

# Preoperative Localization and Radioguided Parathyroid Surgery\*

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Clinical or subclinical hyperparathyroidism is one of the most common endocrine disorders. Excessive secretion of parathyroid hormone is most frequently caused by an adenoma of  $\geq 1$  parathyroid gland. Unsuccessful surgery with persistent hyperparathyroidism, due to inadequate preoperative or intraoperative localization, may be observed in about 10% of patients. The conventional surgical approach is bilateral neck exploration, whereas minimally invasive parathyroidectomy (MIP) has been made possible by the introduction of <sup>99m</sup>Tc-sestamibi scintigraphy for preoperative localization of parathyroid adenomas. In MIP, the incision is small, dissection is minimal, postoperative pain is less, and hospital stay is shorter. Localization imaging techniques include ultrasonography, CT, MRI, and scintigraphy. Parathyroid scintigraphy with <sup>99m</sup>Tc-sestamibi is based on longer retention of the tracer in parathyroid than in thyroid tissue. Because of the frequent association of parathyroid adenomas with nodular goiter, the optimal imaging combination is <sup>99m</sup>Tc-sestamibi scintigraphy and ultrasonography. Different protocols are used for <sup>99m</sup>Tc-sestamibi parathyroid scintigraphy, depending on the institutional logistics and experience (classical dual-phase scintigraphy, various subtraction techniques in combination with radioiodine or <sup>99m</sup>Tc-pertechnetate). MIP is greatly aided by intraoperative guidance with a  $\gamma$ -probe, based on in vivo radioactivity counting after injection of <sup>99m</sup>Tc-sestamibi. Different protocols used for  $\gamma$ -probe-guided MIP are based on different timing and doses of tracer injected.  $\gamma$ -Probe-guided MIP is a very attractive surgical approach to treat patients with primary hyperparathyroidism due to a solitary parathyroid adenoma. The procedure is technically easy, safe, with a low morbidity rate, and has better cosmetic results and lower overall cost than conventional bilateral neck exploration. Specific guidelines should be followed when selecting patients for  $\gamma$ -probe-guided MIP.

**Key Words:** hyperparathyroidism; parathyroid adenomas, minimally invasive surgery; parathyroid adenomas, preoperative local-

ization; parathyroid adenomas,  $\gamma$ -probe-guided surgery; <sup>99m</sup>Tc-sestamibi scintigraphy

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**P**rimarily hyperparathyroidism (PHPT) is due to excessive secretion of parathormone (parathyroid hormone [PTH]) by  $\geq 1$  enlarged parathyroid gland (1). Since the introduction of routine serum calcium measurement in the 1970s, this disorder has become one of the most common endocrine diseases in the world (2). During the last 40 y, its estimated prevalence in the United States jumped from about 0.08 per 1,000 (18% asymptomatic) to about 0.5 per 1,000 (51% asymptomatic) (3,4). The prevalence of PHPT in American women  $>40$  y old may be as high as 2 per 1,000 (0.5 per 1,000 in men) (5). In Europe, the estimated prevalence of PHPT is 3 per 1,000 overall, reaching 21 per 1,000 in women 55–75 y old (6). The prevalence in Asia seems to be lower, especially in those countries where serum calcium is not yet routinely measured, with some differences in the pattern of clinical presentations (7).

The classical presentation of PHPT is a clinically overt pattern of recurring nephrolithiasis associated with frank hypercalcemia and low serum phosphate, invalidating bone disease, deep weakness, and reduced life expectancy. During the last 10 y, the more widespread use of screening has allowed clinicians to identify an earlier and more subtle presentation of PHPT: Hypercalcemia is mild (combined usually with normal or borderline-low serum phosphate) and symptoms are absent or subtle.

The earlier recognition of PHPT has increased the number of parathyroidectomies performed for PHPT, considering that about one tenth of all patients with PHPT undergo surgery in an early phase of disease.

## ANATOMY, PHYSIOLOGY, AND PATHOPHYSIOLOGY

A detailed discussion of the pathogenesis, development, and clinical presentation of the various forms of hypercal-

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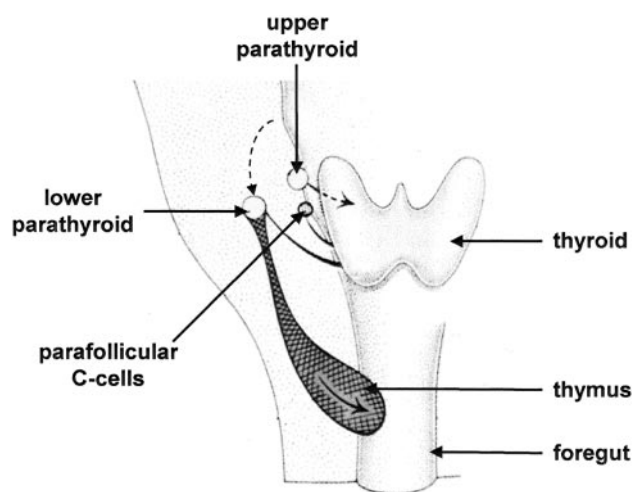
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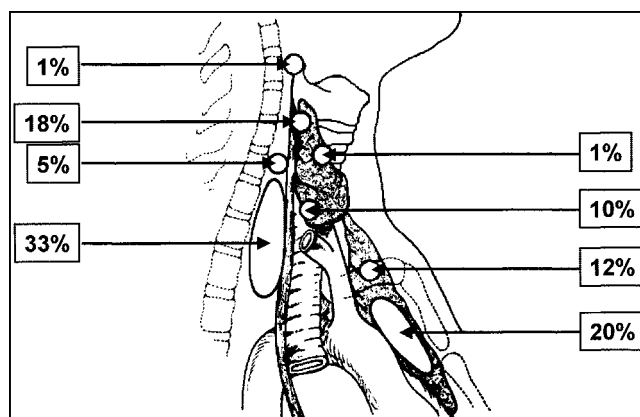
emia and hyperparathyroidism is outside the scope of the present work. The interested reader is referred to excellent reviews on these topics (1,8,9). However, it is necessary to review the basic surgical anatomy and physiology to understand the diagnostic and therapeutic challenges and surgical treatment strategies.

### Anatomy and Embryology of Parathyroid Glands

Normally, there are 2 pairs of parathyroid glands in adult humans. Each gland measures approximately  $6 \times 4 \times 2$  mm and weighs approximately 30–50 mg (total weight, approximately 130–140 mg). Although supernumerous parathyroid glands are present in approximately 2%–5% of the population, the presence of <4 glands is a rarity. Embryologically, the parathyroid glands originate from the endoderm of the third and fourth pharyngeal pouches. Their relative position, however, is inverted as they migrate during fetal life toward their final location (Fig. 1). The glands that are originally positioned in the third pharyngeal pouch (more cranially) initially follow the descent of the thymus and reach their final location at the posterolateral surface of the lower lobes of the thyroid. These glands occasionally leave their connection to the thymus. The glands that are originally positioned in the fourth pharyngeal pouch (more caudally) are closely associated with the embryologic structure of the thyroid gland; they maintain a close association with the fetal thyroid until the descent of both structures to their final location in the neck. These parathyroid glands are positioned at the posterolateral surface of the upper poles of the thyroid lobes.



**FIGURE 1.** Diagrammatic representation of routes of descent of thymus, parathyroid glands, and “last branchial body” during fetal life. Parathyroid glands originating more cranially in third branchial pouch migrate in close association with thymus to reach final position more caudally with respect to parathyroid glands originating in fourth branchial pouch. Final location of last branchial body is intimately embedded in thyroid gland, to constitute parafollicular C-cells producing calcitonin. Thyroid gland originates at “blind foramen” along midline and migrates down to first tracheal ring (modified from (115)).



**FIGURE 2.** Anatomic locations of abnormal parathyroid glands found at reoperation by single group. Most common ectopic sites mirror routes of descent of upper parathyroid glands (short migration path) and of lower parathyroid glands (longer migration path in association with thymus) (modified from (116)).

Migration of the parathyroid glands during fetal development from their original location to the final juxtathyroidal location explains why the surgical approach to the parathyroid glands can be intricate and variable. In most cases, normal upper glands are located posterior to the middle and upper third of the thyroid lobe and posterior to the recurrent laryngeal nerves, cranially to the inferior thyroid artery. The location of normal inferior parathyroid glands, however, is more variable, probably as a consequence of the more complicated migration process, which brings them from a cranial position to a caudal position relative to the other pair of parathyroid glands. In approximately 50% of explorations, the lower parathyroid glands are found posteriorly or laterally to the lower pole of the thyroid lobe, usually within a 20-cm radius. With decreasing frequency, they are found within the thyrothymic ligament, within the thymus in the mediastinum, and intrathyroidal. When parathyroid glands become adenomatous or hyperplastic and enlarge, their location may change somewhat.

Although 80%–85% of parathyroid adenomas are found adjacent to the thyroid gland in their normal location, 15%–20% are ectopically placed (Fig. 2). Ectopic abnormal glands may be found in the anterior superior mediastinum, either within or outside of the thymus, along the esophagus into the posterior superior mediastinum, or very rarely in the midlower mediastinum. Occasionally, they may be found within or even lateral to the carotid sheath. Rarely, an undescended lower parathyroid gland is found high in the neck, anterior to the carotid bifurcation. Finally, 2%–3% of all parathyroid adenomas are intrathyroidal, usually within the lower pole of the thyroid gland. The term “major ectopy” refers to parathyroid adenomas located in the mediastinum, or high in the neck, in or lateral to the cervical neurovascular bundle, or into the thyroid gland. The variability in the number of glands may lead to situations in

which a patient has 4 normal glands in the neck and an abnormal fifth gland located in the mediastinum.

