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# 4D SPECT/CT: A Hybrid Approach to Primary Hyperparathyroidism

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Our rationale was to review the imaging options for patients with primary hyperparathyroidism and to advocate for judicious use of 4-dimensional (4D) SPECT/CT to visualize diseased parathyroid glands in patients with complex medical profiles or in whom other imaging modalities fail. We review the advantages and disadvantages of traditional imaging modalities used in preoperative assessment of patients with primary hyperparathyroidism: ultrasound, SPECT, and 4D CT. We describe a scheme for optimizing and individualizing preoperative imaging of patients with hyperfunctioning parathyroid glands using traditional modalities in tandem with 4D SPECT/CT. Using the input from radiologists, endocrinologists, and surgeons, we apply patient criteria such as large body habitus, concomitant multiglandular disease, multinodular thyroid disease, confusing previous imaging, and unsuccessful previous surgery to create an imaging paradigm that uses 4D SPECT/CT yet is cost-effective, accurate, and limits extraneous radiation exposure. 4D SPECT/CT capitalizes on the strengths of SPECT and 4D CT and addresses limitations that exist when these modalities are used in isolation. In select patients with complicated clinical parameters, preoperative imaging with 4D SPECT/CT can improve accuracy yet remain cost-effective.

**Key Words:** primary hyperparathyroidism; 4D SPECT/CT; SPECT; 4D CT

**J Nucl Med Technol 2024; 52:86–90**  
DOI: 10.2967/jnmt.123.266990

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**P** rimary hyperparathyroidism (PHPT) is a disease in which one or more parathyroid glands inappropriately produce excessive parathyroid hormone. PHPT is one of the most common endocrine disorders, with nearly 100,000 people in the United States developing the disease each year (1). Eighty to 90 percent of PHPT cases are associated with a single hyperfunctioning parathyroid gland; however,

multiglandular disease, including multiple hyperfunctioning glands, is not infrequently present (2).

The definitive management of PHPT is surgical removal of the diseased parathyroid glands. This can be accomplished with either bilateral neck exploration or minimally invasive parathyroidectomy (3). Minimally invasive parathyroidectomy is an advanced surgical technique designed to reduce the extent of operation, incision length, and postoperative pain, using a directed approach to the abnormal parathyroid glands (4). Although minimally invasive techniques vary in their surgical details, they all require preoperative imaging not only to lateralize the lesion but to localize its quadrant in the neck. Minimally invasive parathyroidectomy has been associated with shorter operating times, shorter postoperative stays in the hospital, and lower costs (5). Preoperative imaging serves to guide minimally invasive exploration in conjunction with intraoperative parathyroid hormone monitoring and identification of concomitant thyroid disease, which may require additional preoperative evaluation and intraoperative intervention. Reoperation is necessary in about 10% of cases and can be particularly challenging because of scarring of the surrounding tissues and obscuration of normal anatomy. Reoperation has a lower success rate than primary surgery and an increased risk of complications, including recurrent laryngeal nerve injury and permanent hypoparathyroidism (6).

Historically, hyperfunctioning parathyroid glands were presumed to be neoplastic, and the term *adenoma* was universally applied. However, the distinction between hyperfunctioning nonneoplastic glands and true adenomas can be difficult both clinically and pathologically. Thus, the term *adenoma* is reserved for patients whose calcium levels are normal for 6 mo or longer after surgical treatment (7). The generic term *hyperfunctioning parathyroid gland* is used until that criterion is met. Because much of the older literature on hyperparathyroidism uses outdated terminology, we will use the terminology of the literature that we quote in this article.

The 3 imaging techniques that have been most often used for preoperative imaging in PHPT are neck ultrasound, <sup>99m</sup>Tc-sestamibi SPECT, and multiphase high-resolution

