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The Journal of the American Osteopathic College of Radiology (JAOCR) is designed to provide practical up-to-date reviews of critical topics in radiology for practicing radiologists and radiology trainees. Each quarterly issue covers a particular radiology subspecialty and is composed of high-quality review articles and case reports that highlight differential diagnoses and important teaching points.

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Letter from the Guest Editor

“I am among those who think that science has great beauty.”

Marie Curie

In this Issue

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Nuclear medicine and molecular imaging is an ever-expanding field of imaging. Combining functional information from radiopharmaceuticals with anatomic imaging creates a powerful tool. The interpreting physician must not only have a sound basis in radiological principles, but also have a solid foundation in physiology and pathophysiology to understand the normal and abnormal causes of uptake. It is with this goal that we proudly present this nuclear-medicine-themed issue of JAOCR.

Our review article topics were chosen to address common issues in everyday nuclear medicine, F-18 fluorodeoxyglucose (FDG) PET/CT and parathyroid imaging. The PET review article focuses on the variety of pitfalls encountered in oncologic FDG PET/CT imaging. The article is essentially an imaging atlas to illustrate the gamut of potential pitfalls leading to—and strategies to avoid—misdiagnosis. Our parathyroid imaging review provides a comprehensive look at the current state of nuclear medicine’s role in managing primary hyperparathyroidism with a focus on SPECT/CT hybrid imaging.

In our differential case reviews, we present an unusual and unexpected focus of uptake in a radiolabeled leukocyte scan, as well as an atypical thyroid scan in a patient with hyperthyroidism. Finally, we have three beautiful examples of classic nuclear medicine cases for your enjoyment in JAOCR at the Viewbox.

I am forever grateful to the staff, reviewers, and editors at JAOCR. Special thanks must be given to William T. O’Brien, Sr., D.O., for guidance and support throughout this project. Every author worked diligently on these articles and I am forever in their debt. I am also honored to have several residents from the Garden City Division of the Michigan State University Radiology Osteopathic Residency Program participate in this issue. Their hard work with guidance from faculty mentors resulted in excellent articles.

It was fun creating the issue, and I hope you enjoy it. Moreover, I hope this issue solidifies and adds to your knowledge of clinical nuclear medicine.
Over the last decade, F-18 fluorodeoxyglucose (FDG) PET/CT has continued to have an ever-increasing role in staging malignancy, evaluating tumor response to treatment, and evaluating indeterminate masses discovered on CT, MRI and US. Many decisions regarding medical and/or surgical interventions are largely based on functional metabolic information gathered from the PET/CT. It is, therefore, critical for the interpreting physician to be aware of potential pitfalls that may lead to an erroneous diagnosis.

As the name implies, FDG is an analog of glucose that is beneficial in detecting a variety of malignancies. The relative increased uptake of FDG by many malignancies compared to background tissues is due to the increased expression of glucose transporters by cancer cells, as well as variations of intracellular enzyme activity with increased activity of hexokinase and decreased activity of glucose-6-phosphatase. Ultimately, this leads to increased accumulation of FDG in many malignant cells as, unlike regular glucose, FDG does not become further metabolized after initial phosphorylation.

Unfortunately for interpreting physicians, a major limitation of FDG is that it is not specific for neoplastic cells. In addition to the variations of normal human metabolism within organs and tissues that universally rely on glucose as a substrate, a variety of nonmalignant inflammatory processes can also demonstrate significant FDG uptake. In fact, FDG is increasingly used clinically for nononcological purposes, including neurodegenerative disorders, cardiac viability, cardiac sarcoid, as well as replacing traditional radiolabeled leukocyte imaging for detecting infection.

There is also an overlap in the amount of FDG uptake between many benign and malignant lesions. This problem is common in evaluating solitary pulmonary nodules and incidental adrenal nodules, for example. Furthermore, certain benign lesions such as Warthin’s tumors may also display a high degree of FDG uptake.

Additionally, whole-body FDG PET/CT is a technically challenging examination compared to many standard radiology studies. Patient preparation, radiotracer injection, uptake period, image acquisition, and processing all have potential for problems that can affect image interpretation.

This article is a pictorial review of a variety of pitfalls in interpreting FDG PET/CT scans. After discussing a variety of general considerations, details of pitfalls related to specific body regions will be presented. With familiarity and understanding of these processes, the reading physician increases the likelihood of diagnostic pitfall recognition, thus avoiding incorrect interpretations.

**General Considerations**

Although patient preparation can vary by institution, practice guidelines from the Society of Nuclear Medicine and Molecular Imaging suggest that patients fast 4 to 6 hours prior to PET imaging to ensure optimal insulin levels. Injection of FDG and subsequent imaging in nonfasting patients can result in a so-called altered biodistribution, in which there is relative increased FDG uptake throughout the body’s skeletal muscles largely due to insulin effect (Figure 1). Similar findings can be seen in patients on insulin and corticosteroids, as well as in those who have recently exercised. Regardless of cause,
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**FIGURE 1.** Altered biodistribution. FDG PET MIP image demonstrates diffuse increased muscular uptake, most consistent with insulin effect in this nonfasting patient.