### Calcium Homeostasis and PTH

By containing about 95% of all calcium in the body in the form of calcium phosphate or hydroxyapatite ( $\text{Ca}_5[\text{PO}_4]_3[\text{OH}]$ ), bone and teeth serve as a balancing reservoir for the body fluids, ionized calcium in serum being strictly controlled in the approximate range of 1 mmol/L (or 4 mg/dL).

The calcium ion stabilizes cellular and subcellular structures (membranes and chromatin) and promotes cell adhesion. It is also involved in cell-to-cell signaling, through the voltage-activating channels and interaction with the ryanodine receptor and the inositol triphosphate receptor, as well as with the myofibrillar apparatus and the *N*-methyl-D-aspartate receptor channel. Cells use the calcium ion as an intracellular messenger carrying information generated by hormones and neurotransmitters. Parathyroid cells express a calcium ion receptor (CaR). Calcium ion regulates both the secretory balance and the cell proliferation in the parathyroid glands through the CaR. The CaR is also expressed in the parafollicular cells of the thyroid (regulating calcitonin secretion), in the kidney (regulating calcium and water homeostasis), in osteoblasts and osteoclasts (regulating mineral homeostasis), and in several cell types of the small bowel and proximal colon (regulating intestinal absorption). Additionally, the CaR is also present in many tissues that are not known to be directly involved in the regulation of calcium metabolism. The function of the CaR in such cells—for example, neurones and keratinocytes—is possibly associated to a calcium-sensor-regulated hormone secretion, ion channel function, gene expression, cell proliferation, and cell apoptosis.

PTH, an 84-amino acid single-chain polypeptide with a molecular weight of 9,500 Da, controls the level of ionized calcium in blood and in the extracellular fluid. PTH is synthesized as a 115-amino acid large peptide called the preproparathyroid hormone (prepro-PTH). The “pre” sequence (a “signal” 25-amino acid peptide) is cleaved and rapidly degraded, thus leaving the pro-PTH peptide constituted by 90 amino acids, during the endoplasmic reticular transmembrane transportation. Further cleavage of the “pro” sequence (6 amino acids) produces mature PTH, which is concentrated in the secretory vesicles and granules of parathyroid cells. Granules of a distinct subtype also contain cathepsin B and H proteases in addition to PTH. The proteases’ effect in the granules results in formation of PTH fragments with carboxy-terminal fragments (a small portion of PTH secreted by the parathyroid cells) that are biologically inactive on calcium balance. Intracellular fragmentation of PTH probably represents a regulatory inactivating pathway operating under as yet unidentified conditions.

Although catecholamines, magnesium, and other stimuli can affect PTH secretion, the major determinant of PTH secretion is the blood ionized calcium level. Small reduc-

tions in the extracellular calcium concentration result in increased PTH secretion aimed at restoring the normocalcemia. This regulation is mediated by different concomitant effects of PTH, primarily on the kidney, by increasing tubular reabsorption of calcium, increasing excretion of phosphorus, and increasing the transformation of precursors into the active form of vitamin D (which, in turn, stimulates increased absorption of calcium in the gastrointestinal tract). The resulting restoration of normal calcium levels in the extracellular fluid terminates the feedback loop in the parathyroid glands.

There is a steep inverse relationship between extracellular calcium concentration and PTH secretion, so that a small increase in calcium levels results in a large decrease in PTH secretion (sigmoidal relationship). This effect, which is triggered by the CaR and is mediated via the G-protein and other modulators in the parathyroid cells, involves cellular events ranging from PTH gene expression to transcription, translational and posttranslational processing, and intracellular trafficking regulating vesicular transport, vesicular fusion, and exocytosis.

The mechanism by which lowering of calcium in the extracellular fluid stimulates PTH secretion is less well understood. Acute hypocalcemia induces the release of preformed PTH stored in the parathyroid cells within minutes. However, hypocalcemia lasting several hours stimulates synthesis of PTH at translational level (increased PTH messenger RNA [mRNA]). Persistent or chronic hypocalcemia increases PTH secretion both by increasing the maximal secretory rate per cell through an enhanced expression of the PTH gene and by stimulating proliferation of the parathyroid cells.

Secreted PTH is rapidly metabolized by the liver (70%) and kidneys (20%), disappearing from the circulation with a biologic half-life of 2–3 min. Variations in the blood levels of calcium or  $1,25(\text{OH})_2$  vitamin D, even in a wide range, do not affect this fast peripheral metabolism of PTH. Therefore, the PTH blood levels are determined mostly by the rate of PTH secretion.

Less than 1% of secreted hormone eventually finds its way to PTH receptors in target organs. Cell-surface PTH receptors are mainly located in bone and kidneys, where they trigger responses that increase calcium levels in blood. In the liver, only small amounts of hormone bind to PTH receptors, while most of the intact PTH is cleaved or degraded by cathepsins. In addition to representing one of the main target organs for PTH activity, the kidneys also represent an important metabolic clearance site for PTH, through glomerular filtration and tubular degradation, a mechanism that also involves the PTH carboxy-terminal fragments.

### PHPT

PHPT is a condition characterized by the inappropriate secretion of PTH with respect to the extracellular calcium

concentration. This condition can be caused by parathyroid adenoma(s), parathyroid hyperplasia, or carcinoma. Parathyroid cells exhibit both increased proliferative activity (leading to enlarged glands) and decreased sensitivity to the inhibiting effect of increased calcium concentration on PTH secretion (altered set point). Hyperparathyroidism due to hyperplasia may also be a component of a familial syndrome, such as the multiple endocrine neoplasia 1 (MEN-1) syndrome (87%–97%), MEN-2 (5%–20%), familial hypocalciuric hypercalcemia, hyperparathyroidism-jaw-tumor syndrome, and familial isolated hyperparathyroidism.

In the nonfamilial disease, molecular biology investigations have shown that sporadic parathyroid tumors are clonal in origin, and there is evidence for both activation of oncogenes and inactivation of tumor suppressor genes. In 23%–40% of the parathyroid adenomas, the overexpression of PRAD 1, a cyclin D1 oncogene product involved in cell cycle regulation, has been identified. Using comparative genomic hybridization, candidate loci for dominant oncogenes involved in the genesis of sporadic parathyroid adenomas have been identified on chromosomes 1q, 9q, 16p, 19p, and Xq. The loss of heterozygosity or suppression function on chromosomes 1p, 6q, 9p, 11q, 13q, and 15q has also been detected. The loss of heterozygosity at the MEN-1 locus has been identified in 25%–40% of patients with sporadic parathyroid adenoma, and, to date, this is the only suppressor gene implicated in the genesis of this disease. Evidence for the loss of the suppressor oncogenes retinoblastoma, p53, 1p, 4q, and 13q has been reported in parathyroid carcinoma. Oncogene activation at 1q, 9q, 16p, 19p, and Xq is also seen more frequently in parathyroid carcinomas than in benign parathyroid tumors.

The characteristic abnormality in hyperparathyroidism is the downregulated response of parathyroid cells to reduce PTH secretion in response to elevated calcium. In vitro and in vivo studies have focused on the CaR to explore the role of the calcium sensor in the development of hyperparathyroidism. Abnormalities in CaR expression or function as a consequence of some as yet unidentified genetic mutation(s) may contribute to the failure of PTH secretory regulation.

Also, genetic variations of vitamin D metabolism have been found to be associated with some hyperparathyroidism states. In particular, certain vitamin D receptor (VDR) allelic variants (VDRb, VDRa, and VDRT) are overrepresented in patients with PHPT and are associated with the decreased expression of VDR mRNA; this combination makes the parathyroid cells less susceptible to inhibition by active vitamin D and, therefore, more likely to undergo hyperplastic or adenomatous changes.

Finally, a well-known risk factor for the development of hyperparathyroidism is irradiation of the neck and upper chest for benign diseases, including  $^{131}\text{I}$  treatment for Grave's disease. Interestingly, such risk association has not been demonstrated in  $^{131}\text{I}$  treatment for thyroid cancer. Genetic analysis of radiation-associated parathyroid tumors has disclosed multiple alterations, most commonly involv-

ing losses in 11q and 1p. Such changes in molecular profile are similar to those encountered in those adenomas showing MEN-1 gene abnormalities, thus suggesting some vulnerability of this gene to irradiation.

### Histopathology

Histopathologic criteria used to distinguish adenoma from hyperplasia are not well defined. Current evidence on the histopathogenesis of parathyroid adenoma and hyperplasia is also unclear. Although most adenomas are monoclonal proliferations, suggesting a neoplastic origin, histopathologic and cytogenetic evidence suggests evolution to a monoclonal adenoma from polyclonal hyperplasia and vice versa (10).

Parathyroid adenoma and hyperplasia could well be the same disease entity, representing the opposite ends of the spectrum of phenotypic expression. To avoid confusion and speculation, we prefer using the term "adenoma" interchangeable with "single-gland disease" and "hyperplasia" interchangeable with "multigland disease." MEN and the familial hyperparathyroidism syndromes are associated with multigland disease as a rule. In sporadic PHPT, classically, single-gland involvement (adenoma) is observed in approximately 80%–85% of the cases, and hyperplasia is seen 15%–20% of the cases.

