

## Parathyroid Localization and Implications for Clinical Management

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**Clinical Context:** The prevalence of hyperparathyroidism, especially primary hyperparathyroidism, has increased in recent decades due to improvements in diagnostic techniques with a corresponding surge in parathyroid surgery, leading to the development of focused, minimally invasive surgical approaches. Focused parathyroidectomy is predicated on preoperative localization of suspected parathyroid pathology. As a result, there has been a proliferation of parathyroid imaging modalities and protocols, resulting in confusion about their indications and applications.

**Evidence Acquisition:** Bibliographies from clinical trials and review articles published since 2000 were reviewed and supplemented with targeted searches using biomedical databases. We also employed our extensive clinical experience.

**Evidence Synthesis:** The best-studied modalities for parathyroid localization are nuclear scintigraphy and sonography and are widely applied as initial studies. Multiple variations exist, and several additional noninvasive imaging techniques, such as computed tomography and magnetic resonance, are described. The exquisite anatomical detail of 4-dimensional computed tomography must be balanced with significant radiation exposure to the thyroid gland. Invasive venous PTH sampling and parathyroid arteriography have important roles in remedial cases. Due to considerable heterogeneity in imaging, multidisciplinary collaboration between endocrinologists, surgeons, and radiologists is beneficial.

**Conclusions:** Parathyroid localization is indicated in surgical candidates. Crucial considerations when selecting an imaging study include availability, cost, radiation exposure, local expertise, and accuracy. Additional factors include the patient's anticipated pathology and whether it is de novo or refractory disease. An approach to imaging for patients with primary hyperparathyroidism is presented. (*J Clin Endocrinol Metab* 98: 902–912, 2013)

Patients with suspected primary hyperparathyroidism (1°HPTH) are frequently referred to endocrinologists to confirm a diagnosis and recommend treatment. Once a diagnosis of 1°HPTH is confirmed, imaging studies are often obtained both to assist in determining disease etiology and to direct operative planning. The purpose of this manuscript is to assist endocrinologists and parathyroid surgeons to obtain appropriate and effective imaging studies.

Early efforts at parathyroid localization were of limited utility. The remark by noted interventional radiologist

John L. Doppman (1) in 1986 that, “In my opinion, the only localizing study indicated in a patient with untreated 1°HPTH is to localize an experienced parathyroid surgeon,” reflects the initial attitude toward routine preoperative parathyroid imaging. Since that time, the benefits of focused parathyroidectomy as shown in Table 1, including shorter operative times, lower incidence of postoperative hypocalcemia when unexplored parathyroids are left in situ, and decreased risk of recurrent laryngeal nerve injury, encouraged the development of improved localization techniques (2). A surge of interest and the

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Abbreviations: BCE, bilateral cervical exploration; CT, computed tomography; 4D, 4-dimensional; FNA, fine-needle aspiration; 1°HPTH, primary hyperparathyroidism; 2°HPTH, secondary hyperparathyroidism; 3°HPTH, tertiary hyperparathyroidism; MGD, multigland disease; MR, magnetic resonance; PET, positron emission tomography; SPECT, single-photon emission CT; SVS, selective venous sampling.

**Table 1.** Comparison of Traditional Surgery to Minimally Invasive Parathyroidectomy

	Traditional Surgery	Minimally Invasive Parathyroidectomy
Preoperative		
Evaluation/workup	Same	Same
Indications for surgery	Same	Same
Preoperative imaging	Not required, often obtained	Always obtained
Operative		
General anesthesia	Almost always	Not required
Bilateral exploration	Always	Not required in most cases
Extent of surgery	Moderate	Limited
Visualize all parathyroid glands	Always	Not required in most cases
Intraoperative PTH assay	May be used	Essential
Complications		Decreased
Postoperative		
Inpatient admission	Often	Rare
Follow-up	Same	Same
Economic		
Total cost (including intraoperative PTH, imaging, stay length, etc.)		Decreased; mean savings of \$1471/case vs traditional approach (2)

Note that traditional bilateral cervical exploration may be required in patients with a history of prior neck surgery or remedial, recurrent, or multigland parathyroid disease.

proliferation of parathyroid imaging modalities have facilitated a paradigm shift toward focused, minimally invasive explorations in patients with 1°HPTH. However, parathyroid imaging is often performed without appropriate indications. This may be partially explained when one considers that essentially no patient with parathyroid disease underwent imaging 25 years ago, whereas today many surgeons utilize minimally invasive techniques with preoperative localization (3). This article reviews parathyroid anatomy and pathophysiology and summarizes available imaging modalities and the clinical indications for their employment. When utilized correctly, imaging plays a vital role in the management of parathyroid disease.

Anatomy/Embryology

Parathyroid gland size, number, and location are some of the most variable features of human anatomy (4). The most typical arrangement is of 2 sets of paired glands adjacent to the posterior thyroid gland. The superior glands are derived from the fourth branchial pouch and are less

variable in location owing to their shorter descent during embryological development, with approximately 80% located posterior to the midportion of the thyroid at the level of the cricoid cartilage. The inferior glands, derived from the third branchial pouch along with the thymus, are typically located posterior to the inferior pole of the thyroid but are more inconsistent in location due to their lengthier migration. The location of ectopic glands is directed by embryological relationships. Ectopic superior glands are most commonly found within the thyroid gland or capsule because the parafollicular cells of the thyroid are also derived from the fourth branchial pouch, whereas ectopic inferior glands can be located anywhere along their shared descent with the thymus from the third pouch, including the thyrothymic ligament and within the thymus itself. Other less common ectopic locations include undescended glands high in the neck or carotid sheath, retroesophageal locations, and within the mediastinum.