**FIGURE 2.** Extravasation at the injection site. FDG PET MIP image demonstrates a large focus of uptake in the right upper extremity (solid arrow) with adjacent lymphatic uptake (dashed arrow) due to extravasation at the injection site. Not only does this create an optical distraction for the interpreter, it also decreases the amount of radiotracer in the blood pool and can lead to inaccurate SUV measurements.

**FIGURE 3.** Misregistration artifact. Axial FDG PET (A) and fused PET/CT (B) images demonstrate myocardial FDG uptake erroneously localizing to the left lung (arrow, B). The patient changed position between CT and PET acquisition resulting in this artifact.

**FIGURE 4.** Brown fat uptake. FDG PET MIP image in a pediatric patient demonstrates bilateral uptake in cervical, supraclavicular, and paraspinal fat, as well as additional foci in the upper abdomen (arrows) in a classic pattern of brown fat uptake.

**FIGURE 5.** Normal pediatric red marrow distribution. FDG PET MIP image in a pediatric patient demonstrates heterogenous FDG uptake in the proximal humeri, proximal and distal femurs, and proximal tibias (arrows) reflecting normal FDG uptake in red bone marrow. This uptake is usually minimal or absent in adults due to the conversion of red marrow to yellow marrow, which is typically less metabolically active.
an altered biodistribution can obscure underlying disease and potentially affect tumor-to-background conspicuity. Similarly, artifacts can be related to suboptimal injection technique of the radiopharmaceutical. A small amount of extravasation at the injection site is common, and correlation with injection site documentation is advised when identifying a small focus of abnormal uptake in the subcutaneous tissues of the upper extremities or in draining lymph nodes. However, occasionally a greater amount of the radiotracer extravasates, causing more significant artifacts (Figure 2). The interpreting physician must use caution when reporting such cases and may need to repeat the study to ensure diagnostic accuracy. Specifically, the calculated standardized uptake values (SUVs) of the lesions of concern may not be accurate as the documented injected dose (one parameter for determining SUV) likely does not reflect the true dosage of FDG in the blood pool due to the extravasation.

In addition to the usual motion artifacts present throughout imaging modalities, PET/CT is susceptible to potentially problematic artifacts when patient position changes between CT and PET acquisition, resulting in misregistration. This is common near the diaphragm, as most PET acquisition is not done with a breath-hold, although respiratory gating can help minimize this misregistration. With more significant motion, FDG uptake can project over the incorrect anatomic structures and may lead to incorrect localization (Figure 3). Some software packages allow the user to adjust registration to align data to correct the error, although these are usually limited to rigid realignments in 3 axes. Patient motion between the PET and CT portion of the studies can also cause an incorrect attenuation map to be applied to the PET region, thus affecting the attenuated corrected data set.

In addition, metal or other high-density implants, as well as oral and intravenous contrast, can create a false area of relative increased uptake due to attenuation correction artifacts. Attenuation correction works well in the range of tissue densities within the human body; however, it is prone to falsely overestimate the degree of attenuation correction in regions of higher density materials. As this activity is usually
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not associated with anatomic masses, it is usually discounted by the interpreter by noting the CT findings. However, review of the nonattenuation corrected data set can confirm the artifact, as this activity should disappear on nonattenuation-corrected images.

Lymphoma is one of the more common indications for oncological PET/CT. Some of the most common histological subtypes, including Hodgkin disease and diffuse large B-cell lymphoma, are extremely PET-avid, and PET can be used for staging and assessing treatment response. However, other histological subtypes are less likely to be FDG-avid. These include primary cutaneous anaplastic large T-cell lymphoma, extranodal marginal zone lymphoma, and small lymphocytic lymphoma. When performing initial staging PET/CT on patients with a known lymphoma, occasionally a non-FDG avid lymphoma will be encountered. It is important to alert the referring physician that the disease being evaluated is not FDG-avid and a follow-up FDG PET/CT for determining treatment response may not be useful. Knowledge of neoplasms that have low FDG avidity is important to prevent inappropriate action regarding false-negative findings, including hepatocellular carcinoma, renal cell carcinoma, neuroendocrine tumors, well-differentiated endocrine malignancy, prostate cancers and some genitourinary cancers.

Pediatric Variants, Pitfalls and Artifacts

PET imaging for childhood cancers is predominately performed for lymphoma, osteosarcoma, Ewing sarcoma, and soft-tissue sarcomas including rhabdomyosarcoma and malignant peripheral nerve sheath tumors. Imaging children requires specific knowledge of changes in the physiological processes of maturation; the more frequent need for sedation; and awareness of the spectrum of childhood cancers, genetic predisposition syndromes, and secondary cancers after treatment.

