexplored patients; rather, these patients are explored under cervical block anesthesia, or if the patients prefers, general anesthesia. Additional imaging techniques by ultrasound-guided fine-needle aspiration (FNA) or by SVS are reserved for patients undergoing remedial cervical exploration [25, 27]. Multi-gland parathyroid enlargement appears to be more common in patients with negative imaging studies, and the intraoperative rapid PTH assay is employed and has been validated in the setting of multi-gland parathyroid disease of both primary and secondary HPT [36].

Static PTH post-excision

In about 85% of cases the rapid PTH assay demonstrates a > 50% drop in the intact PTH level after excision of a single enlarged parathyroid gland, which is consistent with a diagnosis of a single parathyroid adenoma. In the remaining patients, a failure of the PTH to drop suggests additional disease, and further exploration is thus mandatory. Continued exploration unilaterally as well as bilaterally can be done under regional block in most cases, but conversion to general anesthesia is sometimes necessary [33]. Because the most advantageous time to cure pHPT is during the first surgical exploration, it is the obligation of the surgeon to perform a meticulous exploration, evaluating both eutopic and ectopic sites. This exploration includes the retroesophageal space, thymus gland, carotid sheaths, and submandibular region for undescended glands. If the occult gland is still not identified, additional intraoperative adjuncts are used, including ultrasound, and bilateral internal jugular vein sampling to determine if an ipsilateral PTH gradient is present. This technique has guided us to explore upstream and locate occult undescended or partially descended glands. Partial or complete thyroid lobectomy can be performed depending on the suspected location of the missing gland. We generally do not recommend partial or complete sternotomy at the initial exploration unless imaging strongly suggest mediastinal disease that is not accessible by less invasive routes [37]. Despite all of these maneuvers, there still remains a subset of patients in whom the elusive parathyroid is not identified. In this setting, ligation of the blood supply to the missing parathyroid gland is performed. This usually involves ligation of the ipsilateral inferior thyroid artery, but it may also involve devascularization of other arterial branches [38].

Coexistent thyroid disease

Coexistent thyroid disease is relatively common, and it may range from benign nodules to thyroid cancer. In patients undergoing a preoperative ultrasound showing thyroid lesions, appropriate work-up should be done prior to parathyroid exploration. In cases where a preoperative ultrasound has not been performed, intraoperative recognition of coexistent thyroid disease sometimes occurs. A thyroid lobectomy can be performed under regional block, but for more extensive thyroid resections, conversion to general anesthesia is sometimes needed [33].

Previously operated patients

Reoperative parathyroid surgery has haunted endocrine surgeons following the first successful operation for pHPT performed by Felix Mandl in Vienna in 1925. Unfortunately, the patient (Albert J.) developed recurrent disease 6 years postoperatively and ultimately died of recalcitrant hypercalcemia. Despite the success rate of parathyroidectomy in the modern era, surgeons still encounter three groups of patients representing challenging management issues: (1) patients with persistent pHPT having failed initial exploration, (2) patients who develop recurrent pHPT having sustained a period of eucalcemia for greater than 6 months after their initial operation, and (3) patients who have undergone previous neck explorations, particularly total thyroidectomy, who then develop pHPT. In each of these settings, remedial cervical explorations are associated with decreased success rates and increased complication rates [38, 39]. Recently, we reported our experience with remedial surgery over the past 15 years in 130 consecutive operations. The explorations were performed under general anesthesia in most cases, but MIP was employed in 23 patients. The cure rate was similar in the two groups: 94% and 96%, respectively. Again, meticulous preoperative work-up enhances the chance of operative success, and it may include sestamibi scanning, ultrasound, MRI, CT, venous localization, or ultrasound combined with FNA of suspected enlarged parathyroid glands.

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