Normal parathyroid glands have a weight of 20–40 mg and are 5–10 mm in length, 2–4 mm in width, and .5–2 mm thick (5). A recent publication suggested that normal glands removed incidentally during parathyroid adenoma resection can range in weight from 18–161 mg (6). However, glands of > 60 mg are usually considered abnormal, with most parathyroid adenomas weighing more than 100 mg. It is not unusual for normal glands to be smaller in patients with PTH hypersecretion from an adenoma due to negative feedback. Most glands are ovoid or bean-shaped, but elongated and multilobed glands are not uncommon. Supernumerary glands occur in up to 13% of patients (4).

Pathophysiology and Treatment

The vast majority of parathyroid disease is benign and manifest by excess secretion of PTH, resulting in hypercalcemia. 1°HPTH is the most common disease of the parathyroids and most often results from a single adenoma consisting of a clonal population of proliferating cells. In contrast, approximately 10–15% of 1°HPTH results from multigland disease (MGD) in the form of 4-gland hyperplasia or, less commonly, 2 independent (“double”) adenomas. Secondary hyperparathyroidism (2°HPTH) is a state of abnormal PTH secretion due to a known stimulus (ie, renal failure, hyperphosphatemia, calcitriol deficiency, prolonged vitamin D deficiency, etc.). Tertiary hyperparathyroidism (3°HPTH) implies the development of autonomous, unregulated PTH secretion. Most commonly, 2°HPTH occurs in renal failure, and 3°HPTH may develop in a subset of patients with 2°HPTH on maintenance dialysis, after renal transplan-

tation, and rarely due to vitamin D depletion (7). Malignancy is the rarest hyperparathyroid disease, accounting for only .005% of all cancers and less than 1% of patients with 1°HPTH diagnosed in the United States annually (8).

Surgery is the treatment of choice for symptomatic 1°HPTH. Some patients with 1°HPTH who meet specific criteria may be followed without surgery if certain recently reviewed guidelines are met (9). Medical therapy is the preferred initial treatment for 2°HPTH and 3°HPTH, but surgery is often required when medical treatment fails. In 1°HPTH, the operative approach is determined by etiology. Resection of the causative adenoma is appropriate for single gland disease, whereas a 3.5-gland resection surgery is employed in most cases of MGD. Another option occasionally employed for MGD, especially in the setting of syndromic disease such as multiple endocrine neoplasia 1, is total parathyroidectomy with immediate heterotopic parathyroid autotransplantation. Bilateral cervical exploration (BCE) is a well-established approach that has a cure rate in excess of 95% in the best centers (10). However, because most 1°HPTH cases are caused by a single adenoma, focused parathyroidectomy has become possible by utilizing preoperative parathyroid localization to limit operative exploration. The absence of MGD as well as biochemical cure can be confirmed in real time by measuring an appropriate intraoperative decrease in PTH after resection of a suspected adenoma (11, 12). Multiple approaches have been described for focused parathyroidectomy (13–15). We have recently shown results for open minimally invasive parathyroidectomy that are superior to BCE in terms of rate of cure, surgical morbidity, length of stay, and cost (2).

## Rationale for Localization

It is crucial to consider parathyroid imaging as an adjunct to surgical therapy because imaging has no role in patients who are not surgical candidates. Furthermore, no localization procedure should be regarded as diagnostic. Imaging has limited ability to differentiate between etiologies of parathyroid pathology and rarely contributes to therapeutic decision making. After a biochemical diagnosis has established 1°HPTH, imaging facilitates surgery if focused parathyroidectomy is planned by suggesting the location of a causative single adenoma or contributing toward increasing the suspicion of MGD. If the initial choice of operative approach is BCE due to the presence of concomitant thyroid pathology, high suspicion of MGD, surgeon preference, or other reasons, preoperative imaging is not required because all 4 parathyroid glands are usually identified intraoperatively. In patients who are candidates

for operative management, the surgeon should be involved in decisions regarding parathyroid localization. Importantly, preoperative localization is essential only for focused parathyroidectomy because BCE is a proven, effective therapy capable of achieving a durable cure.