Brown Fat

Brown fat contains metabolically active mitochondria that burn energy and release heat. Brown fat uptake has been reported in one-third of children imaged with PET, and is more frequent in children than adults. It is more common in cold climates and can be reduced by

FIGURE 8. Photopenic brain metastasis. Axial FDG PET (A) and contrast-enhanced CT (B) images demonstrate a metastasis from lung carcinoma (arrows) appearing relatively photopenic compared to the high background uptake throughout the brain.

FIGURE 9. Prior infarct. Axial FDG PET image (A) demonstrates a wedge-shaped region of photopenia in the right parieto-occipital lobe (arrow), correlating to a prior infarct with a region of encephalomalacia noted on CT (arrow, B).

FIGURE 10. Focal nasopharyngeal uptake. Axial fused FDG PET/CT image demonstrates focal uptake in the right fossa of Rosenmüller (arrow) in a patient with metastatic lung carcinoma. This uptake was inflammatory and resolved on follow-up imaging.
warming techniques. Common locations include the supraclavicular fossa, cervical and axillary soft tissues, mediastinum, thoracic parascapular and paraspinal soft tissues, and the upper abdomen (Figure 4).

Marrow
Red marrow is more metabolically active than yellow marrow and, therefore, demonstrates relatively increased FDG uptake. In neonates, the distribution of red marrow involves the distal long extremities. As infants grow, the red marrow shifts from the skull and extremities to the axial skeleton (spine, pelvic bones, ribs and sternum) with yellow fatty marrow replacement occurring earlier at the epiphyses and diaphysis (Figure 5). By around 15 years of age, this process is largely complete. In adults, only a little hemopoietic red marrow remains in the proximal metaphysis of the femur and humerus. Additionally, the skeleton in children is rapidly growing at the physes and epicondyles, which can appear relatively “hot” on PET imaging.

Thymus
Children, adolescents, and young adults have a greater incidence of thymus visualization on PET imaging, with hyperplasia occurring in the setting of severe stress or chronic disease.
termed thymic rebound when found after chemotherapy. With maturity, the thymus varies considerably in shape, and often can be difficult to distinguish from an anterior mediastinal mass. Neonates have a large thymus, which increases up to 2 years of age. It can cover both the left and right aspects of the heart, and has been described as quadrangular. Gradually, the thymus assumes the more classic sail or spinaker sign. On PET imaging, the thymus should have uniform FDG uptake and smooth convex margins. Cervical thymic extension is an important variant to recognize, wherein thymic tissue extends into the superior mediastinum and lower neck (Figure 6). This represents an embryologic remnant along the track of descent. It may occasionally appear as a lower cervical mass, discontinuous with the thymus, and can be mistaken for a tumor or enlarged lymph node.

**Lymphoid Tissue**

Children have prominent lymphoid tissue compared to adults, including the above-described thymus and in bone marrow. They also have prominent secondary lymphoid tissue, including the adenoid, palatine, and lingual tonsils. Furthermore, they are more prone to symmetric low-grade FDG uptake in reactive lymph nodes due to inflammation or infection in common sites, including cervical, axillary, mesenteric, and inguinal lymph nodes.

**Head and Neck**

Evaluation for brain masses is potentially problematic, largely due to the high physiologic FDG uptake in the gray matter structures. It is critical for the interpreting physician to adjust the window to detect potential hypermetabolic brain masses, such as those resulting from lymphoma, metastatic melanoma, or lung cancer (Figure 7). On the other hand, brain lesions with significant cystic and/or necrotic components may appear relatively photopenic (Figure 8). When encountering subtle foci, it is best to correlate with contrast-enhanced, diagnostic quality CT or MR. Other causes of photopenic defects in the brain include postoperative changes and prior infarcts (Figure 9).

In patients with no history of head and neck cancer, incidental asymmetric uptake in the pharynx poses a diagnostic dilemma, as both malignancy and infection/inflammation can result in focal asymmetric uptake (Figure 10). Focal uptake at the midline of the nasopharynx has also been described in inflamed Thornwaldt’s cysts. Despite a variety of attempts to find a reliable prospective means to differentiate benign from malignant uptake, there is no clinical consensus for a reliable absolute or relative SUV to differentiate inflammation...
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from malignancy. Ultimately, clinical and/or endoscopic evaluation will likely be needed to exclude malignancy.¹⁴

Recent phonation will increase FDG uptake in the vocal cords. When this is symmetric, no diagnostic challenge is present. Focal asymmetric uptake in the vocal cords, however, likely requires further investigation. A common cause of asymmetric uptake is unilateral vocal cord paralysis. Vocal cord paralysis will result in decreased FDG uptake in the affected cord and a search for an underlying cause, such as a thoracic mass impinging the recurrent laryngeal nerve, cervical mass involving the course of the vagus nerve, or history of neck surgery (Figure 11). In the absence of an underlying cause, laryngoscopy will likely be necessary.

