Parathyroid Adenoma Evaluation Utilizing SPECT/CT Imaging

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Primary hyperparathyroidism is a common endocrine disorder classically manifesting with elevated serum parathyroid hormone and calcium levels. The most common cause of primary hyperparathyroidism is a parathyroid adenoma, and the treatment of choice is surgical removal. Modern surgical management benefits from presurgical evaluation and localization of suspected abnormal gland(s), with a shift toward minimally invasive approaches. Complementing anatomic imaging, nuclear medicine offers unique functional evaluation of parathyroid glands that can be used in the workup of patients with hyperparathyroidism.

Historically, it was common to rely solely on planar imaging for identifying parathyroid adenomas in hyperparathyroidism. However, planar imaging is limited by the lack of precise anatomic localization and overlapping of radioactivity from other background tissues. This is particularly problematic in parathyroid scintigraphy, as it is often necessary to distinguish overlying thyroid from closely adjacent parathyroid activity. Combining anatomic information and localization of functional imaging using contemporary SPECT/CT affords more precise localization necessary to guide presurgical treatment planning. In this article, we review imaging protocols, scintigraphic findings, and pitfalls in parathyroid scintigraphy with an emphasis on SPECT/CT imaging.

Primary Hyperparathyroidism

Most people have 4 parathyroid glands in the neck located posterior to the thyroid gland, where any of the 4 glands may be the site(s) of adenoma formation. There are instances, however, of more or fewer than 4 glands with supernumerary parathyroid glands being more common, occurring in about 10% to 13% of cases.[1,2] Furthermore, parathyroid glands may be ectopic, occurring in 16% of cases in one series of 231 patients.[3] Inferior glands (62%) were more often ectopic, which is likely related to the relatively longer path of migration of the inferior glands during embryologic development. Although highly variable, common locations of ectopic glands include the thymus, superior mediastinum, intrathyroidal, tracheoesophageal groove, and retroesophageal regions. Depending on location of the ectopic gland(s), the surgical access may change from a cervical to a transthoracic approach.

A solitary parathyroid adenoma is the most common cause of primary hyperparathyroidism, occurring in approximately 80% of cases. The remaining cases are usually due to multigland hyperplasia, multiple parathyroid adenomas or, rarely, parathyroid carcinoma (< 1%).[4] Certain inherited diseases include a predisposition for parathyroid adenomas/hyperplasia, most notably multiple endocrine neoplasia (MEN) Types 1 and 2A.

Patients with hyperparathyroidism may present with a variety of nonspecific signs and symptoms including vague musculoskeletal pain, abdominal pain/renal calculi, and cognitive changes and/or depression. More commonly, patients today are often asymptomatic with abnormal parathyroid hormone and calcium levels detected on routine serum screening.[5] Surgery is considered the definitive treatment and is generally recommended in patients with symptoms referable to hyperparathyroidism. In otherwise asymptomatic patients, surgery or medical follow-up is recommended. In 2013, the International Workshop on the Management of

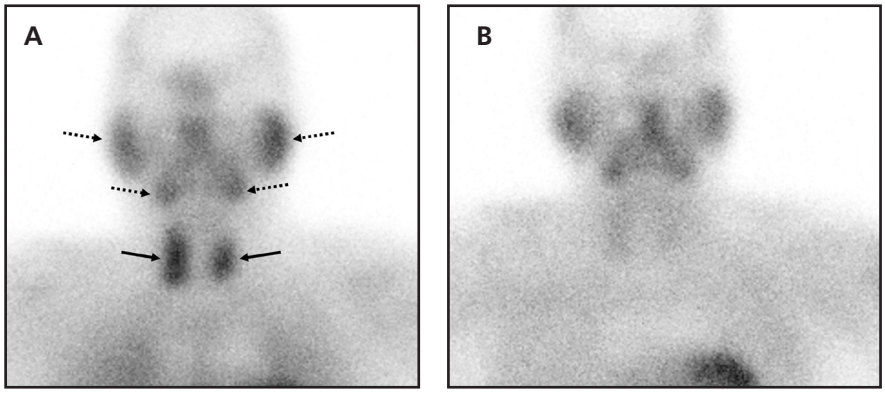

FIGURE 1. *Normal parathyroid scintigraphy. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi demonstrate physiologic biodistribution of the radiotracer with uptake in the salivary glands (dashed arrows, A) and the thyroid gland (solid arrows, A). Thyroid activity is apparent on early imaging, but is largely washed out on delayed imaging. No suspicious abnormal focus is present to suggest the location of a parathyroid adenoma.*