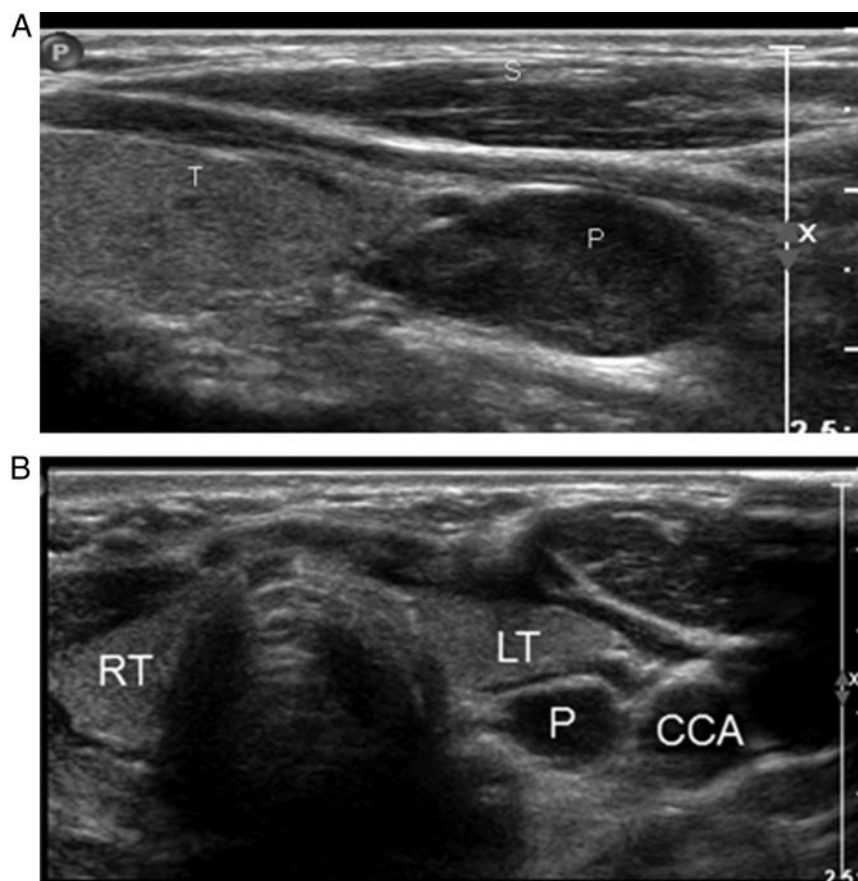
## Localization Modalities

As the number and availability of parathyroid imaging modalities have proliferated, so have the number of studies examining their efficacy. These can be difficult to interpret as heterogeneous definitions are used to evaluate effectiveness. For instance, predicting the correct side of a lesion is distinct from predicting the precise location. Whether a true-positive result refers to the correct laterality or quadrant of a gland is study-dependent. This phenomenon is especially notable in ultrasound and scintigraphy literature, where the reported range of sensitivity and positive predictive values demonstrates a particularly high variance (16). Furthermore, in almost all cases of “negative” imaging, an experienced endocrine surgeon will find disease during exploration. Therefore, any study evaluating parathyroid imaging that does not include correlation with operative findings and cure rates cannot by definition ascribe true positive or negative findings.

## Ultrasound

Parathyroid sonography was initially described in the late 1970s (17, 18). It is performed using a high-resolution transducer with a frequency of 5–15 MHz. The patient is positioned supine with the neck extended; a shoulder roll can facilitate exposure. Longitudinal and transverse images are obtained from the hyoid bone to the clavicle and to the common carotid arteries bilaterally (19). The superior glands are typically assessed first because they are less likely to be ectopic. The search should range from the angle of the mandible to the superior mediastinum in an effort to locate ectopic glands. Grayscale and color Doppler images are obtained, and the thyroid is always imaged.

Normal glands are infrequently visible on ultrasound. Enlarged parathyroids appear as homogeneous, hypoechoic structures that are ovoid and .8–1.5 cm in length (Figure 1). Cystic degeneration is present in 1–2% of enlarged glands, although very large adenomas may be irregularly shaped (20). Doppler images assist in distinguishing suspected parathyroid glands from alternative structures because parathyroid adenomas typically have a peripheral rim of vascularity and asymmetrically increased blood flow compared to the thyroid (21). Identification of a polar feeding artery can discriminate parathyroid glands from lymph nodes, which usually have a



**Figure 1.** A, Sagittal ultrasound demonstrating hypoechoic ovoid parathyroid (P) adenoma inferior and slightly posterior to the left lobe of the thyroid (T) and the sternohyoid/sternothyroid (S) muscles. B, Transverse ultrasound demonstrating parathyroid (P) adenoma posterior to the left thyroid lobe (LT), and medial to left common carotid artery (CCA), right thyroid lobe (RT). In large studies, ultrasound has an overall sensitivity of 70–80% in patients with a single adenoma, and specificity in excess of 90%.

hilar blood supply. Identifying a feeding artery increases ultrasound sensitivity by 10% and accuracy by 54% (22). Graded compression can improve visualization of small adenomas up to 27% of the time because adenomas are less compressible than surrounding tissue (23). Adjunctive techniques such as axial rotation of the patient's head or swallowing may improve visualization of ectopic adenomas by shifting them into the sonographer's view. Despite these maneuvers, the ability of ultrasound to evaluate ectopically located glands is limited by poor penetration of air-filled (ie, trachea, esophagus) and osseous structures.

Due to the continuing improvement in ultrasound technology and its wide employment, sonography has been extensively studied. One meta-analysis noted a sensitivity of 76% (95% confidence interval [CI], 70–81%) for patients during their initial presentation with 1°HPTH regardless of etiology (16). A second meta-analysis that included patients with recurrent and persistent 1°HPTH examined sensitivity with respect to etiology and found that for patients ultimately found to have a single adenoma, sensitivity was 79% (95% CI, 77–80%), but dropped to

35% (95% CI, 30–40%) for patients with MGD and to 16% (95% CI, 4–28%) for those with double adenomas (24). Specificity is somewhat better, with 2 case series reporting values of 91 and 96% (25, 26). In comparing 298 cases (23% of which had MGD), 1 study demonstrated correct prediction of the laterality of a single adenoma in 74% of patients, whereas the exact quadrant was identified in 72% (27).