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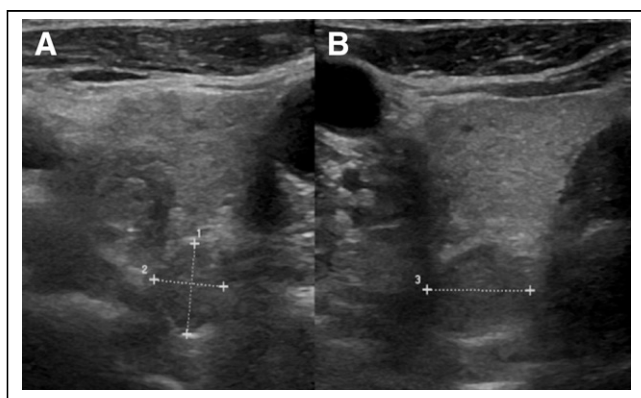
Received Nov. 1, 2023; revision accepted Jan. 17, 2024.  
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Published online Mar. 12, 2024.  
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CT (4-dimensional [4D] CT) (8). Each of these techniques comes with advantages and disadvantages that have prompted significant debate among surgeons and radiologists. The controversy is further complicated by factors such as practitioner preferences, radiologist expertise, availability of specific imaging modalities, quality differences among available scanners at different institutions, radiation exposure, cost, and patient parameters such as previous parathyroid surgery, multinodular thyroid, and obesity. This article examines a combined technique, 4D SPECT/CT, that capitalizes on the strengths of the individual techniques of 4D CT and SPECT/CT. Our purpose is to review how ultrasound, SPECT, and 4D CT can best help surgeons prepare for PHPT surgery and to advocate for the judicious use of 4D SPECT/CT in carefully selected patients.

## ULTRASOUND

Neck ultrasound is widely used as first-line preoperative imaging in patients with thyroid and parathyroid pathology (Fig. 1). Normal parathyroid glands are not visible by ultrasound; however, glands larger than 1 cm should be identifiable (9). A parathyroid gland on ultrasound appears as a well-defined mass with uniform low to intermediate echogenicity. A polar artery is also commonly evident on Doppler ultrasound (5). Neck ultrasound may also identify concomitant thyroid pathologies that should be addressed before parathyroid surgery. The sensitivity of ultrasound for detection of parathyroid adenoma varies from 50% to 80% in the literature (10).

Advantages of ultrasound include low expense, high availability, and lack of ionizing radiation, making it an appropriate screening modality. Additionally, it is a good modality for detecting concomitant thyroid disease. Studies have shown that preoperative thyroid ultrasound reveals that 93.5% of patients with PHPT have thyroid pathology, with 66.7% of patients having at least 1 thyroid nodule (11). This may confound imaging assessment, as thyroid nodules can be easily confused with parathyroid glands (12). When using ultrasound and SPECT in the presence of thyroid nodules, there is a 6% and 29% false-positive rate,



**FIGURE 1.** Ultrasound for hyperfunctioning parathyroid gland. Sagittal (A) and transverse (B) images through thyroid gland reveal mass of uniform echogenicity deep to, and hypoechoic to, thyroid gland.

respectively, indicating that ultrasound is preferable for parathyroid detection in the setting of thyroid disease (13). A systematic review of 20,225 cases of PHPT determined that the sensitivity of preoperative ultrasound is 79% for localizing solitary parathyroid adenomas; this decreases to 34.9% for localizing multiglandular hyperplasia and 16.2% for localizing multiple glands (6).

Disadvantages of ultrasound include operator dependence and decreased accuracy with deep structures. This is especially true with superior hyperfunctioning parathyroid glands, which are typically deep-seated within the tracheoesophageal groove. Multiglandular parathyroid disease is difficult to diagnose because of the small gland size. Ectopic glands, especially those in the mediastinum, carotid sheaths, hypopharynx, and retrotracheal area, are also difficult to localize.

## SPECT AND SPECT/CT

SPECT can be performed with either single-tracer double-phase imaging or dual-tracer single-phase imaging. With the former technique, intravenous  $^{99m}\text{Tc}$ -sestamibi washes out more quickly from the thyroid gland than from the parathyroid gland (14). In the dual-tracer technique,  $^{99m}\text{Tc}$  is used with a second radiotracer, either  $\text{Na}[^{99m}\text{Tc}]\text{TcO}_4$  or  $\text{Na}[^{123}\text{I}]\text{I}$ , or, historically,  $^{201}\text{Tl}$ .  $^{99m}\text{Tc}$  is taken up by both thyroid and parathyroid tissue, whereas the other tracer is taken up only by the thyroid gland (15,16). Regardless of which technique is used, SPECT imaging is more sensitive than ultrasound in localizing hyperfunctioning parathyroid glands, at 89% versus 59% (17). The emerging PET technology of fluorine-labeled choline analogs shows promise but has not yet reached routine clinical practice (18). Choline PET is poised to play a role in the assessment of PHPT, but it is too early to know how it will optimally affect imaging paradigms.