As with pediatric patients, brown fat FDG uptake is a common cause of focal uptake in adult necks, and is potentially problematic when evaluating patients with head and neck cancers as well as lymphoma.¹⁵ The key for identifying this pitfall is localization of the uptake to fat density on CT and lack of corresponding soft-tissue mass. At times, however, it can be difficult to separate this activity from closely adjacent lymph nodes. This entity occurs more in colder climates. Because brown fat is sympathetically innervated, patient anxiety at the time of the PET scan may contribute to its visualization. A variety of means can help minimize this brown fat uptake, the simplest of which is to ensure adequate warming prior to injection and uptake.¹⁶ Several drugs, including propranolol, diazepam, and fentanyl, have also shown to decrease brown fat uptake; however, the routine clinical implementation of these medications is challenging in the outpatient setting. Although uncommon, hibernomas, which are benign neoplasms composed of brown fat, can demonstrate increased FDG uptake.

Incidental uptake in the thyroid gland is often encountered on PET imaging. Diffuse increased FDG uptake throughout the thyroid gland is usually benign; correlation can be made for diffuse thyroid diseases, including Graves’ disease or chronic lymphocytic (Hashimoto’s) thyroiditis (Figure 12).²⁰ Although rare, diffuse FDG uptake has been associated with malignancy, including cases of thyroid lymphoma²¹ and metastatic non-small cell lung carcinoma.²² Focal thyroid FDG uptake, on the other hand, requires additional evaluation with ultrasound and possible tissue sampling, as there is a significant association with malignancy. In one study, Choi et al demonstrated malignancy in 18 of 49 focal thyroid lesions detected on FDG PET/CT and it is generally accepted that one-third of FDG-avid thyroid nodules are malignant, with the remainder being benign thyroid adenomas (Figure 13).²³

Muscle uptake in the neck is variable and mostly related to recent use, pain,
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anxiety or inflammation. As with brown fat uptake, this muscular uptake can be readily localized to muscle with CT correlation and the lack of a correlating mass lesion. Regardless, this should be minimized, particularly when evaluating patients with head and neck cancer, as this uptake may obscure small disease foci. Most patient protocols request withholding eating and chewing gum prior to the exam, as this can result in intense FDG uptake throughout the muscle of mastication (Figure 14).

Additional hypermetabolic lesions may be encountered incidentally in the head and neck. Most commonly, these include incidental foci in the salivary glands (Figure 15) and sinuses (Figure 16). When encountering such lesions, it is appropriate to suggest additional work-up with imaging and/or tissue sampling. Seo et al. documented focal FDG uptake in the parotid gland in 2.1% of patients with head and neck malignancy, of which 33.3% were metastatic foci disease and 66.7% demonstrated a variety of benign pathologies.24

Thorax

Evaluation of the solitary pulmonary nodule is one the most common indications for FDG PET/CT, which aids characterization of indeterminate pulmonary nodules. In a study evaluating 89 patients with solitary pulmonary nodules, FDG PET/CT demonstrated a sensitivity of 92% and specificity of 90% for detecting

FIGURE 22. Cardiac melanoma metastases. Axial CT (A) and fused FDG PET/CT (B) images demonstrate multiple hypermetabolic cardiac masses (arrows) in a patient with widely metastatic melanoma.

FIGURE 23. Adrenal nodular hyperplasia. Axial FDG PET (A) and fused PET/CT (B) images demonstrate low-level FDG uptake, equal to slightly less than liver background, and nodular thickening of the adrenals (arrows) in a patient with lung carcinoma. These findings correspond to benign nodular adrenal hyperplasia.

FIGURE 24. Fibroid uptake. Sagittal CT (A) and fused FDG PET/CT (B) images show intense FDG uptake in a large fundal fibroid (arrow, B). FDG PET cannot readily distinguish leiomyomas from leiomyosarcomas.

FIGURE 25. Physiologic ovarian uptake. Fused FDG PET/CT image in a young woman with lymphoma demonstrates focal uptake in the right ovary (arrow), a normal finding representing functional changes in a premenopausal female.
malignancy. However, smaller nodules pose potential problems given the spatial resolution of PET (7 to 8 mm). Both the 2013 American College of Chest Physicians practice guidelines for pulmonary nodules and the 2017 Fleischner Society guidelines for incidental pulmonary nodules have indications for FDG PET/CT for nodules > 8 mm. In routine clinical practice, any non-FDG avid nodule ≤ 8 mm should be considered too small to accurately characterize by PET, and continued CT followup should be considered to ensure stability.

In addition to issues with small pulmonary nodules, PET/CT has been shown to be less sensitive for several types of pulmonary malignancy. Adenocarcinoma in situ (formerly called bronchoalveolar carcinoma) and carcinoid are classically associated with being falsely PET negative, although other low-grade or early bronchogenic malignancies have also been shown to be falsely PET negative. Given the relatively low metabolic rate of these malignancies, it is necessary to continue CT surveillance of pulmonary nodules that demonstrate low (less than mediastinal vascular blood pool) FDG uptake (Figure 17). Continued follow-up is recommended, as the referring physician may not be aware of these potentially significant false negatives. The 2017 Fleischner Society guidelines provide generally accepted follow-up intervals.