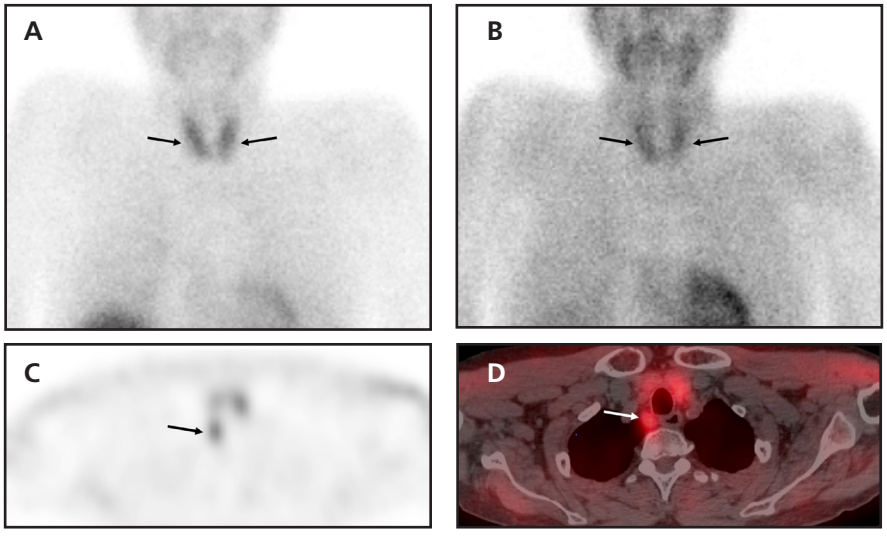

FIGURE 2. *Falsely negative planar imaging. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi demonstrate expected radiotracer uptake in the thyroid gland (arrows) without a convincing abnormal focus of uptake. Axial SPECT (C) and fused SPECT/CT (D) reveal a parathyroid adenoma (arrows) in the right tracheoesophageal groove that is obscured on the planar images due to persistent activity in the thyroid gland on delayed imaging. This case illustrates the usefulness of SPECT/CT in overcoming the inherent limitations of planar imaging.*

Asymptomatic Primary Hyperparathyroidism proposed consensus guidelines for surgical intervention in patients without symptoms.[6] Surgery should be considered in asymptomatic patients who wish for definitive treatment and do not desire longer-term medical surveillance. Surgery is also recommended in asymptomatic patients ages 49 years or younger, or who have any of the following: osteoporosis or evidence of vertebral fractures on imaging, renal calculi, decreased creatinine clearance (< 60 cc/min), hypercalcuria (> 400 mg/24 hours), or hypercalcemia > 1.0 mg/dL above normal.

Surgical procedures vary per healthcare facility and local surgical preference. It is critical for the interpreting imager to be familiar with the possible procedure(s) that the referring surgeon performs and how imaging findings (or lack thereof) affect procedure choice. Exploration of the bilateral neck allows the surgeon to identify normal glands and to remove enlarged or otherwise abnormal parathyroid glands. In this so-called "bilateral 4-gland" technique, preoperative scintigraphy can exclude an ectopic adenoma and lead the surgeon to the suspected location of the abnormal gland if one is identified on imaging. More limited approaches, whereby the surgeon may opt for a unilateral procedure choosing the side most likely to contain the adenoma based on imaging, have the advantage of reduced surgical and recovery time, fewer scars, and similar rates of successful cure compared to bilateral approaches. If the initial site of exploration is unremarkable, or if intraoperative parathyroid hormone levels fail to confirm the expected decline in levels after resection of a suspected adenoma, the surgical approach can be modified to a bilateral neck exploration. Whether unilateral or bilateral, an open or minimally invasive (endoscopic, video-assisted, robotic, etc.) procedure may be planned based on imaging findings.

Additionally, other intraoperative assistance may affect the procedure. Much like nuclear lymphoscintigraphy, a hand-held gamma probe may be used intraoperatively to guide identification of the parathyroid adenoma. This technique requires the surgery to be performed on the same day as nuclear imaging, or an additional injection of tracer must be administered on the day of the planned surgery. The surgeon may also monitor intraoperative serum parathyroid hormone level sampling shortly (about 10 minutes) after the removal of a suspected adenoma with an expected significant decrease (> 50% decline from preoperative levels) with successful removal of the offending gland. If a significant decrease is not identified, the surgeon can opt for additional parathyroid gland exploration to locate other hyperfunctioning glands.[7]