Most institutions use combined SPECT/CT, which is more sensitive than planar imaging alone in the localization of parathyroid glands (Fig. 2). The CT in SPECT/CT is unenhanced and is used primarily for anatomic localization and attenuation correction of the SPECT images. In a study conducted by Bural et al., traditional SPECT imaging correctly localized and identified an adenoma in 61% of patients, as compared with 97% by SPECT/CT (19). Another study found that the sensitivity for SPECT/CT was 93.7%, as opposed to 80% for SPECT, and concluded that SPECT/CT was better able to identify multiple adenomas and ectopic parathyroid glands than SPECT (19).

Overall, SPECT and SPECT/CT are less operator-dependent and can better detect ectopic or deeper lesions that are difficult to evaluate with ultrasound (5). There is, however, substantial radiation exposure. Thyroid nodules can interfere with interpretation when they demonstrate delayed washout, a problem exacerbated by the inconstant washout of parathyroid adenomas themselves (14). In the presence of multiglandular disease, cervical nodal metastases, or small lesions, SPECT becomes less accurate in detecting parathyroid glands but is still more sensitive than ultrasound (20).



**FIGURE 2.** SPECT/CT for hyperfunctioning parathyroid gland.  $^{99m}\text{Tc}$ -sestamibi delayed-washout image reveals focus of intense uptake along posterior margin of cervical trachea (arrow).

#### 4D CT

4D CT uses the differential perfusion characteristics of hyperfunctioning parathyroid glands. A high-resolution neck CT is performed, with images extending into the upper mediastinum. The examination is most often performed without contrast medium, followed by imaging in the arterial phase of enhancement, and then again in the venous phase (Fig. 3). The exact protocol varies among institutions. The early washout and polar arteries of hyperfunctioning parathyroid glands distinguish them from thyroid lesions, surgical scars, and lymph nodes, which may be challenging to differentiate on ultrasound and SPECT/CT. Although these radiologic findings are not uniformly present, they can nevertheless be used to improve the accuracy of diagnosis (21–23).

4D CT localizes subcentimeter lesions that would be undetectable with ultrasound or SPECT/CT. It also performs better in the setting of multiglandular disease and patients undergoing reoperation (6). In a study comparing the sensitivity for lateralization of adenomas among 4D CT, SPECT, and ultrasound, 4D CT was the most sensitive, at 77.4% versus 46% and 38.5%, respectively (24). 4D CT is less operator-dependent than ultrasound. The sensitivity for 4D CT is between 62% and 92%, and 4D CT has a positive predictive value of 88%–94% when used as the initial imaging study. In patients with nonlocalizing or inconclusive ultrasound or SPECT images, sensitivity ranges from 67% to 89% and positive predictive value from 65% and 87% (5).



**FIGURE 3.** 4D CT for hyperfunctioning parathyroid gland. Coronal reformatted image in late enhanced phase reveals rounded enhancing mass within left trachea–esophageal groove. Presence of polar artery (arrow) is specific for parathyroid gland origin.

The disadvantages of this modality are the relatively high radiation dose, higher cost, time-intensive interpretation, and need for iodinated intravenous contrast medium. Additionally, not all radiologists have sufficient experience in the interpretation of 4D CT, making it less accessible than SPECT/CT or ultrasound (5).

#### 4D SPECT/CT

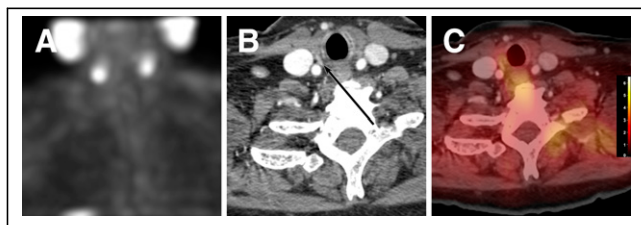
There has been extensive controversy over which second-line imaging technique is best for patients with nonlocalizing or inconclusive ultrasound results. The discussion is often limited to 4D CT and SPECT/CT. On one hand, 4D CT allows for accurate anatomic visualization, but on the other hand, SPECT/CT provides physiologic information. The choice of modality is often determined by physician preference and institutional availability. At our institution, we have embraced the hybrid modality of 4D SPECT/CT, which capitalizes on the advantages of both SPECT/CT and 4D CT. In 4D SPECT/CT, the CT used in SPECT/CT is replaced with 4D CT on a combined scanner, enabling precise anatomic and physiologic information in a single imaging session.