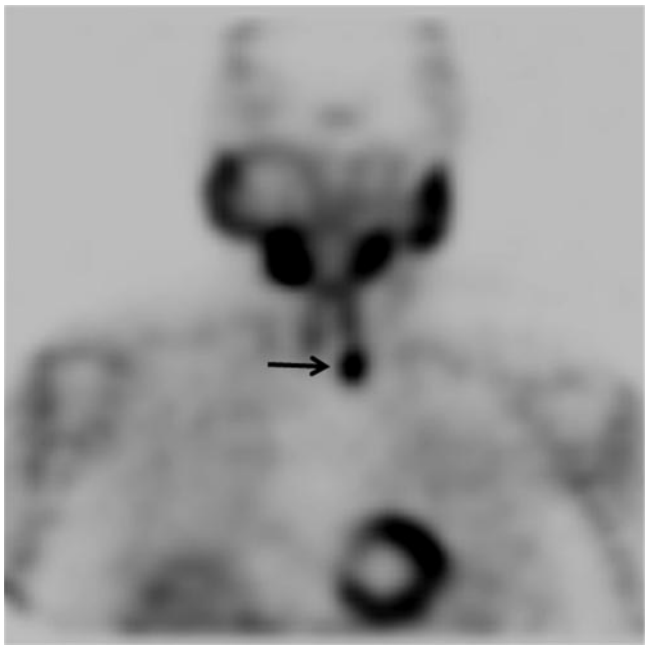
Ultrasound is inexpensive and widely available. It does not expose the patient to ionizing radiation and has satisfactory sensitivity to be employed as a first-line imaging study. Furthermore, it permits concomitant evaluation for thyroid pathology, which occurs in 29–51% of 1°HPTH patients (28, 29). Ultrasound also facilitates percutaneous biopsy; preoperative sonography combined with fine-needle aspiration (FNA) of thyroid nodules can reduce the need for simultaneous thyroid surgery from 30% of 1°HPTH patients to 6% (30). However, sonography is limited by body habitus and gland morphology (31). Parathyroid gland size and volume are key predictors of ultrasound de-

tection threshold. Also, ultrasound is highly dependent on an experienced sonographer performing and interpreting the study. For instance, characterization errors are widespread even in large glands because 62% of adenomas missed on ultrasound are ultimately found to be more than 1 cm in size (32). Also, because sonography is limited in its ability to assess ectopic glands, many practitioners choose to utilize ultrasound in a complementary role with another modality.

### Scintigraphy

Successful radioisotope scintigraphy for imaging of parathyroid adenomas was first reported in 1983 (33). Multiple radiopharmaceuticals have been employed, but the description of technetium 99m ( $^{99m}\text{Tc}$ )-sestamibi scintigraphy in 1989 greatly increased the utilization and sensitivity of nuclear imaging and remains the agent of choice (34). Older techniques, such as selenium-75-methionine and thallium-201/ $^{99m}\text{Tc}$ -pertechnetate subtraction have largely been abandoned due to suboptimal results. Sesta-





**Figure 2.** <sup>99m</sup>Tc-sestamibi scintigraphy demonstrating left lower parathyroid adenoma (arrow). Physiological uptake is seen in the heart, thyroid, submandibular, and parotid glands. Sensitivity of scintigraphy ranges from 54–96%, with the best results obtained by utilizing adjunctive SPECT techniques.

mibi is a lipophilic cation that accumulates in the mitochondria due to the transmembrane electrical potential (35). Normal parathyroid glands are not visible on sestamibi images. Differential release of the tracer from surrounding tissues, namely the thyroid, allow for distinguishing abnormal parathyroids as shown in Figure 2. Sestamibi scintigraphy has several advantages. It is widely available and there is much less ambiguity or operator

dependence in interpreting the results compared to sonography. It is also relatively inexpensive and features a wide field of view to assess for ectopic glands.

The clearest disadvantage of sestamibi scintigraphy is the potential for false-positive results. Both benign and malignant thyroid nodules can cause incorrect characterization of sestamibi nuclear imaging; a nodular thyroid reduces sensitivity by 15–39% (36, 37). Follicular and Hürthle cell thyroid neoplasms are particularly prone to sestamibi accumulation (38). Inflammatory thyroiditis and cervical lymphadenopathy are other common causes of false-positive scans. Overall, effectiveness of <sup>99m</sup>Tc-sestamibi imaging is strongly correlated with adenoma size, with gland weight of < 600–800 mg associated with false-negative results (39). Greater aberrations in serum PTH, calcium, and vitamin D levels have also been correlated with improved scan effectiveness (40, 41). Unlike ultrasound, scintigraphy does not allow simultaneous evaluation of the thyroid and results in a modest dose of radiation (Table 2).