Radiopharmaceuticals and Imaging Protocols

Overview

Parathyroid nuclear imaging has evolved as radiotracers and imaging

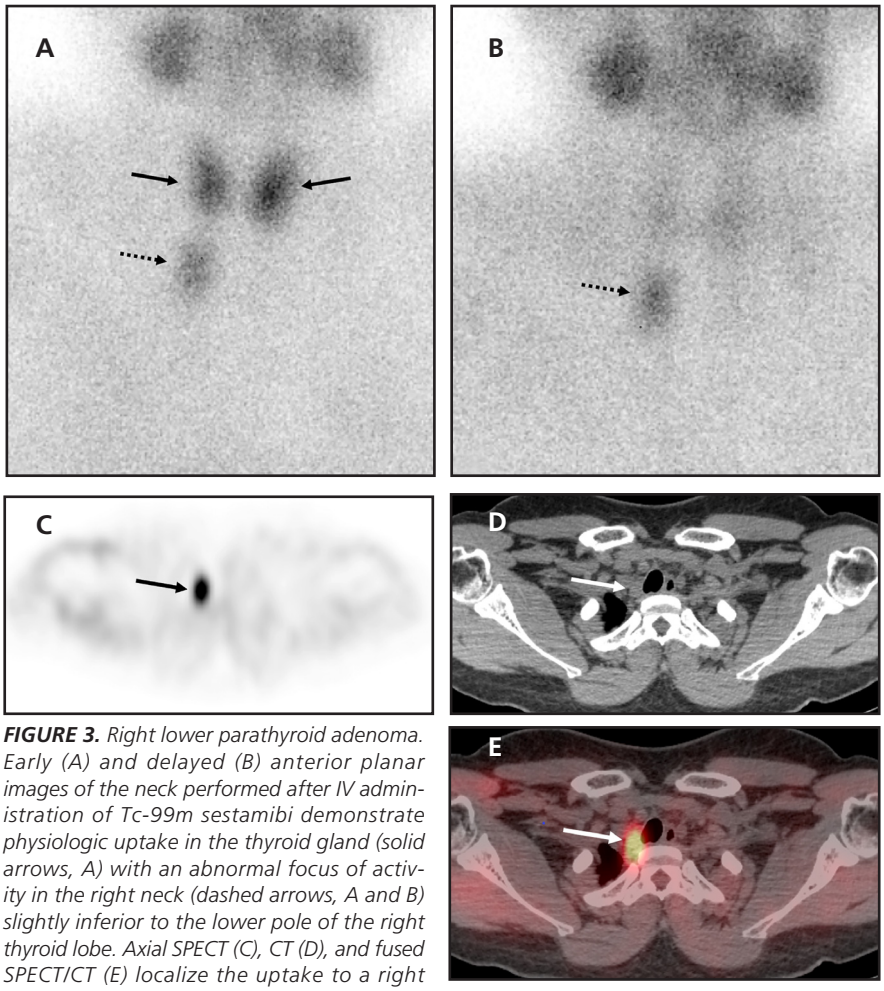

FIGURE 3. *Right lower parathyroid adenoma. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi demonstrate physiologic uptake in the thyroid gland (solid arrows, A) with an abnormal focus of activity in the right neck (dashed arrows, A and B) slightly inferior to the lower pole of the right thyroid lobe. Axial SPECT (C), CT (D), and fused SPECT/CT (E) localize the uptake to a right parathyroid adenoma abutting the trachea (arrows).*

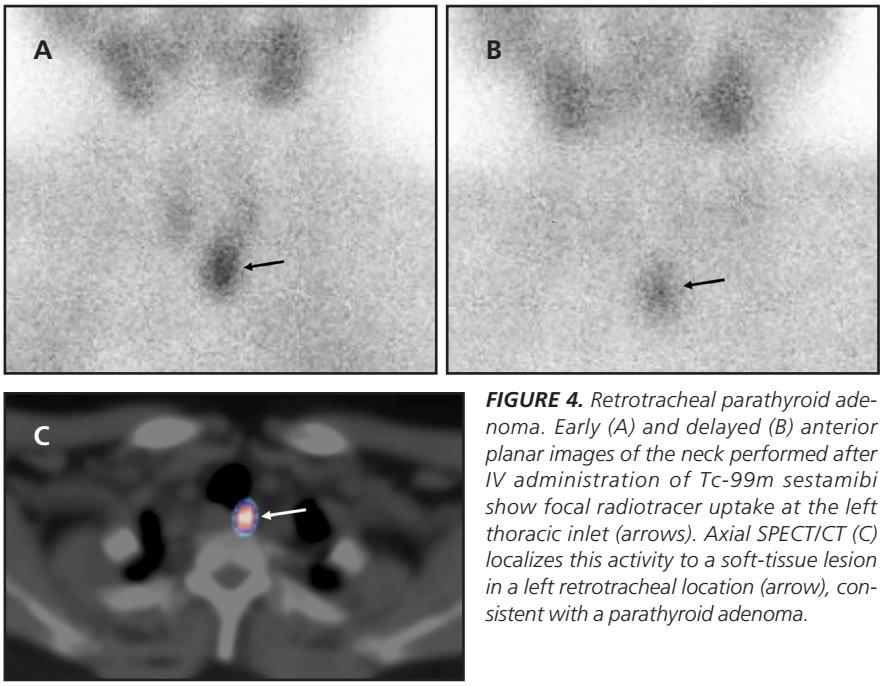

FIGURE 4. *Retrotracheal parathyroid adenoma. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi show focal radiotracer uptake at the left thoracic inlet (arrows). Axial SPECT/CT (C) localizes this activity to a soft-tissue lesion in a left retrotracheal location (arrow), consistent with a parathyroid adenoma.*

techniques become available. Historically, TI-201 was often used. TI-201 demonstrates uptake in both the thyroid and parathyroid glands, and was often performed in conjunction with a radioiodine or pertechnetate thyroid scan. So-called "subtraction scintigraphy" removed counts originating from the thyroid from that of the TI-201 scan to "reveal" a parathyroid adenoma. TI-201 ultimately fell out of favor for parathyroid imaging when a newer perfusion-based radiotracer, Tc-99m sestamibi, became available. Tc-99m sestamibi proved an effective radiotracer in localizing parathyroid adenomas compared to TI-201.[8] Additional advantages of Tc-99m sestamibi include less radiation exposure and a more optimal photopeak for gamma camera imaging. The greater retention of Tc-99m sestamibi in parathyroid adenomas vs. normal thyroid tissues allows for temporal separation of thyroid from parathyroid tissues based on early versus delayed postinjection imaging.

Contemporary parathyroid scintigraphy is based on Tc-99m sestamibi. Imaging protocols vary among institutions, and practice guidelines regarding parathyroid scintigraphy are available from national societies such as the Society of Nuclear Medicine and Molecular Imaging.[9] Most parathyroid scintigraphy protocols call for either dual-time-point imaging with a single radiotracer (Tc-99m sestamibi) or dual radiotracer imaging combining thyroid with parathyroid scintigraphy.