The prevalence of hyperplasia varies considerably in different series, and there appears to be a strong influence of clinical (surgical) diagnosis on the pathologist's diagnosis (11). When subtotal parathyroidectomy is performed, more hyperplasia is diagnosed. When a focused operation is performed with removal of a single gland, it is likely to be called an adenoma. The importance of mild hyperplasia and the best way of diagnosing this condition are yet to be determined. Parathyroid carcinoma is a rare cause of PHPT, accounting for <1% of all cases.

### Secondary Hyperparathyroidism

The most common cause of secondary hyperparathyroidism is chronic renal failure. Even in its early stages, renal impairment results in phosphorus retention; the strict inverse balance existing between the serum levels of phosphorus and calcium induces hypocalcemia, which in turn stimulates PTH secretion. Second, the impaired renal parenchyma cannot fully respond to the increased PTH stimulation by activating the tubular calcium-sparing mechanism and by increasing production of the active form of vitamin D  $1,25\text{-(OH)}_2\text{-D}_3$ . Lastly, there is a certain skeletal resistance to the calcemic action of PTH, due in part to a direct inhibiting effect of phosphorus retention, to downregulation of the PTH receptors (possibly related to decreased CaR expression), and to increased calcitonin secretion.

All of these mechanisms progressively augment and perpetuate the hyperparathyroid state. The altered cellular mechanisms in parathyroid glands in secondary hyperparathyroidism include the decreased inhibiting effect of the

extracellular calcium on PTH secretion consequent to the decreased expression of CaR, despite increased PTH mRNA, and the decreased inhibiting effect of  $1,25\text{-(OH)}_2\text{-D}_3$  on PTH synthesis or secretion as well as on the proliferative activity of parathyroid cells.

### Tertiary Hyperparathyroidism

Secondary hyperparathyroidism usually subsides after successful renal transplantation, which restores a nearly normal mass of functioning renal parenchyma. However, in a few instances, hyperparathyroidism persists after successful renal transplantation. This is due to the development of functional autonomy in  $\geq 1$  enlarged parathyroid gland and is termed “tertiary hyperparathyroidism.” The incidence and true clinical significance of this condition are still a matter of debate. The term tertiary hyperparathyroidism is also used for patients in whom the PTH response due to secondary hyperparathyroidism exceeds the hypocalcemic demands, resulting in hypercalcemia. The related term “refractory secondary hyperparathyroidism” denotes patients who have nonsuppressible PTH secretion, but who are normocalcemic. In both instances, the hyperparathyroid state has reached an autonomous stage and is no longer sensitive to medical treatment.

### Persistent and Recurrent Hyperparathyroidism

Persistent or recurrent hyperparathyroidism occurs in 5%–10% of all patients who undergo surgery for PHPT. Persistent hyperparathyroidism is the most common situation (75%) and is defined as a continuation of the preoperative abnormalities in calcium metabolism in the immediate postoperative period. Causes for the immediate failure of surgical treatment include failure in localization of adenomas, inadequate resection of unrecognized multigland disease, and presence of metastatic parathyroid carcinoma. Factors contributing to the failure involve inexperience on the surgeon’s part and errors in intraoperative frozen section examination on the pathologist’s part. Persistent hyperparathyroidism after surgery is particularly frequent in patients with familial hyperparathyroidism, especially the MEN-1 syndrome (usually in <25% of patients, but up to 40%–60% for less-experienced surgeons (12)).

Hyperparathyroidism presenting after a period of >6 mo of normocalcemia following surgery is termed “recurrent hyperparathyroidism” and is usually linked to continued growth of the remaining parathyroid tissue.

A rare case of recurrent or persistent hyperparathyroidism is termed “parathyromatosis,” which is described as multiple remnants of hyperfunctioning parathyroid tissue scattered throughout the neck or upper mediastinum. This condition probably is due either to inadvertent implantation of parathyroid tissue at the time of parathyroidectomy or to growth of nests of parathyroid tissue left along the route of descent during embryologic development of the parathyroid glands.

## SURGICAL TREATMENT

### Conventional Surgical Approach

The first successful parathyroidectomy was performed in 1925 with bilateral neck exploration (13) and, ever since, has remained the standard treatment of PHPT (14). This time-honored approach, based on excision of any grossly enlarged gland with or without biopsy of the remaining glands, yields a 95% success rate with minimal morbidity, even with 4-gland hyperplasia, in the hands of an experienced endocrine surgeon (15,16). When >1 gland is enlarged, the operative techniques include a  $3\frac{1}{2}$ -gland resection (leaving approximately 50–100 mg of the most “normal-appearing” gland), excising only those glands that are grossly enlarged at the exploration, and a less-common 4-gland parathyroidectomy with subsequent autotransplantation. Success with this approach as measured by return to normal calcium levels depends primarily on the experience and the judgment of the surgeon in recognizing the difference between enlarged or normal-sized glands, although the size of the parathyroid gland does not always correlate well with the secretion of PTH.

When no preoperative imaging was available, bilateral exploration was mandatory, because discrimination between single-gland and multigland disease was solely based on macroscopic appearance of all glands. Introduction of the earlier imaging techniques (US and  $^{201}\text{Tl}/^{99\text{m}}\text{Tc}$ -pertechnetate subtraction scintigraphy) did not really affect such surgical strategy, especially in the case of the first operation, because these techniques were unreliable in detecting multigland disease. Difficulties associated with parathyroidectomy for PHPT relate to the variability in the number of parathyroid glands, the different locations of normal and abnormal glands, and problems in distinguishing normal glands from those that are subtly diseased.

An especially challenging aspect of parathyroid surgery is to distinguish an adenoma from hyperplasia, a distinction that can be difficult not only intraoperatively but also histopathologically. In general, most experienced surgeons believe that by evaluating the size, shape, and color of the parathyroid glands at surgery they can distinguish normal glands from abnormal ones. If 1 gland is enlarged and the others are perfectly normal visually, the diagnosis is an adenoma. Some surgeons attempt to confirm this presumptive diagnosis by obtaining a frozen section of a biopsy of a normal gland. On the other hand, hyperplasia (multigland disease) should result in enlargement of all 4 glands. However, asymptomatic hyperplasia may appear with 1 or 2 normal-sized glands and confuse the diagnosis, even with biopsy. In the absence of a reliable pre- or intraoperative imaging study to identify or localize abnormal parathyroid glands, conventional 4-gland exploration is mandatory.

### Minimally Invasive Parathyroidectomy

With the introduction of  $^{99\text{m}}\text{Tc}$ -sestamibi scintigraphy to identify and locate the parathyroid adenoma preoperatively,

the era of focused exploration or minimally invasive parathyroidectomy (MIP) began (17–19). MIP is gradually replacing the traditional 4-gland exploration as the procedure of choice in many institutions, with comparable cure rates (19,20). The different techniques associated with focused exploration or MIP include  $\gamma$ -probe–guided exploration and novel endoscopic techniques.

The goal of surgery for PHPT is to return the patient's calcium level to normal, although this cannot be the sole index of successful parathyroid surgery; surgery should be accomplished with minimal morbidity, no mortality, low recurrence rates, and a reasonable cost. The success of the surgical treatment depends on the success in localization and identification of abnormal glands. In this respect, the increased sensitivity of parathyroid imaging allows the surgeon to plan a localized exploration designed to remove the common single focus of disease. The incision is small, dissection is minimal, postoperative pain is less, and hospital stay is shorter. These procedures may be done as outpatient surgery, even with local anesthesia.

Other relevant changes in the management of PHPT have been the introduction of intraoperative quick PTH (QPTH) assay and the fact that PHPT is caused in 85%–90% of the cases by a single adenoma. The first clinical application of these concepts resulted in the development of unilateral cervical exploration (21–23), and the assay was refined and clinically popularized by Irvin (24) and Irvin and Carneiro (25).

This assay measures intact PTH levels in the patient's plasma using an immunochemiluminometric technique and can be performed during the operation. Intact PTH has a biologic half-life of 2–3 min. Therefore, a significant drop in QPTH level is observed 5–10 min after removal of the abnormal gland. A fall in QPTH level of >50% of the preoperative level is considered indicative of successful removal. Under these conditions, the QPTH assay has a sensitivity and a specificity of 98% and 94%, respectively, and an overall accuracy of 97% in predicting success of surgery (24,25).

A recent survey of the members of the International Association of Endocrine Surgeons indicated that, in the year 2000,  $^{99m}\text{Tc}$ -sestamibi-based MIP had been adopted by >50% of the surgeons worldwide (59% from America, 56% from Australia, and 49% from Europe and the Middle East). The most popular surgical technique (92%) was the focused approach with a small incision, followed by a video-assisted technique (22%), and true endoscopic technique with gas insufflation (12%). Techniques used to ensure completeness of resection include the QPTH (68%) assay and  $\gamma$ -probe guidance (14%) (20).

MIP has been used for only about 6–7 y; thus, no large-scale long-term follow-up data are available as yet. However, the >95% success rate reported by most authors (as assessed by postoperative normalization of serum calcium and PTH levels) constitutes a sound basis for the favorable MIP results similar to those experienced with the conventional surgical approach also in the long run.