A wide variety of sensitivities have been reported for <sup>99m</sup>Tc-sestamibi parathyroid scintigraphy, ranging from 54 to 96% (42, 43). The large number of trials and their discordant results reflect numerous imaging protocols. In a meta-analysis of 20 225 patients with 1°HPTH (not all of which underwent nuclear imaging), Ruda et al (24) pooled all reported protocols for sestamibi scintigraphy and found an overall sensitivity of 88% for detection of a single adenoma. Sensitivity was decreased to 45 and 30% in patients found to have 4-gland hyperplasia or double adenomas, respectively. Like ultrasound, sestamibi scin-

**Table 2.** Comparison of Features, Radiation Dose, and Cost for Parathyroid Imaging

	Relative Advantages	Relative Disadvantages	Calculated Effective Radiation Dose (Ref.)	Medicare Reimbursement
Cervical ultrasound	Widely available, no radiation	User-dependent interpretation, limited evaluation ectopic glands	None	\$125.10
Sestamibi scintigraphy	Ease of interpretation, assessment for ectopic glands	Radiation, cannot assess thyroid	Sestamibi/SPECT, 6.7–7.8 mSv (58, 71); SPECT/CT, +.9 mSv (72)	Sestamibi/SPECT, \$546.76; sestamibi alone, \$262.53
CT	Assessment for ectopic glands	Radiation, limited sensitivity	~3–6 mSv (71); varies by protocol	\$371.83
4D-CT	Increased anatomical detail, assessment for ectopic glands	Significant radiation to thyroid, not widely available	10.4 mSv (58)	\$424.51
MR	Assessment for ectopic glands	Limited sensitivity	None	\$644.33
Catheter-based localization	Less affected by prior interventions, wide assessment for ectopic glands	High level of expertise required	~.8–19.6 mSv (71); varies by case	\$2,310.85

Cost figures listed are current aggregate Medicare reimbursement rates for technical and professional fees. Note that effective total radiation dose is not reflective of absorbed dose to an individual organ or tissue (see Axial Imaging). For comparison, average natural background radiation in the United States is approximately 3.1 mSv/y.

tigraphy is more effective at correctly predicting the side (68%) vs the quadrant (50%) of the lesion in cases of a single adenoma (27).

One of the most useful variants of sestamibi scintigraphy is 3-dimensional single-photon emission computed tomography (SPECT). When compared to traditional 2-dimensional planar imaging, SPECT assists surgical exploration by demonstrating lesion location in all 3 dimensions and allows visualization of posterior adenomas in the retroesophageal position that is otherwise masked by thyroid tracer uptake. As a result, sestamibi-SPECT demonstrates improved sensitivity vs planar imaging. One recent meta-analysis evaluating the initial presentation of 1°HPTH of all etiologies found an overall sensitivity and positive predictive value of 78.9 and 90.7%, respectively, for sestamibi-SPECT (16). Specificity of sestamibi-SPECT has been reported in excess of 98% (42). For these reasons, sestamibi-SPECT is the preferred modality for parathyroid scintigraphy (44, 45).

Additional variants in sestamibi scintigraphy include dual-phase imaging, which adds an early image acquisition phase at 10–15 min after sestamibi administration in addition to the standard 90- to 180-min window. The early phase allows localization of tracer uptake in relation to the thyroid and can visualize the uncommon parathyroid adenoma that exhibits rapid sestamibi washout not visible on late phase images. Dual-phase imaging results in a small gain in sensitivity vs single-phase protocols (42). Subtraction imaging is performed by adding a second thyroid-specific radiopharmaceutical such as  $^{99m}\text{Tc}$ -pertechnetate or  $^{123}\text{I}$  to allow digital subtraction of the thyroid signal from  $^{99m}\text{Tc}$ -sestamibi signal. As a result, sensitivity is increased. However, due to longer acquisition times, patient motion artifact is a significant problem, and it increases the false-positive rate. Thus, despite improved sensitivity, the positive predictive value is similar or slightly worse when compared to single-tracer protocols (42, 46).

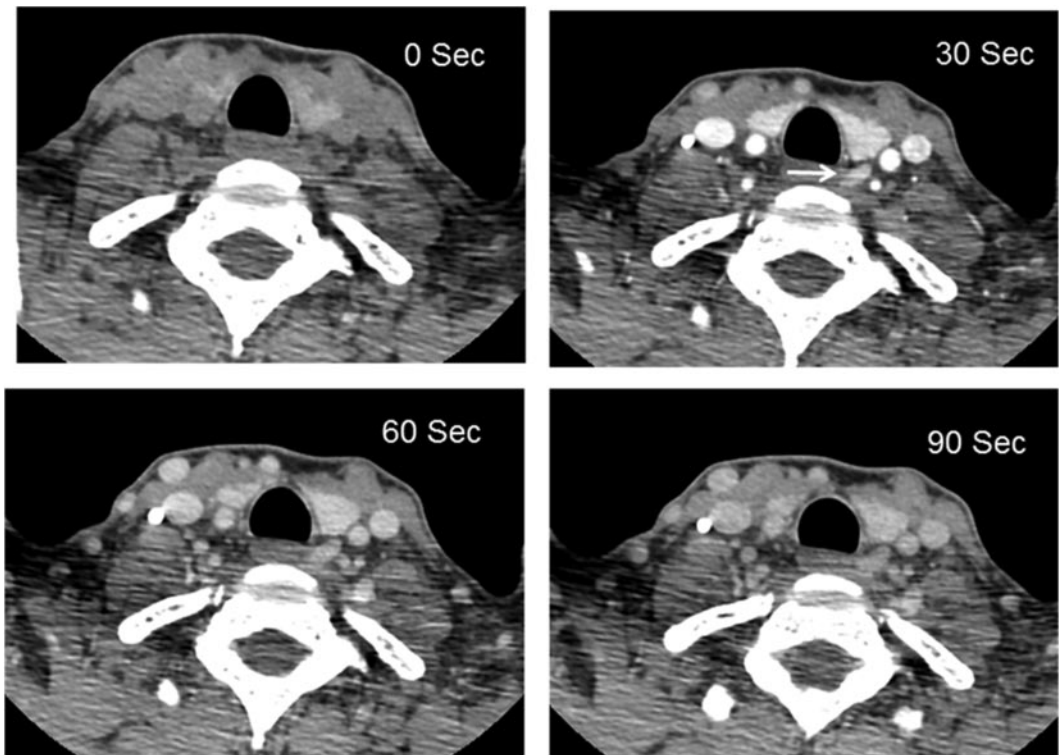
An emerging technique involves the combination of  $^{99m}\text{Tc}$ -sestamibi SPECT scintigraphy and computed tomography (CT). Although the timing of the hybrid SPECT/CT protocol results in CT images of less detail than conventional diagnostic CT, the improvement in anatomical detail over SPECT alone is notable. This results in improved differentiation between spurious sources of  $^{99m}\text{Tc}$ -sestamibi uptake such as the thyroid or cervical lymph nodes and also provides improved anatomical information for ectopically located parathyroid adenomas (47). A comprehensive study by Lavery et al (42) examined 110 patients with 1°HPTH who underwent dual-phase  $^{99m}\text{Tc}$ -sestamibi with planar, SPECT, and SPECT/CT imaging. Early SPECT/CT in combination with any modality