Parathyroid patients who present for 4D SPECT/CT imaging undergo hybrid  $^{99m}\text{Tc}$ -sestamibi fusion scintigraphy on a Discovery NM/CT 670 SPECT/CT scanner (GE Healthcare). SPECT images are obtained after the intravenous injection of approximately 925 MBq (25 mCi) of  $^{99m}\text{Tc}$ -sestamibi immediately (early phase) and 120 min (delayed phase) after injection. Diagnostic CT imaging is performed during the early phase of the study, 30 s after the intravenous administration of 75 mL of Isovue 300 or

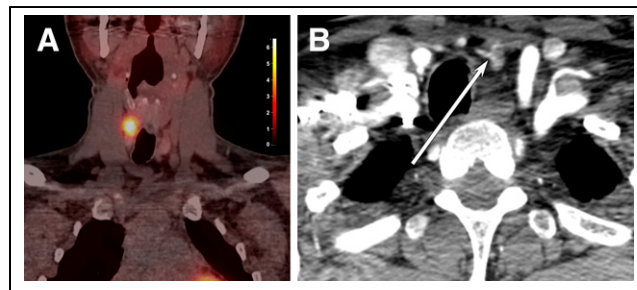
370 (Bracco). These images constitute the arterial phase of the CT; we consider this the most important phase for hyperfunctioning parathyroid gland characterization, although each phase of enhancement contributes to the diagnosis (23). A lower-dose noncontrast CT acquisition is repeated immediately after the delayed phase of the SPECT portion of the imaging, for localization and attenuation-correction purposes. In addition, this delayed CT helps confirm the hyperfunctioning parathyroid gland, as these lesions tend to have significantly lower CT attenuation without contrast medium than on early contrast-phase CT. The SPECT images are displayed in the axial, coronal, and sagittal planes using scatter correction attenuation as well as resolution recovery correction SPECT reconstruction algorithms. Automatic coregistration of SPECT and CT is performed on a GE Healthcare Xeleris workstation. The nuclear medicine technologists check the images for any possible coregistration errors and manually correct them if found. A board-certified neuroradiologist and a board-certified nuclear medicine physician jointly participate in the interpretation of all 4D SPECT/CT studies. When patients arrive at our institution with inconclusive outside scans, we initiate our imaging paradigm from the beginning. We have not yet encountered difficulties with contrast allergies preventing imaging.

4D SPECT/CT is not intended to be first-line imaging for most patients with PHPT. In fact, this model has been proven inefficient (25). However, the use of 4D SPECT/CT allows for optimization and individualization of imaging, particularly in complicated patient profiles such as obesity, suspected multiglandular disease, or multinodular thyroid disease or in cases of reoperation. 4D SPECT/CT provides surgeons and radiologists improved confidence in localizing the diseased parathyroid tissue. It is especially useful for localizing ectopic lesions in retrotracheal locations.

4D SPECT/CT has disadvantages, including cost and increased radiation dose. When used judiciously in complicated patient profiles, however, the benefits of this modality outweigh the disadvantages. Typical patient examples are shown in Figures 4 and 5.



**FIGURE 4.** Sensitivity of 4D SPECT/CT. A 64-y-old man with PHPT underwent conventional SPECT (A) that showed only physiologic uptake of radiotracer. Corresponding contrast-enhanced CT (B) showed thin enhancing lesion (arrow) in trachea-esophageal groove that was difficult to characterize further. Once attention was drawn to this region by CT findings, 4D SPECT/CT (C) showed uptake associated with CT lesion. Lesion was resected and shown to be parathyroid adenoma, clearly visible only with combined 4D SPECT/CT.