## PREOPERATIVE PARATHYROID LOCALIZATION

### Ultrasonography

The advantages of ultrasound imaging (US) as a noninvasive, low-cost, and nonionizing procedure are somewhat counterbalanced by the fact that this technique is highly dependent on the operator. The accuracy of the parathyroid tumor's localization by US varies as a function of the size and location of the adenoma, whose location in the substernal, retrotracheal, and retroesophageal spaces entails poor sensitivity due to acoustic shadowing from overlying bone or air. The sensitivity of US identification of parathyroid adenomas ranges between 70% and 80% (26,27), whereas the range is much wider (30%–90%) when the detection of simply enlarged parathyroid glands is considered (28). Moreover, the sensitivity of US evaluation falls to 40% in patients who have had prior failed surgical exploration (29).

US is highly sensitive in detecting parathyroid adenomas located behind the thyroid gland (the upper parathyroid glands usually bulge out behind the thyroid lobe) or located beyond the lower contour of the thyroid. However, it can be difficult to visualize upper parathyroid glands located medially (close to the larynx and trachea), located deep in the neck in the para- and retropharyngeal space (28,30,31), or located close to the carotid bifurcation (32,33).

Moreover, parathyroid enlargement can be mimicked by other structures in the neck, such as muscles, vessels, enlarged lymph nodes, and esophagus (33). Therefore, the rate of false-positive US results is not negligible, with specificities reported between 40% and 100% (26–32,34).

On the other hand, US is often used in combination with other imaging procedures for the preoperative localization of parathyroid adenomas before unilateral neck exploration. In particular, the combination of US with thyroid scintigraphy is useful to differentiate enlarged parathyroid glands from thyroid nodule(s) (28,30,35). Thus, US evaluation might be more important in geographic areas where the prevalence of nodular goiter is high. Detection of thyroid nodular disease by US may identify individual patients who may not be appropriate candidates for minimally invasive surgery, even if presenting with a single parathyroid adenoma (28,36). The diagnostic value of such US–thyroid scintigraphy combined imaging approach is limited in identification of intrathyroidal parathyroid adenomas, which usually appear as hypoechoic, low-uptake areas similar to most of the thyroid nodules (33). US-guided fine-needle aspiration has been used to discriminate thyroid nodules from enlarged parathyroid glands (33). The combination of US and thyroid scintigraphy appears to be of value in detecting parathyroid enlargement, particularly in patients with secondary hyperparathyroidism (28,31), and these patients should routinely be investigated with such combined imaging procedure, possibly at a same session (27,28,35).

Despite the fact that it has a lower sensitivity and accuracy than scintigraphy for detecting parathyroid tumors, in some circumstances US imaging plays an important clinical

role. In particular, US is useful to confirm the presence of a scan-positive solitary parathyroid adenoma (the cause of 60%–70% of all cases of PHPT). In such patients, US imaging provides additional information on the depth of the parathyroid adenoma, a feature that is especially useful in distinguishing parathyroid adenomas located behind and close to the thyroid gland from the  $^{99m}\text{Tc}$ -sestamibi-avid thyroid nodules. Furthermore, morphologic imaging provided by US can identify those rare adenomas that are negative on parathyroid scintigraphy because of their prevalent cystic component. Moreover, in patients with hyperparathyroidism due to multigland disease, US can be helpful for detecting nondominant, scan-negative enlarged parathyroid glands. Finally, by providing accurate morphologic evaluation of the thyroid gland, US allows identification of small thyroid nodules (<1 cm), some of which should be considered for US-guided fine-needle aspiration cytology in case of equivocal features such as inhomogeneous echoic pattern, irregular margins, microcalcifications, and intranodular hypervascularization.

### CT and MRI

CT and MRI are often used in the preoperative evaluation of hyperparathyroid patients, especially when the probability of ectopic glands is high, as in patients with recurrent or persistent hyperparathyroidism. When the ectopic adenomas are located in the mediastinum, the high anatomic definition of either CT or MRI provides topographic information of value for planning the most appropriate surgical approach.

Although CT localizes parathyroid adenomas located in the retrotracheal, retroesophageal, and mediastinal spaces better than US, it performs poorly for ectopic lesions located in the lower neck at the level of the shoulders and lesions close to or within the thyroid gland (37–39) and even in discriminating upper from lower parathyroid glands (39,40). The overall sensitivity of CT for preoperative identification of hyperplastic parathyroid glands ranges between 46% and 80%. The sensitivity consistently approaches 80% with intravenous contrast enhancement because adenomas and hyperplastic parathyroid glands are hypervascular. Prior neck surgery affects the sensitivity of CT imaging. Artifacts caused by metallic clips from previous surgery (“sparkler” effect) lower the sensitivity of CT to 46%–58% (39,41).

Imaging of normal parathyroid glands by MRI is poor due to their small size (<5 mm) (42). However, its ability to characterize nodular lesions on the basis of intensity changes in the T1- and T2-weighted images as well as the possibility of contrast enhancement and 3-dimensional reconstruction make this technique particularly attractive (38). On MR examination, enlarged parathyroid glands display a medium intensity on T1-weighted images (like thyroid tissue or muscle) but have considerably increased intensity on T2-weighted and proton density images (43,44). These image patterns, however, do not distinguish parathyroid adenomas from either simple hyperplasia or carcinoma.

Paired evaluations in the same patients have shown that the sensitivity of MRI is equivalent to that of parathyroid scintigraphy. However, the specificity has been found to be consistently lower (44–47). Discrepancies reported by different authors probably depend on the different patient populations studied (primary or secondary hyperparathyroidism, before first or second operation, presence or absence of thyroid nodules) and on the different imaging techniques used.

Most authors believe that MRI is worth performing when parathyroid scintigraphy is negative or equivocal or when it suggests an ectopic gland (46–48). However, some authors suggest the systematic use of combined MRI and parathyroid scintigraphy (despite the associated high costs) because this approach should increase the accuracy and reliability of preoperative identification and localization of parathyroid lesions (43,47).

Because of the less-than-optimal accuracy of conventional imaging techniques, the National Institutes of Health consensus statement on the treatment of PHPT in 1990 concluded that preoperative localization in patients without prior neck surgery was rarely indicated and not proven to be cost-effective, recommending 4-gland exploration as the operation of choice (49).

The whole scenario has dramatically changed more recently, after the introduction of more effective preoperative localization modalities, especially parathyroid scintigraphy with  $^{99m}\text{Tc}$ -sestamibi.

### Parathyroid Scintigraphy

To date, no specific radiopharmaceutical that is capable of concentrating solely in the parathyroid glands has been developed. Scintigraphic exploration of parathyroid tissue is further complicated by the intrinsic close proximity of parathyroid glands to (sometimes true “embedding” within) a metabolically active thyroid gland. Early attempts to circumvent this limitation included the concept of using 2 tracers with different uptake patterns in thyroid and parathyroid glands (50). The first such technique used  $^{75}\text{Se}$ -methionine/ $^{131}\text{I}$  subtraction scanning.  $^{75}\text{Se}$ -Methionine is actively concentrated in both thyroid and parathyroid tissues because of their high metabolic activity. Simultaneously or sequentially administered  $^{131}\text{I}$ -iodide localizes in the thyroid. After applying some “normalization” factor to the 2 scintigraphic acquisitions, the thyroid-only image ( $^{131}\text{I}$ ) was subtracted from the thyroid + parathyroid image ( $^{75}\text{Se}$ -methionine), thus visualizing residual areas of radioactivity concentration corresponding to abnormal parathyroid glands. The technique was rather disappointing due to the technical limitations linked to the imaging equipment available at the time and to radiodosimetric considerations (51).

The subtraction imaging technique was later improved by Ferlin et al. (52), replacing  $^{75}\text{Se}$ -methionine with  $^{201}\text{Tl}$ -chloride and  $^{131}\text{I}$  with  $^{99m}\text{TcO}_4^-$ . Although  $^{201}\text{Tl}$  and  $^{99m}\text{Tc}$  were more suitable radionuclides than  $^{75}\text{Se}$  and  $^{131}\text{I}$  for gamma-camera imaging, the new technique still lacked op-

timal imaging properties for parathyroid glands. Furthermore, there was a nonnegligible radiation burden to patients deriving from  $^{201}\text{Tl}$ , due to its low-energy x-ray emission resulting from electron capture decay. The dual-isotope  $^{201}\text{Tl}/^{99\text{m}}\text{TcO}_4^-$  procedure failed to demonstrate a definite advantage over other imaging modalities due, in part, to a certain degree of intrinsic variability and low reproducibility in interpreting the results among different centers (53,54).

#### $^{99\text{m}}\text{Tc}$ -Sestamibi

After initial experience with  $^{99\text{m}}\text{Tc}$ -sestamibi for myocardial perfusion studies, Coakley et al. incidentally observed that this tracer exhibited significant uptake and retention in the abnormal parathyroid glands of patients with PHPT (55). Successful utilization of  $^{99\text{m}}\text{Tc}$ -sestamibi imaging for localizing abnormal parathyroid glands was subsequently confirmed by numerous reports (56–60) and, with some protocol modifications, has become the parathyroid imaging technique worldwide (61).