for delayed imaging emerged as the best overall protocol, with an accuracy of approximately 86%. The increased anatomical detail offered by SPECT/CT is demonstrated in 1 study of 23 patients that noted the mean distance from predicted to actual adenoma location at surgery was  $16.3 \pm 2.7$  mm (48). Another study noted a decrease in exploration time from 62 to 36 min when preoperative imaging was obtained with SPECT/CT rather than conventional SPECT (49). Although these findings are promising, SPECT/CT results in both increased cost and radiation, and its role outside localization in patients with persistent and/or recurrent 1°HPTH is being defined.

Positron emission tomography (PET) has also been evaluated in patients with 1°HPTH for preoperative localization.  $^{18}\text{F}$ fluorodeoxyglucose-PET detects increased glucose metabolism and has a reported sensitivity in 1°HPTH of 86% (50), but it has not been widely employed. A PET/CT hybrid technique using  $^{11}\text{C}$ -methionine, which detects increased amino acid metabolism, has also been recently described. Sensitivity approximates standard  $^{99m}\text{Tc}$ -sestamibi scintigraphy (approximately 83%), but has an increased sensitivity for MGD (67%) (51). Thus far, PET has not seen extensive adoption as a parathyroid localization technique.

### Axial imaging

Conventional CT for parathyroid localization has generally been inferior to other modalities, with a mean sensitivity of approximately 40–70% (52–54). Intravenous contrast is a requirement for detection of parathyroid adenomas, most of which appear hyperintense on CT and can be differentiated from adjacent tissue by density. However, conventional CT is infrequently utilized due to its mediocre results and radiation exposure. Recently, a new CT-based parathyroid imaging modality termed 4-dimensional (4D)-CT has emerged, with the extra dimension referencing time. 4D-CT relies upon the perfusion characteristics of parathyroid adenomas. The rapid uptake and washout of contrast from adenomas is captured via multiple CT passes, resulting in highly detailed, multiplanar images highlighting abnormal parathyroid glands as demonstrated in Figure 3 (55). 4D-CT has been shown to be highly effective in cases of reoperative neck surgery; in one study of 45 patients with 1°HPTH who had undergone a previous neck exploration, 4D-CT demonstrated a sensitivity for abnormal glands of 88 vs 54% for  $^{99m}\text{Tc}$ -sestamibi SPECT and 21% for ultrasound (56). Furthermore, 4D-CT has been shown to be an effective primary localization study for all patients with 1°HPTH, correctly localizing the quadrant of the neck in 85.7% of patients (57). In that study, 4D-CT also correctly pre-



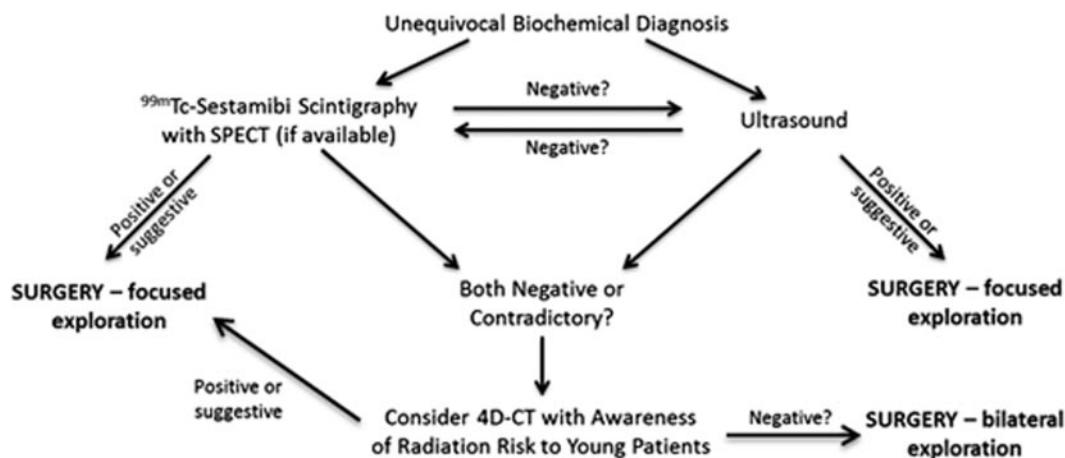
**Figure 3.** 4D-CT demonstrating noncontrast (0 sec), contrast enhanced (30 sec), and delayed washout views (60 and 90 sec). The arrow in the 30-sec view demonstrates a left upper parathyroid adenoma. Overall 4D-CT sensitivity is approximately 90% and can correctly localize the quadrant of a single adenoma in 85% of cases.