Single Radiopharmaceutical Dual-time-point Technique

The simplest, most common protocol is dual-time-point imaging with two sets of images, early and delayed, after a single injection of Tc-99m sestamibi. Tc-99m sestamibi is a perfusion agent used in a variety of nuclear medicine studies including parathyroid imaging, myocardial perfusion imaging, and breast imaging. It is lipophilic and is thought to localize to the intracellular mitochondria. As with other Tc-99m-labeled radiopharmaceuticals, it has a

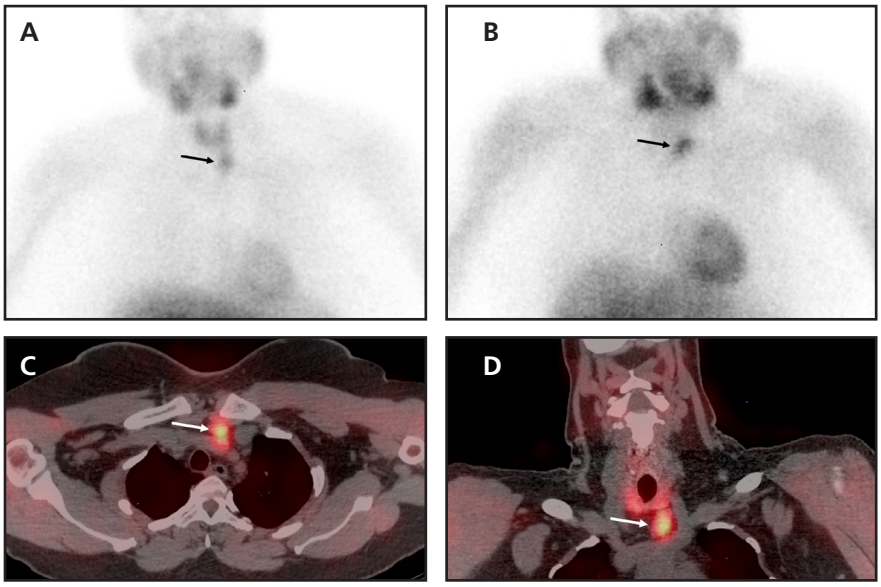

FIGURE 5. *Left lower parathyroid adenoma with minor ectopia. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi demonstrate an abnormal focus of activity in the left neck inferior to the lower pole of the left thyroid lobe (arrows). Axial (C) and coronal (D) SPECT/CT demonstrate a parathyroid adenoma at the thoracic inlet immediately posterior to the left clavicular head and adjacent to the great vessels (arrows). SPECT/CT allows for precise localization to minimize unsuccessful surgeries.*

photopeak of 140 keV and a half-life of 6 hours. The typical dose is 20 to 30 mCi, and is administered intravenously.[9] Imaging is performed early, at 10 to 20 minutes, and delayed at 2 to 2.5 hours (**Figure 1**). Longer delayed imaging times have not been found to improve the distinction of parathyroid adenomas from thyroid tissue.

Tc-99m tetrofosmin is a similar perfusion radiopharmaceutical also commonly used in myocardial perfusion imaging that has potential applicability in parathyroid imaging. However, in a study comparing sestamibi to tetrofosmin, tetrofosmin demonstrated less intense uptake in parathyroid adenomas compared to background thyroid uptake.[10] This makes tetrofosmin a less ideal radiopharmaceutical compared to sestamibi for dual-time-point imaging.

Dual Radiotracer Technique

Instead of dual-time-point imaging with sestamibi, thyroid imaging (with Tc-99m pertechnetate or I-123 sodium iodide) can be combined with parathyroid imaging (with Tc-99m sestamibi or tetrofosmin). As Tc-99m pertechnetate and I-123 localize to the thyroid without significant parathyroid activity, the images can be compared and digitally subtracted to detect a parathyroid adenoma.

However, dual-tracer techniques can be technically challenging, making implementation difficult. Theoretically, parathyroid and thyroid imaging could be obtained on two separate days allowing for decay of the initially used tracer. However, multiple day studies are not practical for most patients. Therefore, a variety of single-day protocols exist.[9,11] Regardless of protocol, both images need to be normalized to allow subtraction to occur. After normalization, the I-123/Tc-99m pertechnetate image can be subtracted from the Tc-99m sestamibi/tetrofosmin image. The result would be an image of only parathyroid glands, allowing identification of the abnormal gland(s). Images could also be critiqued for thyroid nodules that may complicate interpretation. To minimize artifacts on the subtraction imaging, patient positioning must be near identical for both scans. Additionally, movement should be minimal, as excessive motion artifacts will also lead to artifacts on subtraction imaging.

To minimize these artifacts, Hindié et al have proposed an imaging protocol in which the thyroid and parathyroid scans are obtained simultaneously, which requires the use of I-123.[12] Tc-99m pertechnetate cannot be used since it has the same photopeak as Tc-99m sestamibi and tetrofosmin at 140 keV. As I-123 has a different photopeak (159 keV) than Tc-99m-sestamibi and tetrofosmin, image acquisition may be performed simultaneously.