The localization of  $^{99\text{m}}\text{Tc}$ -sestamibi in the parathyroid tissue is a function of metabolic activity, accumulation occurring specifically in the mitochondria. The overall uptake in hyperplastic or adenomatous parathyroid glands is linked to the blood flow, gland size, and mitochondrial activity (62). Like other radioactive imaging agents (such as  $^{201}\text{Tl}$ ),  $^{99\text{m}}\text{Tc}$ -sestamibi accumulates both in the thyroid and in the parathyroid tissue within minutes after intravenous administration. However, what makes this tracer especially useful for parathyroid imaging is its different washout rate from the 2 tissues, in that  $^{99\text{m}}\text{Tc}$ -sestamibi is released much faster from thyroid than from parathyroid tissue. This differential retention might be related to some downregulation of the P-glycoprotein system (normally acting as an outflux carrier molecule for various substrates, including  $^{99\text{m}}\text{Tc}$ -sestamibi) in the parathyroid tissue (63–66). When feasible, concomitant suppression of thyroid uptake (induced by exogenous thyroid hormone administration) obviously improves scintigraphic localization of parathyroid lesions with  $^{99\text{m}}\text{Tc}$ -sestamibi (67).

High-quality scintigraphy with  $^{99\text{m}}\text{Tc}$ -sestamibi can accurately localize parathyroid adenomas in 85%–95% of patients with PHPT. The addition of SPECT imaging considerably improved the localization of particular ectopic sites otherwise difficult to explore, such as the retroesophageal space or mediastinum (68–72). It is vital to include the entire chest in the imaging field in all  $^{99\text{m}}\text{Tc}$ -sestamibi imaging protocols for evaluation of potential ectopic sites.

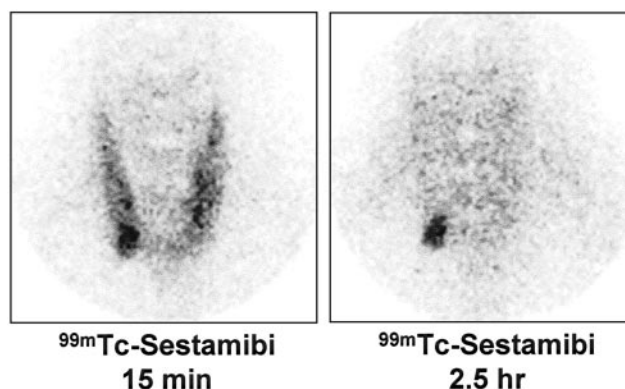
A great wealth of information currently supports the utility of  $^{99\text{m}}\text{Tc}$ -sestamibi scintigraphy in preoperative localization and successful MIP with unilateral neck exploration (73–76). Different  $^{99\text{m}}\text{Tc}$ -sestamibi imaging protocols have been adopted based on the institutional logistics and experience.

*Single-Tracer, Dual-Phase Scintigraphy.* This is the simple basic procedure as originally described by Taillefer et al.

(57), based solely on the differential washout rate of  $^{99\text{m}}\text{Tc}$ -sestamibi from the thyroid and the parathyroid tissue. Planar imaging of the neck and thorax is recorded starting 15 min and then 2–3 h after the intravenous injection of  $^{99\text{m}}\text{Tc}$ -sestamibi (approximately 740 MBq [20 mCi]) (Fig. 3). The scan is considered positive for parathyroid disease when an area of increased uptake that persists on late imaging is found (57). This dual-phase imaging technique is easy to perform and has proven to be highly sensitive and specific, especially in patients with PHPT (77).

There are 2 potential caveats in this dual-phase scintigraphy procedure. First, solid thyroid nodules can concentrate  $^{99\text{m}}\text{Tc}$ -sestamibi quite avidly, regardless of whether they are benign or malignant and whether they appear as “hot” or “cold” on the  $^{99\text{m}}\text{TcO}_4^-$  scan (78). Given the frequent association of nodular goiter with hyperparathyroidism (in >50% of patients according to a recent survey in Italy (79)), this occurrence may produce false-positive results (61,77). In this regard, a delayed  $^{99\text{m}}\text{Tc}$ -pertechnetate or  $^{123}\text{I}$ -iodide scan in patients with known or suspected concomitant nodular goiter may help more accurate interpretation of the  $^{99\text{m}}\text{Tc}$ -sestamibi images (77). The second caveat with the dual-phase, single-isotope technique is the false-negative results. In such cases, absence of an abnormal uptake on delayed images is explained by rapid  $^{99\text{m}}\text{Tc}$ -sestamibi washout, similar to that of thyroid tissue, in some parathyroid adenomas (80,81).

*Dual-Tracer Subtraction Scintigraphy.* This technique combines dual-phase  $^{99\text{m}}\text{Tc}$ -sestamibi imaging with administration of a second radiopharmaceutical that accumulates specifically in the thyroid gland and not in the parathyroid tissue; images are then subtracted to allow detection of focal uptakes specific for abnormal parathyroid tissue. Various protocols have been described based on the type of thyroid-



**FIGURE 3.** Classical single-tracer, double-phase parathyroid scintigraphy with  $^{99\text{m}}\text{Tc}$ -sestamibi. (Left) Image at 15 min shows physiologic early uptake in thyroid gland, with clear focus of moderately increased accumulation at lower pole of right thyroid lobe. (Right) Late scan shows almost complete washout of  $^{99\text{m}}\text{Tc}$ -sestamibi from thyroid gland, with obvious focal retention of radioactivity at lower pole of right thyroid lobe. Minimally invasive radioguided surgery confirmed presence of parathyroid adenoma.



imaging agent used and the sequence of the administration of tracers.

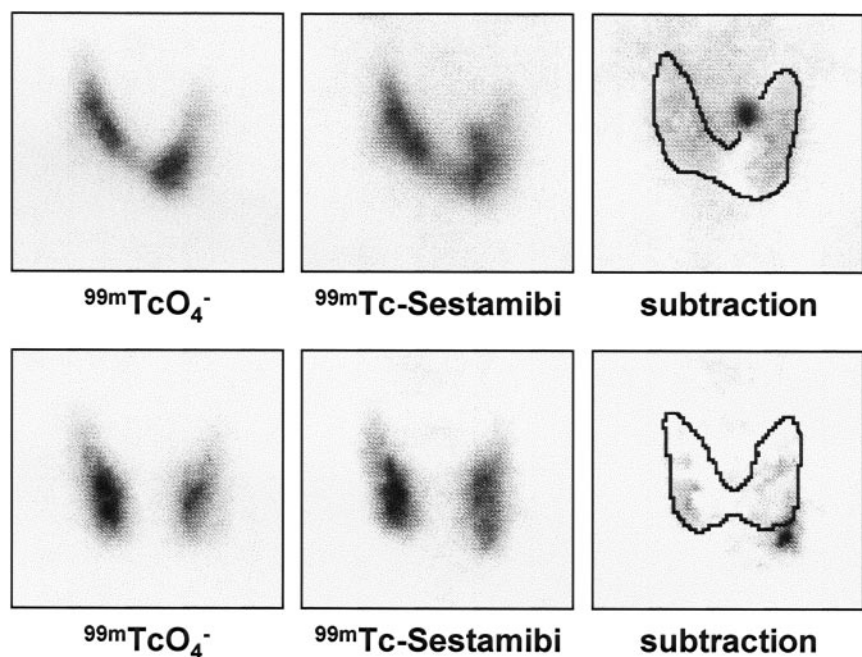
The first such imaging protocol is the  $^{123}\text{I}/^{99\text{m}}\text{Tc}$ -sestamibi, dual-tracer subtraction technique. Patients are administered 10 MBq  $^{123}\text{I}$ -NaI 2–4 h before  $^{99\text{m}}\text{Tc}$ -sestamibi injection. Imaging is performed at different times or simultaneously using 2 separate energy windows (140 keV for  $^{99\text{m}}\text{Tc}$ , 159 keV for  $^{123}\text{I}$ ). The  $^{123}\text{I}$  thyroid image is subtracted from the  $^{99\text{m}}\text{Tc}$ -sestamibi combined thyroid–parathyroid image (58). Wide routine application of this procedure is constrained by the high cost and limited availability of  $^{123}\text{I}$ . The long imaging time required to obtain satisfactory counting statistics at the doses used also is a limiting factor for  $^{123}\text{I}$  thyroid imaging.

Another practical parathyroid imaging technique is the  $^{99\text{m}}\text{TcO}_4^-$ / $^{99\text{m}}\text{Tc}$ -sestamibi, dual-tracer subtraction technique. Patients are injected with 185 MBq  $^{99\text{m}}\text{Tc}$ -pertechnetate and imaging is performed 20 min after injection. Immediately after completion of  $^{99\text{m}}\text{Tc}$ -pertechnetate imaging, patients are injected with 300 MBq  $^{99\text{m}}\text{Tc}$ -sestamibi without changing the patient's position, and a 20-min dynamic acquisition is performed. Although the technique has been reported to have 89% sensitivity and 98% specificity (82), it has its own shortcomings. The technique is hampered by high counting rates originating from  $^{99\text{m}}\text{Tc}$ -pertechnetate uptake in the thyroid tissue overriding those originating from  $^{99\text{m}}\text{Tc}$ -sestamibi uptake. The identification of parathyroid adenomas located behind the thyroid contour, especially on planar images, may not be possible. Geatti et al. modified the technique by reducing the  $^{99\text{m}}\text{Tc}$ -pertechnetate dose to 40 MBq and increasing the  $^{99\text{m}}\text{Tc}$ -sestamibi dose to 400–500 MBq. By adopting this modified protocol, a sensitivity of 95% was achieved in patients with PHPT, without

any false-positive result due to thyroid nodules being observed (27).