FIGURE 26. Occult bladder mass. Fused FDG PET/CT (A) and unfused CT (B) images demonstrate a subtle polypoid bladder mass (arrows) that is largely obscured on fused imaging due to the physiologic FDG uptake in the urine.

FIGURE 27. Renal cell carcinoma. Contrast-enhanced coronal CT image (A) demonstrates a small enhancing exophytic right lower pole renal mass consistent with renal cell carcinoma (arrow). However, on FDG PET/CT (B), the lesion is metabolically indistinguishable from high physiologic background uptake of the kidney.

FIGURE 28. Crohn’s disease. Axial CT (A) and fused PET/CT (B) images show focal FDG uptake localizing to a short segment of small bowel in the right lower quadrant with wall thickening (arrows).
for indeterminate pulmonary nodules. If a non-FDG avid nodule demonstrates enlargement at follow-up, tissue sampling should be considered.

A variety of infectious or inflammatory processes can be incidentally detected on PET/CT. Unfortunately, there is no reliable SUV threshold that can routinely differentiate infection/inflammation from malignancy with certain infectious/inflammatory processes being hypermetabolic and certain malignancies being non-FDG avid, including cystic or necrotic neoplasms. Additionally, measured SUVs depend on numerous factors independent of the target lesion of concern, including body fat composition, uptake time, and patient blood glucose levels. In the chest, pneumonia, tuberculosis, mycobacteria avium complex, aspergillosis, sarcoidosis, rheumatoid nodules, postsurgical inflammatory changes, tule pleurodesis, esophagitis, and postradiation inflammation are common (Figures 18-20). The sequelae of chronic granulomatous infections often include FDG-avid lung nodules and mediastinal lymph nodes that are often calcified.

Cardiac uptake is highly variable in fasting FDG PET/CT, ranging from essentially background to diffuse, intense FDG uptake. This is largely due to the heart’s ability to metabolize carbohydrates or fatty acids with a switch to glucose in the presence of insulin or glucose loading. Unfortunately, this makes interpreting PET findings challenging. Occasionally, an infarct may be encountered as a focal area of photopenia (Figure 21). Although uncommon, malignancies can occasionally involve the heart with regions of hypermetabolic activity, most often due to metastases with primary cardiac neoplasms being rare (Figure 22).

Abdomen and Pelvis

The adrenal glands are common locations for metastases and, therefore, should be closely evaluated on oncologic PET/CT. Studies have shown PET/CT to be reasonably sensitive and specific for differentiating benign from malignant lesions. However, one must be careful not to misdiagnose a variety of common benign adrenal processes...
as metastases (e.g., adrenal adenomas, hyperplasia, myelolipomas, benign pheochromocytomas, oncocytomas, hemorrhage, and cysts), as some of these benign entities can demonstrate mild FDG uptake (Figure 23).\(^{35}\) Although no absolute SUV threshold exists for differentiating benign from malignant uptake, Boland et al suggest a combination of CT characteristics (< 10 HU indicating a benign adenoma) and ratio of adrenal lesion to liver background PET activity (with a ratio of > 1 suspicious for malignancy) to be a reasonable means to characterize adrenal lesions as malignant with a sensitivity of 100% and specificity of 99%.\(^{36}\)

Expected uptake in the uterus and ovaries depends on a patient’s menopausal status. Uptake in the endometrium can vary during the menstrual cycle, with greatest levels during menstrual flow and ovulatory phases.\(^{37}\) This can pose particular diagnostic problems when evaluating women with cervical carcinoma. Consideration may be given to coordinating PET/CT with menstrual cycle phase to perform the PET/CT in the late secretory or early proliferative phases (just before or after menstruation).\(^{38}\) Increased FDG uptake can also be seen in uterine fibroids; however, PET cannot reliably distinguish leiomyomas from leiomyosarcomas (Figure 24).\(^{39,40}\)

**FIGURE 31.** Focal FDG uptake in a benign rib fracture. Axial-fused FDG PET/CT image demonstrates focal FDG uptake in a non-pathological traumatic left rib fracture (arrow).

**FIGURE 32.** Bone metastases and bone marrow stimulation. FDG PET MIP image (A) demonstrates innumerable hypermetabolic osseous metastases. After treatment (B), there is evidence of marrow stimulation with diffuse increased uptake throughout the red marrow as well as the spleen, hampering treatment assessment.

**FIGURE 33.** Chronic radiation changes. FDG sagittal PET (A) and fused PET/CT (B) images demonstrate relative decreased uptake in the thoracic spine (arrows) due to chronic radiation changes.
Similarly, ovarian activity in premenopausal women can be physiologic and related to ovulation (Figure 25). In postmenopausal women, focal increased FDG uptake in either the endometrium or the ovary should be further evaluated to exclude malignancy. Other portions of the genitourinary system may pose difficulty for the interpreting physician, largely due to the high physiologic FDG uptake in the urine, which can obscure small disease foci. It is advisable to adjust PET window and fusion level to avoid missing subtle lesions (Figure 26). Similarly, the relatively high background uptake in the kidneys, FDG PET/CT has questionable utility in characterizing renal masses (Figure 27), although higher-grade, clear-cell and papillary subtypes have been shown to have greater activity than renal background. Additionally, pooling of radioactive urine in the ureters can often be difficult to distinguish from retroperitoneal or pelvic lymph nodes, often at the pelvic brim where the ureters cross the psoas muscles.