Regardless of whether I-123 or Tc-99m pertechnetate are used to image the thyroid gland, there are additional inherent limitations of dual-radiotracer imaging. A second radiotracer will increase examination costs, especially with the use of cyclotron-produced I-123. A second radiotracer also will increase radiation exposure of the patient.

Future Possibilities with PET

Given the increased resolution of PET and near widespread availability of PET/CT cameras, there has been a significant academic and clinical interest in developing a suitable PET radiopharmaceutical for localization of a hyperfunctioning parathyroid gland.

Unfortunately, the most readily available and clinically familiar PET radiopharmaceutical, F-18 fluorodeoxyglucose (FDG), is not particularly useful in detecting parathyroid adenomas.[13] In a small case series of 8 patients with surgically proven parathyroid adenomas or hyperplasia, Sisson et al did not find a single case of abnormal uptake on FDG.[14]

Both C-11 choline and C-11 methionine have shown potential use in detecting parathyroid adenomas.[13,15] However, the 20-minute half-life of C-11 will likely limit clinical use to large facilities with access to onsite PET isotope production and synthetic capabilities.

F-18 fluorocholine is currently the most likely PET radiopharmaceutical to have widespread appeal in the clinical imaging of parathyroid adenomas. The F-18 label with 110-minute half-life allows for commercial distribution.

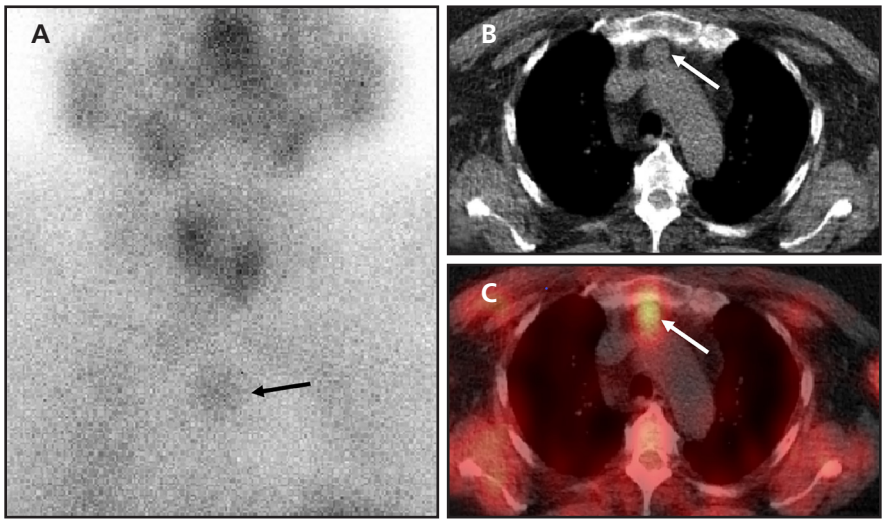

FIGURE 6. *Ectopic parathyroid adenoma. Anterior early planar image (A) performed after the IV administration of Tc-99m sestamibi shows subtle focal radiotracer uptake in the midline thorax (arrow). Axial CT (B) and SPECT/CT (C) localize this activity to a soft-tissue density lesion in the anterior mediastinum, consistent with an ectopic parathyroid adenoma (arrows).*