To achieve a rapid washout of  $^{99\text{m}}\text{Tc}$ -pertechnetate from the thyroid tissue, potassium perchlorate ( $\text{KClO}_4^-$ ) has been used in the  $^{99\text{m}}\text{TcO}_4^-$ / $^{99\text{m}}\text{Tc}$ -sestamibi protocol (83): 150 MBq  $^{99\text{m}}\text{TcO}_4^-$  are injected intravenously; 20 min later, just before positioning the patient under the gamma camera, 400 mg  $\text{KClO}_4^-$  are administered orally. A 5-min thyroid scan is acquired. Then, 550 MBq  $^{99\text{m}}\text{Tc}$ -sestamibi are injected intravenously without changing the patient's position. A dynamic planar acquisition of seven 5-min frames covering the neck and the entire mediastinum is obtained. The  $^{99\text{m}}\text{Tc}$ -sestamibi dynamic sequence is evaluated sequentially. The most satisfactory 5-min frame is selected and, after proper normalization, is used as a static scan for subtraction of the  $^{99\text{m}}\text{Tc}$ -pertechnetate scan. The frame selection helps in reducing motion artifacts (Fig. 4). By applying this protocol (which also included a US scan of the neck performed in the same imaging session) to a group of 115 patients with PHPT due to a solitary parathyroid adenoma, Casara et al. reported a sensitivity of 94%, with no false-positive results (despite concomitant nodular goiter in 29% of the cases) (28).

The  $^{99\text{m}}\text{Tc}$ -sestamibi/ $^{99\text{m}}\text{TcO}_4^-$ , dual-tracer subtraction technique is a third practical way of improving image interpretation in conventional dual-phase,  $^{99\text{m}}\text{Tc}$ -sestamibi parathyroid scintigraphy. The thyroid imaging agent,  $^{99\text{m}}\text{Tc}$ -pertechnetate, is administered after completion of the late (2–3 h)  $^{99\text{m}}\text{Tc}$ -sestamibi image acquisition. At this late time, most of the  $^{99\text{m}}\text{Tc}$ -sestamibi has already washed out from the thyroid, which, therefore, is easily imaged. The image at 20 min after  $^{99\text{m}}\text{TcO}_4^-$  injection combines  $^{99\text{m}}\text{Tc}$ -pertechnetate uptake with some residual activity from the earlier  $^{99\text{m}}\text{Tc}$ -sestamibi injection (at this time, most of the  $^{99\text{m}}\text{Tc}$ -

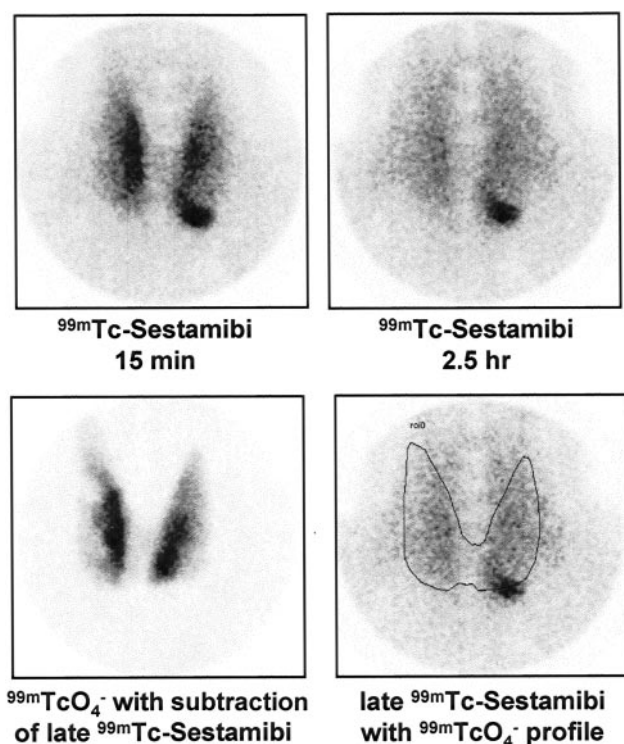


**FIGURE 4.** Parathyroid scintigraphy according to dual-tracer protocol ( $^{99\text{m}}\text{Tc}$ -pertechnetate and  $^{99\text{m}}\text{Tc}$ -sestamibi), with administration of  $\text{KClO}_4^-$  at start of  $^{99\text{m}}\text{Tc}$ -pertechnetate imaging. (Top left) Virtually normal thyroid gland. (Top center) Five-minute scan recorded within 35 min of  $^{99\text{m}}\text{Tc}$ -sestamibi injection shows summation scan suggesting presence of adenoma of upper left parathyroid gland, better outlined when subtracting  $^{99\text{m}}\text{Tc}$ -pertechnetate scan from summation scan (top right). Minimally invasive radioguided surgery confirmed presence of parathyroid adenoma. (Bottom left) Virtually normal thyroid gland. (Bottom center) Five-minute scan recorded within 35 min of  $^{99\text{m}}\text{Tc}$ -sestamibi injection shows summation scan suggesting presence of adenoma of lower left parathyroid gland, better outlined when subtracting  $^{99\text{m}}\text{Tc}$ -pertechnetate scan from summation scan (bottom right). Minimally invasive radioguided surgery confirmed presence of parathyroid adenoma.

sestamibi would be already washed out from the thyroid). The late  $^{99m}\text{Tc}$ -sestamibi image is subtracted from the combined scan to obtain a “pure”  $^{99m}\text{Tc}$ -pertechnetate image, the profile of which will clarify the origin (thyroid vs. parathyroid) of abnormal  $^{99m}\text{Tc}$ -sestamibi uptake (Fig. 5).

Factors affecting the diagnostic accuracy of  $^{99m}\text{Tc}$ -sestamibi imaging of parathyroid glands include regional perfusion, gland size and functional activity, cell cycle phase, and prevalence of mitochondria-rich oxyphil cells (84,85). As little as 100 mg hyperfunctioning parathyroid glands can be detected with application of an appropriate imaging protocol and technique (28,86–89). The use of a pinhole collimator in the neck, with a trade-off in image acquisition time, increases imaging resolution. The chest is best evaluated with a parallel-hole collimator either in the planar or in the SPECT mode with its added information on the depth of the lesion and topographic correlation with other anatomic structures. Although, in principle, SPECT offers the

advantage of better discrimination of focal  $^{99m}\text{Tc}$ -sestamibi retention in thyroid nodules and the parathyroid tissue, in a busy clinical practice this technique is rarely used for evaluating the neck alone. SPECT is most helpful in evaluation of the mediastinum for possible sites of ectopic parathyroid glands, especially to better guide the surgeon in preoperative planning (Figs. 6 and 7). Because detection of parathyroid tumors in ectopic locations is usually not hampered by proximity with the thyroid gland, SPECT can easily be performed, with satisfactory counting statistics, relatively soon after injection of  $^{99m}\text{Tc}$ -sestamibi (e.g., within 30–40 min, immediately after imaging of the neck and thorax with the early planar views). Although only a marginal improvement in the overall detection rate of parathyroid adenomas is reported with SPECT (90,91) (so that the added cost of its systematic routine use is not always justified), most authors now favor a wider application of this imaging modality, especially in patients with recurrent hyperparathyroidism after prior surgery (30,32,68,72,85,91–93).



**FIGURE 5.** Double-phase parathyroid scintigraphy with  $^{99m}\text{Tc}$ -sestamibi in patient with multinodular goiter. (Top left) Image at 15 min shows physiologic early uptake in thyroid gland, with clear focus of increased accumulation at lower pole of left thyroid lobe. (Top right) Late  $^{99m}\text{Tc}$ -sestamibi scan shows some residual activity in thyroid gland, with obvious focal  $^{99m}\text{Tc}$ -sestamibi retention at lower pole of left thyroid lobe. Second tracer ( $^{99m}\text{Tc}$ -pertechnetate) was administered after recording delayed  $^{99m}\text{Tc}$ -sestamibi scan. (Bottom left) Image obtained by subtracting delayed  $^{99m}\text{Tc}$ -sestamibi scan from summation scan recorded after  $^{99m}\text{Tc}$ -pertechnetate administration was used to draw profile of thyroid gland, which was then superimposed on delayed  $^{99m}\text{Tc}$ -sestamibi scan (bottom right) for better anatomic localization of parathyroid adenoma (confirmed by minimally invasive radioguided surgery).