dicted the presence of MGD in 6 out of 7 patients, a significant improvement over both <sup>99m</sup>Tc-sestamibi scintigraphy and ultrasound. 4D-CT is particularly effective for discovery of ectopic glands. The main disadvantages of 4D-CT are its difficult interpretation, general lack of availability, and radiation exposure. A summary of radiation dosages, as well as relative advantages, disadvantages, and costs of parathyroid imaging modalities can be seen in Table 2. Compared to scintigraphy, 4D-CT results in a modest increase in total radiation dose, but a thyroid-specific radiation dose that is 50 times that of sestamibi-scintigraphy in matched patients (58). In a prototypic 20-year-old female, this translates into a calculated lifetime risk of 104 cases of thyroid cancer per 100 000 individuals exposed. However, this risk drops to 4 cases/100 000 individuals in 50-year-old females (58). Accordingly, 4D-CT should be employed sparingly in younger individuals but can be reasonably employed in older patients or those with prior neck surgery.

Magnetic resonance (MR) has a reported sensitivity for abnormal parathyroid glands ranging from 43–71% (54, 59). The MR characteristics of parathyroid adenomas are closely related to their histology (60); most commonly, adenomas have low to moderate signal intensity on T1-weighted imaging and are hyperintense on T2 imaging. However, up to 40% of adenomas vary from these characteristics (61). Utilizing gadolinium contrast may result in improved sensitivity (62). Similar to CT, the chief advantages of MR are lack of radiation, detailed anatomical information, and the ability to widely evaluate ectopic glands. MR is largely limited to an adjunctive role during reoperative cases because it is costly and prone to motion artifact due to the lengthy image acquisition times. MR may have a role in patients with negative or discordant localization studies; 1 recent study demonstrated that high-resolution MR using a 3.0 T magnet could detect adenomas in 57% of patients with 1°HPTH and negative <sup>99m</sup>Tc-sestamibi scintigraphy (63).

**Table 3.** Selected Cited Estimates for Accuracy of First-line Imaging Modalities for a Patient with De Novo 1°HPTH

	Sestamibi Scintigraphy	Ultrasound	4D-CT
Sensitivity (95% CI) (16)	78.9% (64–90.6%)	76.1% (70.4–81.4%)	89.4%
Positive predictive value (95% CI) (16)	90.7% (83.5–96.0%)	93.2% (90.7–95.3%)	93.5%
Localization–correct side (single adenoma)	68% (27)	74% (27)	93.9% (57)
Localization–correct quadrant (single adenoma)	50% (27)	72% (27)	85.7% (57)