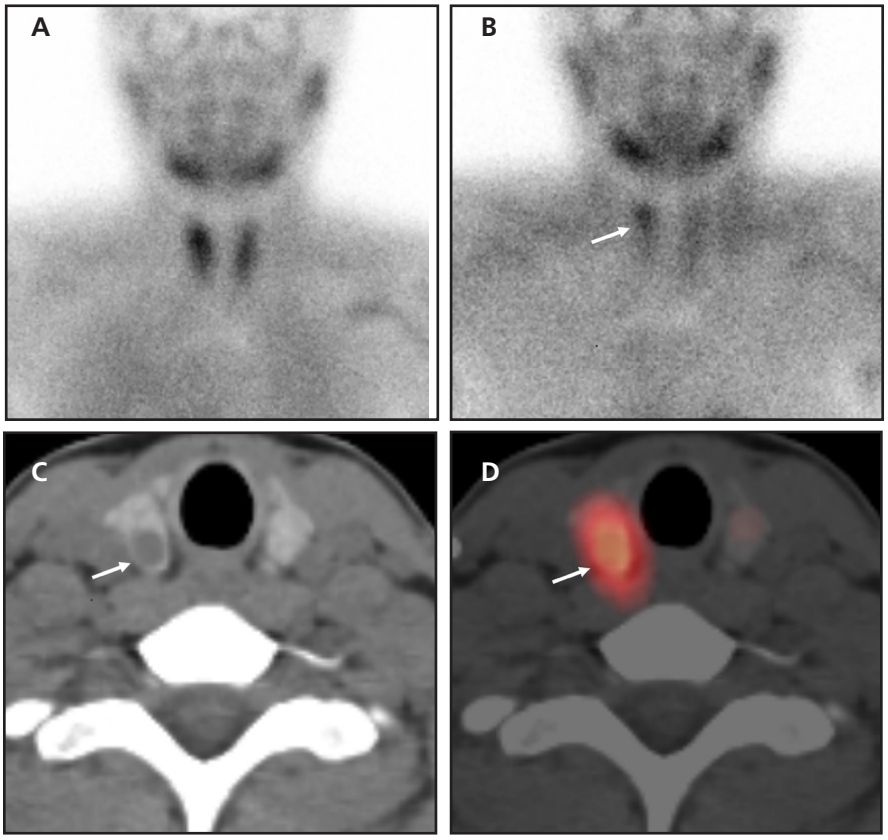

FIGURE 7. *Intra-thyroidal parathyroid adenoma. Following intravenous injection of Tc-99m sestamibi, anterior early (A) and delayed (B) planar images show uniform uptake in the thyroid gland with appropriate washout. Focal radiotracer uptake overlies the right superior thyroid pole on the delayed planar images (arrow, B). Axial CT (C) and fused SPECT/CT (D) localize this activity to a low-attenuation density in the right superior thyroid pole (arrows). Given the diagnosis of primary hyperparathyroidism and the solitary nature of this intra-thyroidal focus, it was suspected to be an intra-thyroidal parathyroid adenoma. This was surgically removed and confirmed as parathyroid tissue.*

Recent studies demonstrate F-18 fluorocholine to be sensitive in evaluating parathyroid adenomas.[16,17] In a study comparing F-18 fluorocholine to Tc-99m sestamibi for parathyroid imaging, both radiotracers demonstrated 100% specificity, with F-18 fluorocholine demonstrating 92% sensitivity compared to 64% from Tc-99m sestamibi.[18] Although further work is required, this is an intriguing radiotracer with potential clinical implications.

Imaging Findings

Tc-99m sestamibi accumulates in normal thyroid tissue as well as abnormal parathyroid tissue. Classically, the radiotracer washes out of the thyroid gland faster than the parathyroid adenoma. Thus, on early imaging, depending on location(s), parathyroid adenomas may be readily identified or obscured by otherwise physiologic thyroid uptake (**Figure 2).** On delayed imaging, thyroid activity should diminish, revealing a parathyroid adenoma (**Figures 3 and 4**).

SPECT/CT Imaging

SPECT/CT imaging with complementary anatomic and functional mapping has special applicability in parathyroid scintigraphy. Given the relative small size of parathyroid adenomas, closely adjacent viscera, and incidence of minor and major ectopy, SPECT/CT combines imaging modalities in an advantageous way to assist in localization and surgical treatment planning (**Figures 5 and 6**).

Neumann et al evaluated dual-isotope SPECT and SPECT/CT in primary hyperparathyroidism. Although sensitivities were similar, SPECT/CT was more specific, 96% compared to 48% for SPECT.[19] A meta-analysis of 24 studies, however, demonstrated the superior sensitivity of SPECT/CT compared to SPECT and planar techniques.[20] Dual-phase Tc-99m sestamibi SPECT/CT showed an estimated pooled sensitivity of 86% (CI 81% to 90%), which was superior to that of SPECT at 74% (66% to 82%) and planar imaging 70% (61%