#### $^{99m}\text{Tc}$ -Tetrofosmin

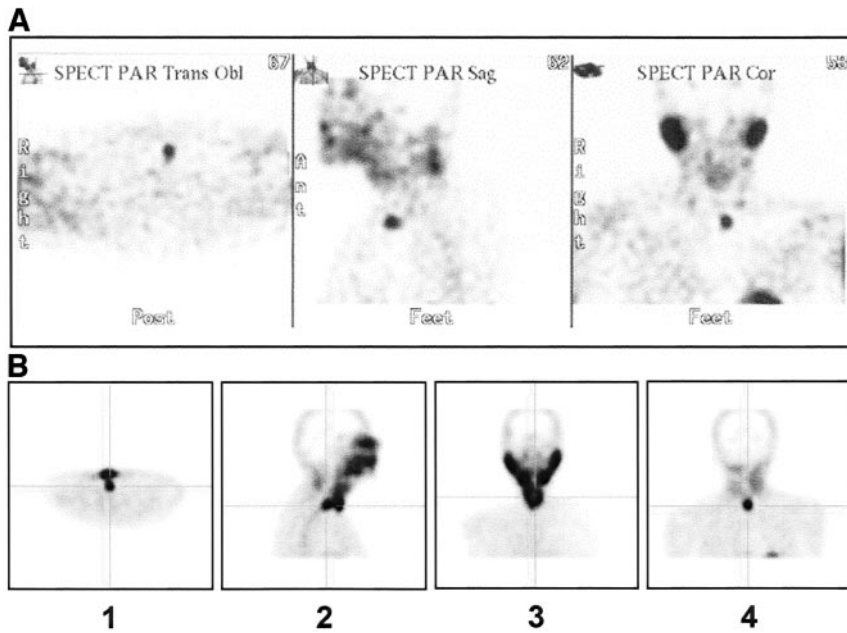
As an alternative to  $^{99m}\text{Tc}$ -sestamibi, several authors have proposed the use of  $^{99m}\text{Tc}$ -tetrofosmin for parathyroid scintigraphy. Although their mechanism of intracellular accumulation and retention differs somewhat ( $^{99m}\text{Tc}$ -sestamibi accumulates primarily in the mitochondria, whereas  $^{99m}\text{Tc}$ -tetrofosmin is retained primarily in the cytosol fraction), these 2 tracers are used virtually interchangeably as myocardial perfusion agents and as nonspecific oncotropic agents. However, washout of  $^{99m}\text{Tc}$ -tetrofosmin from the thyroid parenchyma is considerably slower than that of  $^{99m}\text{Tc}$ -sestamibi, so that the single-tracer, dual-phase procedure is not always reliable when using  $^{99m}\text{Tc}$ -tetrofosmin (94–97). Therefore, the use of a second, thyroid-avid tracer is mandatory for better discrimination of thyroid or parathyroid areas of focal uptake in the neck. In conclusion,  $^{99m}\text{Tc}$ -tetrofosmin can be used for parathyroid scintigraphy, provided it is used within a dual-tracer subtraction protocol (96).

#### INTRAOPERATIVE PARATHYROID LOCALIZATION

Radioguided minimally invasive surgery for PHPT is feasible when preoperative scintigraphy identifies a single focus of radiotracer uptake, indicating a parathyroid adenoma.

#### Timing in Radioguided Surgery

$^{99m}\text{Tc}$ -Sestamibi is the only radiopharmaceutical currently used to identify the site of parathyroid adenomas by pre- or intraoperative radioguidance. The success of radioguided surgery is dependent on the differential kinetics of  $^{99m}\text{Tc}$ -sestamibi in thyroid and parathyroid glands.  $^{99m}\text{Tc}$ -Sestamibi washes out more rapidly from the thyroid than from the parathyroid glands. Intraoperative  $\gamma$ -probe localization of an adenoma is most successful within a very narrow time window, 2–3 h after tracer injection. To opti-



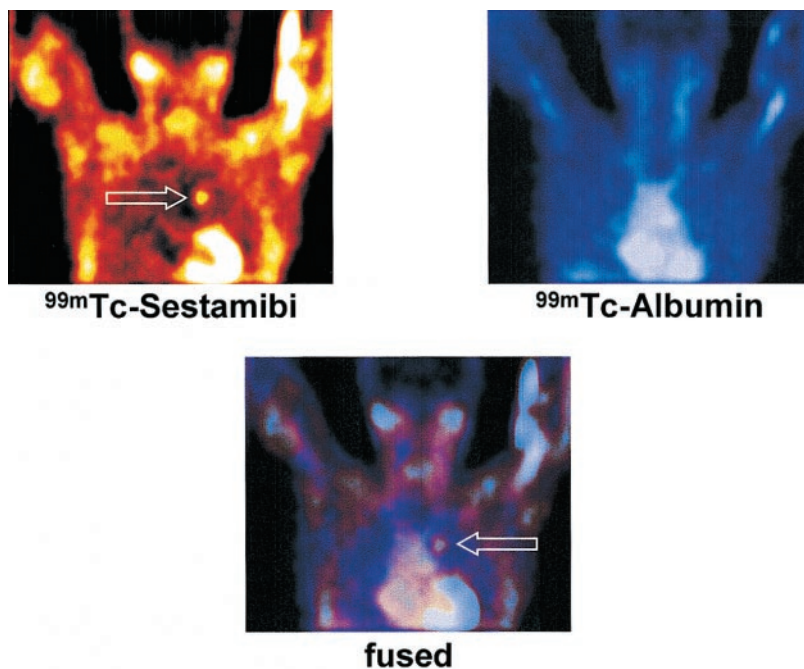
**FIGURE 6.** Anatomic localization of ectopic parathyroid adenomas by  $^{99m}\text{Tc}$ -sestamibi SPECT. (A) Patient with persistent hyperparathyroidism after total thyroidectomy and bilateral neck exploration performed because of concomitant multinodular goiter and PHPT. Tomographic slices in transverse (left), sagittal (center), and coronal (right) planes define anatomic location of single focus of intense  $^{99m}\text{Tc}$ -sestamibi uptake in anterior planes of upper mediastinum. Minimally invasive reoperation under radioguidance enabled surgeon to remove parathyroid adenoma located within thymus. (B) Tomographic slices in transverse (1), sagittal (2), and coronal (3 and 4) planes define anatomic location of single focus of intense  $^{99m}\text{Tc}$ -sestamibi uptake behind thyroid gland. Surgery revealed parathyroid adenoma located in retroesophageal space.

minimize the parathyroid-to-thyroid count ratio, and, thus, improve the  $\gamma$ -probe performance, different protocols have been introduced.

Norman and Cheda (18) perform scintigraphy on the day of surgery. Patients are administered a full imaging dose of  $^{99m}\text{Tc}$ -sestamibi (740 MBq) in the nuclear medicine department, where parathyroid scintigraphy is performed per a dual-phase protocol at 20 min and 2 h.  $\gamma$ -Probe-guided surgery begins at approximately 2.5–3 h after the injection of  $^{99m}\text{Tc}$ -sestamibi. This protocol offers the advantage of performing parathyroid scintigraphy and surgery on the same day (98,99). It implies, however, that the parathyroid

adenoma has already been identified with prior parathyroid scintigraphy or other imaging modalities.

Casara et al. (100,101) and Rubello et al. (102) perform intraoperative  $\gamma$ -probe-guided surgery using a separate-day protocol. Parathyroid scintigraphy with  $^{99m}\text{Tc}$ -sestamibi is performed a few days before surgery usually with a double-tracer subtraction imaging protocol. A low dose of  $^{99m}\text{Tc}$ -sestamibi (37 MBq) is injected in the operating room just before the start of the operation. Intraoperative PTH monitoring (QPTH) is also used to confirm complete removal of the hyperfunctioning parathyroid tissue. This low-dose  $^{99m}\text{Tc}$ -sestamibi protocol offers additional advantages of



**FIGURE 7.** Anatomic localization of ectopic parathyroid adenoma by combined  $^{99m}\text{Tc}$ -sestamibi and  $^{99m}\text{Tc}$ -albumin SPECT. (Top left) Tomographic coronal slice obtained after  $^{99m}\text{Tc}$ -sestamibi administration demonstrates focal area of abnormal tracer uptake in mediastinum, whose exact anatomic location with respect to other mediastinal structures remains uncertain. (Top right) Dose of  $^{99m}\text{Tc}$ -albumin was then injected (without moving patient) as indicator of intravascular space, and another SPECT image was acquired under same conditions as  $^{99m}\text{Tc}$ -sestamibi SPECT. (Bottom) Image fusion of corresponding coronal slices demonstrates that lesion with focal uptake of  $^{99m}\text{Tc}$ -sestamibi is located in aortopulmonary window. Subsequent radioguided surgery confirmed presence of parathyroid adenoma in anatomic location identified by fusion analysis.

minimized radiation exposure to the surgeon and to the team and possibly improves the chance of identification of parathyroid lesions with rapid  $^{99m}\text{Tc}$ -sestamibi washout (80,81). This protocol was also found to be particularly useful in patients with concomitant nodular goiter (27,28), although these patients are not optimal candidates for minimally invasive radioguided parathyroid surgery, due to the high false-positive uptake sites in the thyroid mimicking parathyroid adenomas.

Bozkurt et al. describe a patient-specific, optimal time-to-surgery protocol to improve operative success in  $\gamma$ -probe-guided parathyroid localization (103). Using double-phase  $^{99m}\text{Tc}$ -sestamibi parathyroid scintigraphy (500–700 MBq), the  $^{99m}\text{Tc}$ -sestamibi time-activity curves for both parathyroid and thyroid glands are generated. The optimal time to surgery was determined on the basis of the time at which the target-to-background ratio was maximum. On the day of surgery, patients receive the same dose of  $^{99m}\text{Tc}$ -sestamibi and are taken to the operating room at the time of optimal target-to-background ratio that was determined by the preoperative imaging study.

In addition, several groups use a modified separate-day protocol, in which a higher dose of  $^{99m}\text{Tc}$ -sestamibi is injected immediately before surgery (about 370 MBq) to reach higher target-to-background ratios, which are particularly useful for identification of ectopic parathyroid adenomas.