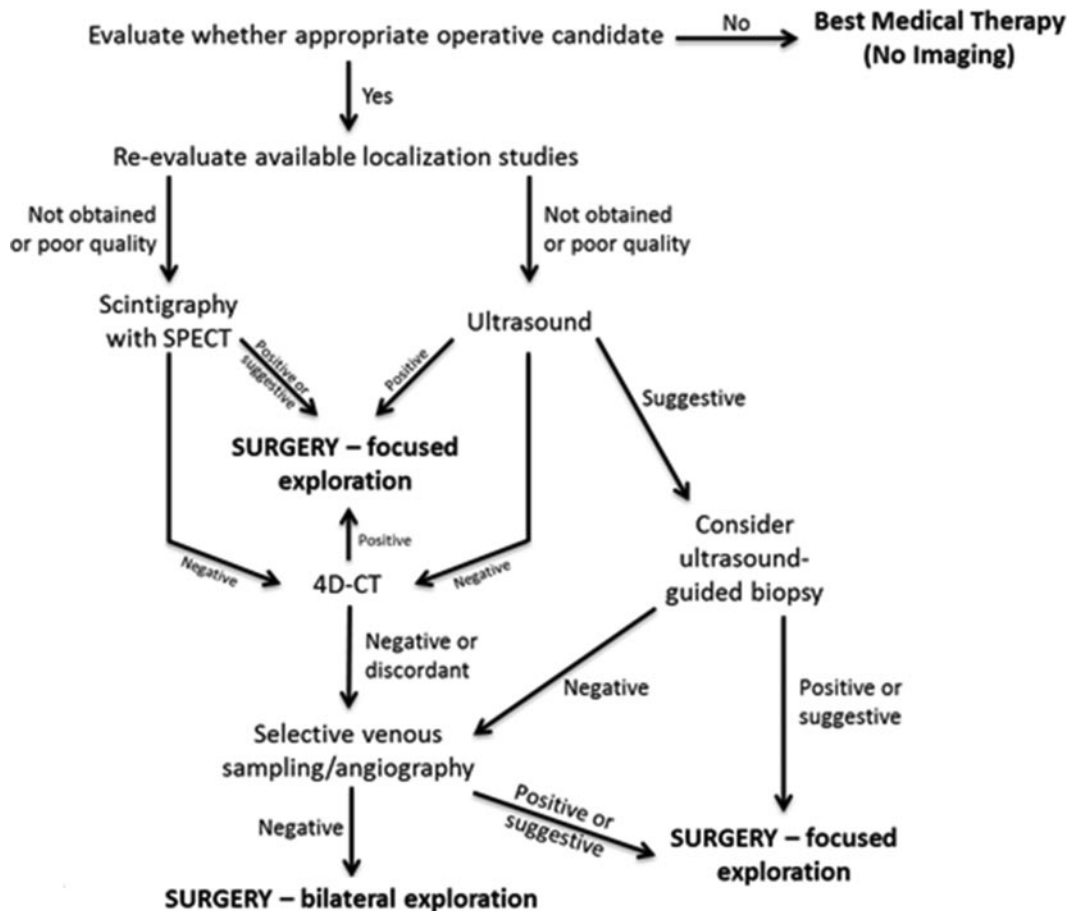


**Figure 4.** Imaging approach in an unexplored patient with a de novo diagnosis of primary hyperparathyroidism. Either scintigraphy or ultrasound may be the initial study of choice depending on local expertise and imaging quality; performing both ultrasound and scintigraphy as an initial evaluation is an acceptable alternative.

### Invasive localization

Catheter-based identification of abnormal parathyroid glands has 2 distinct methodologies—selective venous sampling (SVS) and parathyroid arteriography. Currently, the only indication for invasive localization is in patients with recurrent or persistent hyperparathyroidism

or patients who have previously undergone significant nonparathyroid cervical surgery who are found to have equivocal, discordant, or nondiagnostic noninvasive localization studies. Due to the difficulty of reoperative parathyroid surgery, the benefit of parathyroid localization outweighs the risks of invasive techniques, which in-



**Figure 5.** Imaging approach for a patient requiring remedial cervical exploration (56, 73).



clude catheter injury, hematoma, contrast-induced nephropathy, anaphylaxis, and stroke.

SVS is the “gold standard” invasive technique. Access is typically obtained via the femoral vein. Serial blood samples are drawn from the superior vena cava and bilateral brachiocephalic, internal jugular, vertebral, thymic, superior, middle, and inferior thyroid veins. PTH is assayed in each sample, and the data are analyzed for a gradient indicative of parathyroid location. In-suite utilization of a rapid PTH assay improves response time and data fidelity, as well as facilitating additional sampling, because results are available in near-real time. Sensitivity of SVS in reoperative cases of patients with 1°HPTH ranges from 71–90% (64–66). Parathyroid arteriography is both complementary and an adjunct to SVS. Contrast media infusion near the thyrocervical trunk can demonstrate abnormal parathyroid tissue as a hypervascular blush and guide operative exploration and confirm a gradient suggested by SVS. Arteriography can be especially valuable in patients with prior neck surgery where the usual parathyroid venous drainage can be profoundly altered. When a blush is visualized, the false-positive rate is approximately 9% (66).

Image-guided confirmation of suspicious lesions has also been demonstrated using ultrasound- or CT-guided FNA (67). A PTH assay is performed on the FNA aspirate to determine whether the index lesion is a parathyroid gland. An on-site rapid PTH assay allows quick turnaround and rebiopsy if necessary for inconclusive results (68). Positive identification of a suspicious gland also permits a focused operative approach. Wire-guided explorations after CT- or ultrasound-guided localization have also been described (69).

## Suggested Approach

A summary of the accuracy of first-line modalities for localizing parathyroid disease in patients with 1°HPTH appears in Table 3. The most prevalent approach to localization in a patient with a de novo diagnosis of 1°HPTH is combining <sup>99m</sup>Tc-sestamibi scintigraphy with ultrasound, with 62% of surgeons in the United States reporting this as their preferred approach (70). Scintigraphy is less operator-dependent than ultrasound and is an effective way to visualize ectopic glands, whereas sonography allows simultaneous evaluation of the thyroid and FNA biopsy of suspicious lesions. Both are widely available and relatively inexpensive. We prefer a stepwise approach as illustrated in Figure 4. Either sestamibi SPECT scintigraphy or ultrasound is performed initially; if either result is definitive, we proceed to minimally invasive parathyroid-

ectomy. If both tests are inconclusive or contradictory, we consider 4D-CT in older patients where the risk of increased thyroid radiation exposure is minimal. In younger patients, or those with inconclusive 4D-CT results, we proceed to surgery knowing that bilateral exploration is likely.

In cases of recurrent or persistent 1°HPTH, our initial approach mirrors that of de novo patients. As shown in Figure 5, we begin with sestamibi SPECT or ultrasound if neither has been performed and proceed with 4D-CT in appropriately selected patients. If the results remain inconclusive, we proceed to invasive imaging and usually opt for combined SVS/arteriography (73). If questionable lesions are visible on ultrasound, we perform FNA with immediate on-site PTH testing. If positive or suggestive results are obtained at any time, we proceed to surgery. If all results are negative, we proceed with surgical exploration in appropriate operative candidates. In patients who are poor candidates for extensive exploration, we consider best medical therapy and repeat imaging in the future.

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Disclosure Summary: The authors have nothing to disclose.

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