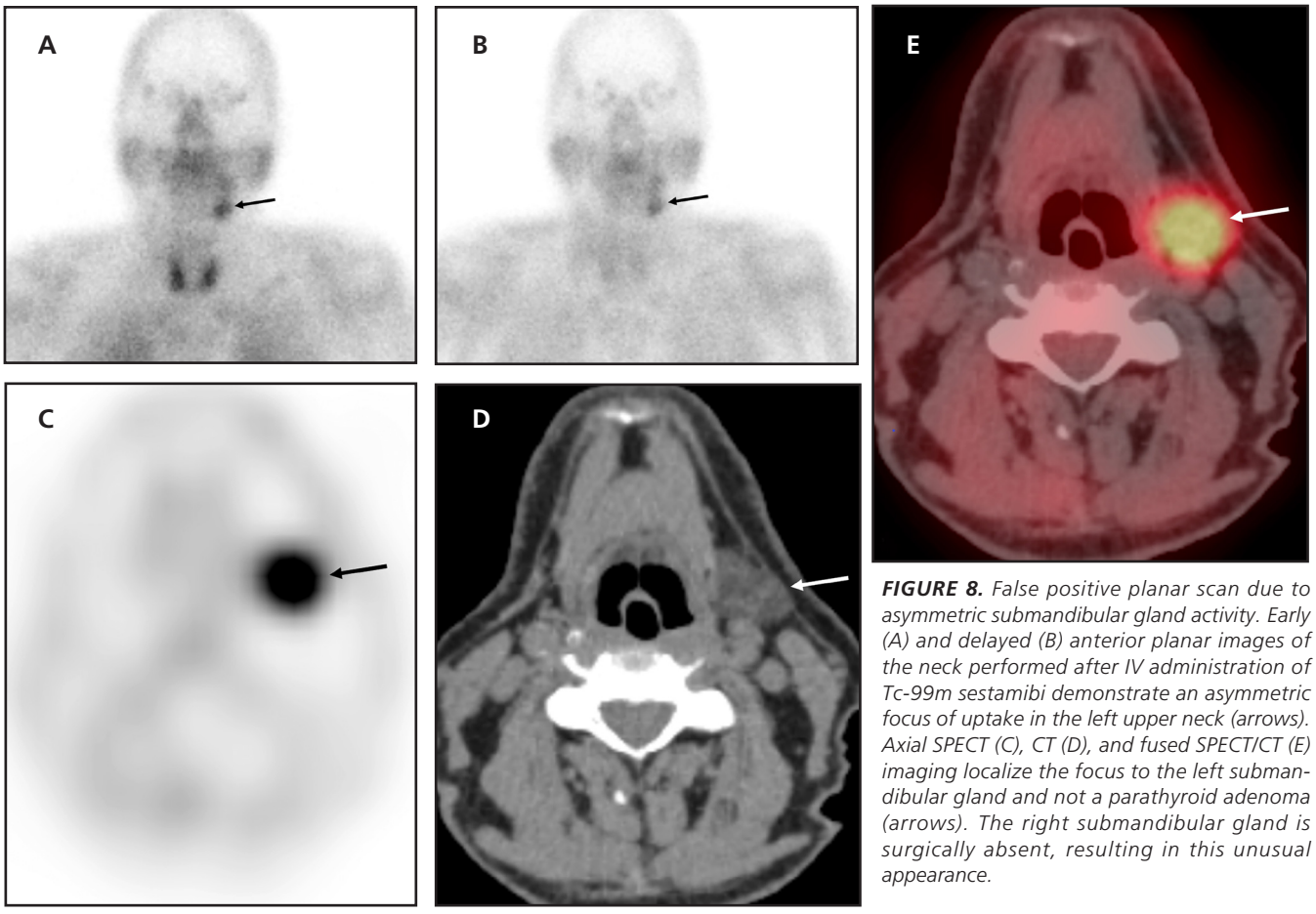

FIGURE 8. *False positive planar scan due to asymmetric submandibular gland activity. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi demonstrate an asymmetric focus of uptake in the left upper neck (arrows). Axial SPECT (C), CT (D), and fused SPECT/CT (E) imaging localize the focus to the left submandibular gland and not a parathyroid adenoma (arrows). The right submandibular gland is surgically absent, resulting in this unusual appearance.*

to 80%). The rate of ectopic parathyroid adenomas ranged from 4% to 20%, and most authors found that SPECT/CT was superior to SPECT and planar imaging for localization of ectopic glands (**Figure 7**).

Most clinical protocols use both planar and SPECT/CT imaging. A large field of view, parallel-equipped collimated gamma camera planar image of the neck and chest can be obtained to evaluate for glandular ectopy. High-resolution planar, pin-hole collimator imaging of neck for fine detail is also likely beneficial. This, combined with SPECT/CT of the neck and chest, yields the greatest amount of functional information (**Figure 8**).

Imaging Pitfalls

The reported performance of parathyroid scintigraphy varies in the literature. In a meta-analysis, Gotthardt et al reviewed 52 studies involving parathyroid scintigraphy in which sensitivities ranged from 39% to > 90%.[21] Several factors likely played a role in this variable rate of false negative studies.

Parathyroid adenomas must be sizable for detection. In a study evaluating 107 parathyroid adenomas, the sensitivity in glands > 500 mg was 91% compared to 80% in glands < 500 mg.[22] In another study comparing characteristics of true positive and false negative parathyroid adenoma Tc-99m sestamibi images, the average true positive had a mean weight of 1336 mg, with the mean weight of false negatives of 475 mg.[23] Additionally, due to their deeper location, superior parathyroid adenomas are more likely to be missed by parathyroid scintigraphy.[23,24]

Although single-gland disease is much more common, multigland disease poses substantial diagnostic challenges. One study estimated multigland disease to occur in at least 11% of cases of sporadic (nonfamilial) primary hyperparathyroidism.[25] Unfortunately, multigland disease is less likely to be detected by parathyroid scintigraphy. Nichols et al demonstrated a sensitivity of planar and SPECT parathyroid scintigraphy in multigland disease of 66%, compared to 90% for single-gland disease.[26] Differences in sensitivity persisted when taking gland size into account. In the setting of glandular hyperplasia, hyperplastic glands tend to be smaller compared to parathyroid adenomas.[27] Similar findings have been described with hybrid SPECT/CT imaging.[28] The incidence of multigland disease and its poor preoperative imaging detection have been used as arguments against unilateral gland surgery.[25]

Several molecular observations also have been described to explain variations of radiopharmaceutical uptake in abnormal parathyroid glands. Parathyroid glands are primarily composed of chief