FDG uptake in the bowel continues to present a diagnostic challenge, as the uptake is highly variable. When focal FDG uptake is identified, further investigation (usually with endoscopy) is recommended, as there is an association with malignant and premalignant conditions. Additionally, correlation with CT findings is warranted, as this may reveal an underlying infectious or inflammatory process such as appendix, diverticulitis, or inflammatory bowel disease (Figure 28). Metformin, an oral diabetic medication, results in diffuse intense uptake in the colon as well as the small bowel (Figure 29). This can unfortunately obscure metabolic activity from foci of malignancy, warranting consideration of holding the medication prior to FDG PET/CT imaging. Postsurgical changes from certain urinary diversion procedures also can result in intense bowel activity as FDG-avid urine enters the bowel (Figure 30).

**Muskuloskeletal**

Focal FDG uptake can be identified in both pathological and nonpathological fractures (Figure 31). Some studies indicate that relatively high SUVs suggest malignant pathological fractures, although no absolute SUV can be used in routine clinical practice to reliably differentiate benign from malignant fractures. Correlation with the co-acquired CT for features suggesting a benign or malignant process is suggested. If the focus of uptake remains indeterminate, consideration can be given to MR if it would change clinical management. Alternatively, attention should be given on follow-up PET/CT, as the activity from benign post-traumatic or postoperative fractures should normalize over several months.

Diffuse red marrow uptake on FDG PET/CT is another common pattern of normal variant uptake. This is most often related to bone marrow stimulation with drugs such as filgrastim and pegfilgrastim. Given the marrow stimulation, this may also result in increased uptake in the spleen. Given the history of marrow stimulation, the interpreting physician can readily identify this marrow uptake as benign. However, occasionally the diffuse uptake can obscure previously present hypermetabolic osseous foci, making it difficult to evaluate response to treatment (Figure 32). Waiting several weeks after discontinuation of such drugs will help decrease this uptake, but must be balanced with the need for timely clinical results.

Patients who have undergone prior radiation therapy may have relative decreased marrow uptake in affected areas (Figure 33). Knowledge of treatment history and location is beneficial in PET interpretation to identify this unusual pattern of uptake. The interpreting physician must be mindful to not misinterpret the normal, nonirradiated marrow as pathologic.

**Conclusion**

Oncologic FDG PET/CT is prone to many pitfalls and incidental findings, largely related to whole-body imaging and the nonspecific mechanism of FDG. This article reviewed a variety of processes that can lead to potential false-positive and false-negative findings. Interpreting radiologists must maintain constant vigilance for these common pitfalls.

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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
Asymptomatic Primary Hyperparathyroidism proposed consensus guidelines for surgical intervention in patients without symptoms. 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 health-care 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.

Radiopharmaceuticals and Imaging Protocols

Overview

Parathyroid nuclear imaging has evolved as radiotracers and imaging...
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. 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. 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.

**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.

**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
photoleak of 140 keV and a half-life of 6 hours. The typical dose is 20 to 30 mCi, and is administered intravenously. 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. 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. 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 criticized 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. Tc-99m pertechnetate cannot be used since it has the same photoleak as Tc-99m sestamibi and tetrofosmin at 140 keV. As I-123 has a different photoleak (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. 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.

Both C-11 choline and C-11 methionine have shown potential use in detecting parathyroid adenomas. 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.
Recent studies demonstrate F-18 fluorocholine to be sensitive in evaluating parathyroid adenomas. 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. 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. A meta-analysis of 24 studies, however, demonstrated the superior sensitivity of SPECT/CT compared to SPECT and planar techniques. 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%
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%. 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. 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. Additionally, due to their deeper location, superior parathyroid adenomas are more likely to be missed by parathyroid scintigraphy.

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. 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. 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. Similar findings have been described with hybrid SPECT/CT imaging. The incidence of multigland disease and its poor preoperative imaging detection have been used as arguments against unilateral gland surgery.

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

References
Focal Uptake in the Left Upper Quadrant on an In-111 White Blood Cell Study

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Case Presentation
A 59-year-old man with a history of a splenectomy presented with bacteremia from an uncertain source. In-111 white blood cell (WBC) imaging was performed. An indeterminate round focus of uptake was noted in the left upper quadrant (LUQ) of the abdomen (Figure A). For further characterization, a SPECT/CT of the abdomen was performed (Figures B, C).