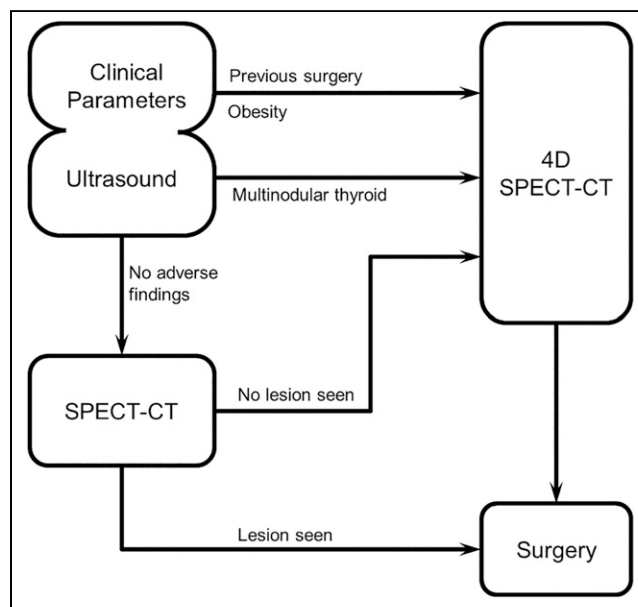


**FIGURE 5.** 4D SPECT/CT for multilesional disease. A 53-y-old woman with PHPT had large right-sided parathyroid adenoma on SPECT/CT (A) but no visible uptake in left neck. SPECT images did not identify contralateral lesion, which was seen only on enhanced-CT component (B) of 4D SPECT/CT. Polar artery (arrow) suggested correct diagnosis of multiglandular disease. Hyperparathyroidism was cured with single bilateral surgery.

## PERSONALIZED IMAGING SCHEME

We propose a decision matrix, developed with the input of surgeons, endocrinologists, radiologists, and nuclear medicine physicians, for choosing an optimal preoperative imaging modality in patients with PHPT (Fig. 6). It is based on individual patient characteristics, bypasses the false dichotomy of SPECT/CT versus 4D CT, and reflects our institutional experience of over 10y. The framework is especially valuable for challenging cases such as failed surgery, large body habitus, and ectopic glands.

Given the ubiquity and low expense of ultrasound, as well as the relatively high rates of coexistent thyroid



**FIGURE 6.** Patient flowchart for preoperative imaging of primary hyperparathyroidism. All patients underwent ultrasound. Worrisome clinical and sonographic parameters (obesity, previous failed parathyroid surgery, multinodular thyroid) prompted use of 4D SPECT/CT. Otherwise, traditional SPECT/CT was performed. But if traditional SPECT/CT failed to identify lesion, then 4D SPECT/CT was used during same patient visit.

pathology, we believe all patients with PHPT should undergo preliminary ultrasound. Because ultrasound can overlook multiglandular disease, a second modality (SPECT/CT, 4D CT, or 4D SPECT/CT) may be used to highlight multiple lesions. If multinodular thyroid disease is found on ultrasound, we recommend progressing to 4D SPECT/CT, as other modalities have inferior performance in this scenario.

Ultrasound is less sensitive in obese patients because of difficulties with probe placement and decreased penetration (13). A body-mass index greater than 30 has also been shown to reduce the accuracy of SPECT/CT for PHPT localization because photons are attenuated by the additional soft tissue (13). 4D SPECT/CT in these patients is ideal as it allows for more precise lesion localization and greater sensitivity than SPECT/CT or 4D CT alone.

Between 5% and 13% of patients with PHPT have persistent disease that requires a second surgery, but these second surgeries have a lower success rate (due to fibrosis and scarring) and an increased complication rate, including hypoparathyroidism and laryngeal nerve injury. Thus, we recommend 4D SPECT/CT in patients with recurrent disease.

If there are no adverse clinical parameters or ultrasound findings, SPECT/CT is the next appropriate step after ultrasound. At our institution, if a lesion is identified with SPECT/CT, there is usually adequate confidence to proceed with surgery. If, however, SPECT/CT fails to identify a lesion, additional imaging with 4D SPECT/CT is used. This is most easily accomplished by switching to 4D SPECT/CT whenever the early phase of the dual-phase SPECT/CT is negative. Early-phase SPECT/CT will identify 70% of lesions (26); therefore, 4D SPECT/CT will most likely be beneficial in the subset of patients with negative early-phase SPECT/CT. Rather than having the patient return on a different day for a second dose of radionuclide, one can perform the contrast-enhanced CT when the patient returns later the same day for the delayed SPECT/CT images.

## CONCLUSION

Accurate preoperative localization decreases operating time, decreases the likelihood of surgical complications, and improves the success rate in resection of hyperfunctioning parathyroid glands. In our experience, the combined modality of 4D SPECT/CT is superior to either SPECT/CT or 4D CT alone in challenging cases. Additionally, the development of a personalized imaging scheme accounting for clinical patient parameters and initial imaging findings leads to optimal use of resources and patient outcomes. This, along with collaboration between nuclear medicine physicians, radiologists, and endocrine surgeons, increases the success rates of minimally invasive parathyroid gland resection in patients with PHPT.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGMENT

This research was presented at the 2022 American Ray Roentgen Society meeting in New Orleans.

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