#### Operative Technique

On the basis of the specific protocol adopted, minimally invasive radioguided parathyroid surgery is started 30 min to 3 h after  $^{99m}\text{Tc}$ -sestamibi administration. After induction of the preferred anesthesia (local, regional, or general), external  $\gamma$ -probe scanning is performed to locate the hot spot. Once the hot spot is identified (cutaneous marking by the nuclear medicine physician could be very helpful), a small incision is made and the space under the strap muscles is entered. The probe is then inserted into the skin incision (maximum, 1–2 cm), directly over the presumed location of the adenoma. The high-pitch signals produced by the  $\gamma$ -probe lead the surgeon toward the location with highest radioactivity. A parathyroid-to-thyroid ratio higher than 1.5 strongly suggests the presence of a parathyroid adenoma, whereas typical parathyroid-to-background ratios (excluding the thyroid tissue) range between 2.5 and 4.5. After the parathyroid lesion is removed, the ex vivo counting rate of an adenoma is at least 20% and usually is 50% higher than the thyroid background (104). The surgical bed is scanned again to ensure the complete removal of the adenoma by establishing a new level of background radioactivity. A ratio greater than 1.2 between the ex vivo lesion counts and the residual background counts is another criterion used to determine successful excision of an abnormal gland (104). The errors due to equivocal or false-positive scans are thus decreased by the use of an intraoperative  $\gamma$ -probe. It should be noted, however, that similar count ratios can occasionally

be observed also when removing simply hyperplastic parathyroid tissue or even a thyroid nodule (89,101). A final assessment of radioactivity in all 4 quadrants at the end of the surgical exploration increases the surgeon's confidence in the completeness of the parathyroidectomy.

$\gamma$ -Probe guidance enables the surgeon to perform a rather small skin incision with improved cosmesis. The technique can also be performed under local anesthesia. The operating time is reduced, and the patient can be discharged from the hospital earlier (18,105,106). As with other radioguided surgical procedures (e.g., sentinel lymph node biopsy), a successful clinical outcome requires a smooth coordination between the nuclear medicine physician, the surgeon, and the pathologist).

#### GUIDELINES AND CONTROVERSIES IN RADIOGUIDED MIP

The guidelines for a  $\gamma$ -probe-guided MIP (GP-MIP) are based on the clinical profile of patients and the preoperative  $^{99m}\text{Tc}$ -sestamibi imaging study findings. GP-MIP is an appropriate approach in patients who have a high probability of a solitary parathyroid adenoma established on the basis of  $^{99m}\text{Tc}$ -sestamibi scintigraphy (and US imaging), significant  $^{99m}\text{Tc}$ -sestamibi uptake in the parathyroid adenoma, no co-existing  $^{99m}\text{Tc}$ -sestamibi-avid thyroid nodules, no history of familial hyperparathyroidism or MEN, and no history of previous neck irradiation (18,28,100). Following these criteria, the fraction of patients who are candidates for GP-MIP is about 60%–70% of all cases of PHPT (39,100,107). Additional settings in which radioguided parathyroidectomy is indicated include reoperation for persistent or recurrent hyperparathyroidism and ectopic adenomas (especially, major ectopy).

In some clinical settings, the most frequent cause of exclusion from GP-MIP was the diagnosis of a concomitant nodular goiter (101). In fact, thyroid nodules can give false-positive results both at preoperative scintigraphy (57,108,109) and at radioguided surgery (109,110) because >50%–60% of them can trap and retain  $^{99m}\text{Tc}$ -sestamibi similarly as parathyroid adenomas (61,110). This problem is partly overcome by double-tracer subtraction protocols ( $^{123}\text{I}/^{99m}\text{Tc}$ -sestamibi or  $^{99m}\text{Tc}$ -pertechnetate/ $^{99m}\text{Tc}$ -sestamibi) that are therefore generally preferred for preoperative localization in areas with high prevalence of thyroid nodular goiter, as in many European countries (61,109).

Considering also the possible association of a parathyroid adenoma with nodular goiter, the use of a double-tracer technique or of  $^{99m}\text{Tc}$ -sestamibi scintigraphy combined with US examination might be useful in planning the type and extent of surgery (89,101): (a) bilateral neck exploration in the case of any PHPT patient with concomitant multinodular goiter; (b) unilateral neck exploration in the case of a solitary parathyroid adenoma with concomitant nodular goiter located in the ipsilateral thyroid lobe; (c) GP-MIP in the case of a solitary  $^{99m}\text{Tc}$ -sestamibi-avid parathyroid adenoma with a normal thyroid gland; and (d) endoscopic

surgery in the infrequent case of a solitary  $^{99m}\text{Tc}$ -sestamibi-negative (but US positive) parathyroid adenoma with a normal thyroid gland. Thus, intraoperative  $\gamma$ -probe guidance can simply be considered as a completion of accurate preoperative scintigraphic imaging.

The advantages of intraoperative  $\gamma$ -probe guidance in parathyroid surgery can be summarized as follows: (a) The  $\gamma$ -probe guides the surgeon to the site of the parathyroid adenoma, thus facilitating the approach and shortening the surgical times, especially for parathyroid adenomas located in an ectopic site or deep in the neck (89,102). (b)  $\gamma$ -Probe guidance is helpful in evaluating the completeness of parathyroid tissue removal (18,89,102,104). (c) Use of the  $\gamma$ -probe for measuring ex vivo radioactivity of the removed specimen helps in verifying the effective removal of parathyroid tissue and, thus, in evaluating the success of surgery (18,89,102,104). As mentioned above, the so-called “20% rule” proposed by Murphy and Norman (104) has been reported to yield a 100% accuracy in distinguishing solitary parathyroid adenomas from hyperplasia. An in vitro  $\gamma$ -probe assessment that does not meet the above criteria should direct the surgeon to continue the exploration, obtain intraoperative QPTH measurement, and perform frozen section analysis of the removed tissue.

Inconsistent results with the 20% rule, or even when using higher thresholds such as 30%–40% above background, reported by other groups, might be related to the variations in administered doses, timing of  $\gamma$ -probe measurements, and background references (89,107,111,112). The different sensitivities of the various  $\gamma$ -probes used and the use of collimated or uncollimated probes also significantly contribute to the variability of reported results with GP-MIP (89,107).

Although  $\gamma$ -probe guidance is highly effective for the intraoperative detection of solitary parathyroid adenomas, difficulties might arise in those rare patients with multigland disease with a “dominant” parathyroid gland. In these patients, intraoperative  $\gamma$ -probe counting in a nondominant, yet adenomatous, parathyroid gland can be significantly lower than the counting rate in the dominant gland, thus leading the surgeon to underestimate the presence of multigland disease (89,107,113). In this clinical setting, intraoperative QPTH assay offers the advantage of identifying patients with multigland disease (114), including those with scan-negative enlarged parathyroid glands. On the basis of these considerations, confirmation of complete parathyroid removal by intraoperative QPTH assay is still advisable, even when performing GP-MIP both at first surgery and at reoperation (89,100,102,107). Although intraoperative QPTH assay does not seem to increase significantly the success rate of surgery in carefully selected patients with a solitary parathyroid adenoma (114), there are no relative or absolute contraindications to using this procedure, alone or in combination with intraoperative  $\gamma$ -probe guidance.

$\gamma$ -Probe guidance has also been useful when performing a standard bilateral neck exploration, because it increases

the accuracy of preoperative  $^{99m}\text{Tc}$ -sestamibi scintigraphy (89,99,110). A negative preoperative  $^{99m}\text{Tc}$ -sestamibi scan and contemplation of bilateral neck exploration should not preclude radioguided parathyroid surgery.

The cost-effectiveness of the image-guided minimally invasive approach—that is, the expense of imaging with equipment required—has been questioned. However, the potential savings from decreased operating time and hospital stay were found to be comparable or in favor of the minimally invasive approach in many analyses (73,107,113). A major concern when using a  $^{99m}\text{Tc}$ -sestamibi-guided focused unilateral surgical approach is a possible failure to diagnose multigland disease. A recent review demonstrated that the reported incidence of multigland disease in a series in which bilateral explorations were done is 20%, whereas the incidence with focused unilateral explorations is only 5% (11). The difference could be explained by the lower sensitivity of  $^{99m}\text{Tc}$ -sestamibi localization in multigland disease, resulting in underdiagnosis of this occurrence. However, the possibility of overdiagnosis of multigland disease with the bilateral approach (biased pathology) cannot be discarded. The evidence-based support for MIP comes from the fact that the recurrence rates following focused unilateral approaches have not been higher than those of the bilateral approach.

## CONCLUSION

GP-MIP is a very attractive surgical approach to treat patients with PHPT secondary to solitary parathyroid adenoma. GP-MIP has proven to be technically easy, safe, and with a low morbidity rate in the hands of a skilled surgeon (18,28,89). The advantages of GP-MIP over bilateral neck exploration in patients with PHPT secondary to solitary adenoma can be summarized as follows: (a) smaller incision, less surgical trauma; (b) shorter length of surgery, anesthesia, and hospital stay; (c) less postsurgical pain; (d) better cosmetic results; and (e) lower overall cost. In contrast to minimally invasive endoscopic surgery, GP-MIP can be performed also for reintervention in patients with persistent or recurrent hyperparathyroidism (89,99).

The guidelines for GP-MIP can be summarized as follows: (a) Only patients with a high probability of a solitary parathyroid adenoma and a normal thyroid gland should be considered. (b) The most appropriate preoperative scintigraphic protocol should be selected on the basis of thyroid and parathyroid imaging information. (c) The radiation exposure dose to the surgeon and operating theater personnel should be minimized by administering the lowest dose of  $^{99m}\text{Tc}$ -sestamibi proven to be effective for performing GP-MIP. (d) Both in vivo or ex vivo  $\gamma$ -probe counting and intraoperative QPTH measurement should be used to evaluate the success and completeness of surgery.

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