**FIGURES A-C.** Anterior and posterior planar images from an In-111 WBC scan (A) demonstrate an indeterminate round region of increased uptake within the LUQ (arrows). Unfused (B) and fused (C) axial images from SPECT/CT better characterize the rounded region of increased uptake (arrows) with absence of the spleen from a prior splenectomy.
Key Imaging Finding
Focal In-111 WBC uptake within a LUQ soft-tissue lesion

Differential Diagnosis
Infection
Neoplasm
Residual splenic tissue

Discussion
Leukocyte scintigraphy is useful for the detection and localization of suspected infectious processes and has largely replaced Ga-67 imaging. WBCs are most commonly labelled using either Tc-99m or In-111. Biodistribution and imaging times differ for the two radiopharmaceuticals. Both imaging agents demonstrate physiologic uptake within the liver, spleen and bone marrow. Tc-99m WBC scans additionally show physiologic uptake in the gastrointestinal and genitourinary tracts 2 to 4 hours post injection. Therefore, early imaging is usually obtained with Tc-99m WBC scans as this physiologic uptake may obscure potential pathology in the abdomen and pelvis. Given the relatively short 6-hour half-life of Tc-99m, imaging can be continued up to 24 hours.

In-111 WBC scans are typically imaged 4 to 24 hours post injection, and the primary advantage of the scans is lack of physiologic bowel and genitourinary activity. Additionally, the much longer 67-hour half-life of In-111 allows for imaging beyond 24 hours. Often needed in patients with neuropathic joints and prosthetic joints, simultaneous acquisition with Tc-99m sulfur colloid marrow imaging is possible due to In-111’s 173 keV and 247 keV photopeaks.

Although leukocyte scintigraphy is a powerful tool, the relatively long imaging times in what are often critically ill patients is a limitation. One potential alternative to leukocyte scintigraphy is imaging with F-18 fluorodeoxyglucose (FDG) PET/CT. Like oncocologic imaging, FDG accumulates at sites of infection. With imaging obtained one hour after injection and CT localization, FDG offers a relatively quick, but nonspecific, alternative to leukocyte imaging.

Post splenectomy, no uptake would be expected in the LUQ, making this finding suspicious. On SPECT/CT, the uptake localizes to a small round soft-tissue mass. Differential diagnosis could be based on either the nuclear or CT findings and are best categorized as: infectious, neoplastic, and normal variant (residual splenic tissue).

Infection
A variety of infectious processes demonstrate focal increased uptake on leukocyte scintigraphy. Both radiolabeled and nonradiolabeled leukocytes accumulate at sites of infection due to the immune system inflammatory cascade resulting in chemotaxis, a shift of leukocytes from the blood stream to the site of infection. Although nearly any infectious process could be responsible for the uptake, the differential is primarily based on location within the LUQ and includes diverticulitis, pancreatitis, and abdominal abscess.

Diverticulitis is a common complication of colonic diverticular disease often resulting from diverticular obstruction and subsequent infection. If left untreated, diverticulitis may progress to abscess formation and/or peritonitis. On CT imaging, diverticulitis can be suggested by wall thickening and inflammatory changes in the pericolonic fat adjacent to diverticula.

Pancreatitis most commonly results from gallstone obstruction or alcohol use. The revised Atlanta classification categorizes acute pancreatitis into two subtypes: interstitial edematous pancreatitis and necrotizing pancreatitis. Each subtype has suggestive imaging characteristics including pancreatic enlargement, edema, and adjacent fat stranding with areas of nonenhancement being indicative of the necrotic subtype.

An abdominal abscess is a localized collection of purulent infected fluid. Typical CT appearance of an abscess is a hypodense, loculated fluid collection with rim enhancement. Internal gas in the absence of surgical intervention is highly suspicious for an infected collection. In the LUQ, an abscess may result from pancreatitis, diverticulitis, or from a postsurgical complication such as from a splenectomy.

Neoplasm
Whenever an abnormal soft-tissue lesion is encountered on CT, neoplasm should be considered by the interpreting physician as a diagnostic possibility. Although the mechanism is not well understood, a variety of noninfected malignancies occasionally demonstrate increased uptake on radiolabeled leukocyte imaging. The differential is usually limited based on the organ in which the mass is visualized. However, this case presents as a stand-alone soft-tissue mass in the LUQ without a clear visceral origin. Given this anatomic finding, a variety of malignancies should be considered.

Peritoneal carcinomatosis is a result of peritoneal spread of certain neoplasms, most commonly ovarian and gastrointestinal adenocarcinomas. The classic “omentum caking” results in conglomerate masses and nodularity throughout the omentum. However, occasionally more discrete soft-tissue nodules (peritoneal seeds) are the primary finding.

Although much less common than metastases, primary malignancies arising from the peritoneum, such as malignant mesothelioma, should be considered. Malignant mesothelioma is a rare condition with an extremely poor prognosis. Most mesotheliomas arise from the lung pleura, while primary peritoneal mesotheliomas account for only 6% to 10% of cases. As with pleural mesothelioma, peritoneal mesothelioma is associated with asbestos exposure. Omental caking and malignant ascites are often present.