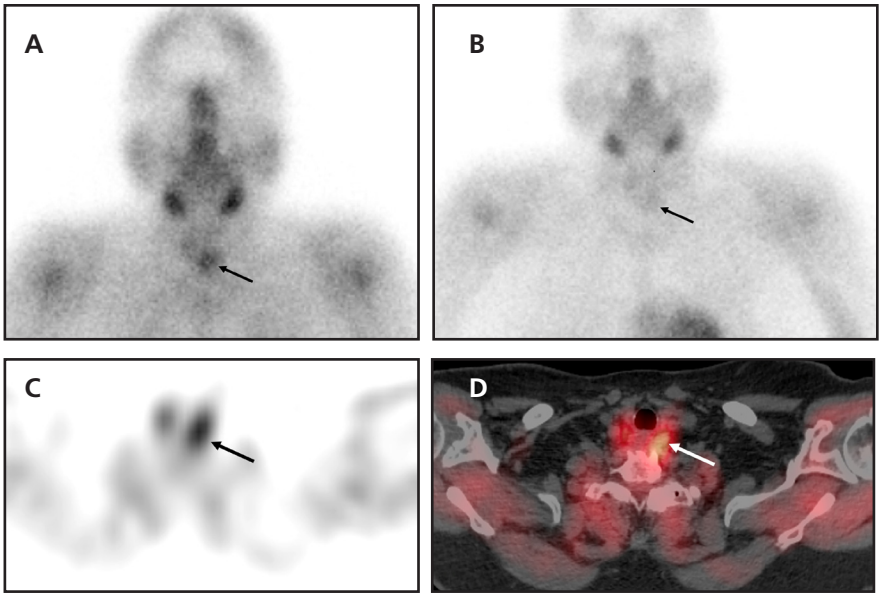

FIGURE 9. *Rapid washout parathyroid adenoma. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi demonstrate a focus of abnormal uptake in the left lower neck on early imaging that is less apparent on delayed imaging (arrows). Relatively low thyroid uptake on both images is related to the patient's history of chronic hypothyroidism. Axial SPECT (C), and fused SPECT/CT (D), confirms the presence of a left lower parathyroid adenoma (arrows).*

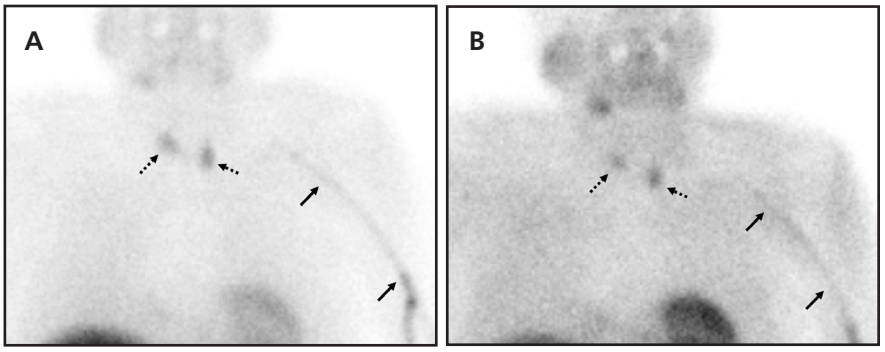

FIGURE 10. *Venolymphatic activity and persistent thyroid uptake. Early (A) and delayed (B) anterior planar images of the neck performed after IV administration of Tc-99m sestamibi demonstrate linear uptake in the left upper arm related to suboptimal injection (solid arrows). Uptake in the thyroid gland (dashed arrows) persists on delayed imaging without the expected washout. This persistent uptake in the thyroid gland makes evaluation for an underlying adenoma difficult without SPECT or SPECT/CT.*

and oxyphil cells. Oxyphil cells demonstrate an abundance of mitochondria, an important site of accumulation of perfusion-based imaging agents. Melloul et al demonstrated a correlation between the intensity of the radiotracer uptake with oxyphil content.[29]

The expression of p-glycoprotein and/or multidrug resistance-related protein may also affect scintigraphic visualization of parathyroid adenomas. These cell membrane pumps have a negative effect upon cellular accumulation of lipophilic agents such as sestamibi.[30] Kao et al evaluated 47 parathyroid adenomas, 39 of which did not express p-glycoprotein or multidrug resistance-related protein and were detected on parathyroid scintigraphy.[31] The 8 expressing p-glycoprotein and/or multidrug resistance-related protein were not detected on scintigraphy. This expression is believed to account for the so-called "rapid washout" parathyroid adenomas, in which the adenoma may be seen on early images (if not obscured by the thyroid gland). However, the adenoma is no longer visualized on delayed imaging due to the efflux of the radiopharmaceutical secondary to membrane pump overexpression. Given this unusual pattern of uptake, the exam may be falsely interpreted as negative (**Figure 9**).

A variety of nonparathyroid processes can result in focal tracer uptake. This is largely related to the nonspecific nature of perfusion radiotracers. Most common and problematic is a variety of thyroid processes that can result in persistent diffuse or focal radiotracer uptake. Thyroid nodules/adenomas can demonstrate focal radiotracer uptake resulting in a false-positive study.[32] Certain malignant processes can demonstrate focal radiotracer uptake, of which breast, lung, and head and neck cancers would most likely be in the field of view. Brown adipose tissue uptake in the neck as a mimicker of parathyroid disease has also been described, which can be confidently evaluated with SPECT/CT.[33] Technical issues can also result in abnormal uptake. Most commonly extravasation in an upper extremity injection site can result in venolymphatic uptake in the upper arm with or without axillary lymph node uptake (**Figure 10**).

Conclusion

Parathyroid scintigraphy continues to play an ever-important role in preoperative evaluation in patients with hyperparathyroidism as the trend toward minimally invasive procedures continues to increase. A successful nuclear medicine specialist must have a strong fundamental understanding of the physiology and pathology of hyperparathyroidism and mechanisms of radiotracer localization. Additionally, an appreciation of imaging pitfalls, both false negative and positive, can aid image interpretation and communication with referring physicians. Hybrid SPECT/CT has additional benefits for both the radiologist and surgeon as precise localization and anatomic correlation

increases reader confidence and can aid in presurgical planning. As this technology becomes more available, SPECT/CT should be routinely performed as an integral part of the contemporary approach to parathyroid scintigraphy.

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