Residual Splenic Tissue
Splenules are benign foci of congenitally ectopic splenic tissue, often
considered variations of normal anatomy. They appear as small rounded nodules most commonly near the splenic hilum. Splenules demonstrate similar characteristics to the normal spleen on all imaging modalities. Given that it is part of the hematopoietic system, splenic tissue demonstrates intense uptake on radiolabeled leukocyte imaging and is considered part of a normal biodistribution of the radiopharmaceutical.

Splenosis is the autotransplantation of splenic tissue into ectopic locations following traumatic or surgical disruption of the normal spleen. Splenosis is often found incidentally, most frequently after trauma, and is usually asymptomatic. In splenosis, foci of splenic tissue are usually identified in the abdomen and pelvis. However, other locations, including thoracic and subcutaneous foci, have been reported.7

Whether congenital or post-traumatic, these splenic foci can often be mistaken for other pathology, including malignancy. Further complicating the diagnosis, these foci of residual splenic tissue can enlarge if the spleen is removed, mimicking a more aggressive process.

Diagnosis
Residual splenic tissue (splenule)

Summary
Leukocyte scintigraphy plays a useful role in the workup of patients with suspected infection. This case is an example of a relatively nonspecific focus of uptake on planar scintigraphy being better characterized on hybrid SPECT/CT imaging due to improved resolution and precise anatomic localization. An initially broad differential was narrowed combining imaging findings with the clinical history. Although infection is usually the primary consideration of any abnormal focus of uptake on leukocyte scintigraphy, the CT appearance in this case was not consistent with infection. Additionally, it would be unusual to see intense focal radiopharmaceutical uptake on leukocyte scintigraphy in a peritoneal malignancy without other evidence of malignancy on this exam or by history. The clinical, CT, and scintigraphy findings were all concordant with residual splenic tissue, making this the most appropriate diagnosis. An awareness of the normal biodistribution of radiolabeled leukocytes combined with the precision of SPECT/CT correctly identified this focus of unusual uptake as a variant of normal anatomy, avoiding the misdiagnosis of an infection in the abdomen.

References
Decreased Thyroid Activity in a Patient with Hyperthyroidism

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Case Presentation
A 45-year-old man presented to nuclear medicine for evaluation of hyperthyroidism with a desire for definitive radioiodine therapy. Thyroid scintigraphy using Tc-99m pertechnetate (Figure) was performed and revealed diffusely decreased uptake of the radiopharmaceutical compared to the salivary glands. No focal nodule was identified. The 24-hour I-131 uptake was 1.7%, which is below the normal range of 7.5% to 25%.

FIGURE. Thyroid scintigraphy using Tc-99m pertechnetate revealed diffusely decreased uptake of the radiopharmaceutical within the thyroid gland (blue arrows) compared to the salivary glands (green arrows). No focal nodule was identified.
Key Imaging Findings

Diffuse decreased uptake of the radiopharmaceutical throughout the thyroid gland with a depressed 24-hour thyroid uptake value

Differential Diagnosis

Graves’ disease
Subacute thyroiditis
Granulomatous thyroiditis
Silent thyroiditis
Postpartum thyroiditis
Iodine-induced thyrotoxicosis
Factitious thyrotoxicosis
Struma ovarii

Discussion

Thyrotoxicosis is the state of symptoms and increased metabolism secondary to elevated thyroid hormone levels. Complementing clinical evaluation and serum lab values, thyroid scintigraphy is a useful tool in determining the cause of thyrotoxicosis.1

The differential diagnosis for thyrotoxicosis includes Graves’ disease and other syndromes that cause elevated thyroid hormones including subacute thyroiditis, iodine-induced thyrotoxicosis, factitious thyrotoxicosis, and even rarer conditions such as struma ovarii. Determining the underlying cause of thyrotoxicosis is essential to determining the appropriate treatment.1

Graves’ Disease

Graves’ disease is an autoimmune disorder characterized by antibodies to the thyroid-stimulating hormone (TSH) receptor that stimulate the thyroid gland to secrete thyroid hormones. Serum TSH levels are classically low due to the pituitary feedback loop. Typically, thyroid radiotracer uptake is increased diffusely on scintigraphy with elevated thyroid uptake values. Patients can be treated with I-131 radioiodine ablation, anti-thyroid medication, or surgery.1

Most patients with thyrotoxicosis have Graves’ disease. Graves’ disease is often seen in middle-aged females and presents with a variety of symptoms including weight loss, insomnia, anxiety, goiter, exophthalmos, and pretibial myxedema.2

Subacute Thyroiditis

Subacute thyroiditis is the most common cause of thyrotoxicosis in the setting of decreased radiotracer uptake on nuclear medicine studies. Subacute thyroiditis can be further classified as granulomatous thyroiditis (deQuervain’s thyroiditis), silent thyroiditis, and postpartum thyroiditis. Regardless of the subtype, thyroid inflammation results in the release of thyroid hormones with the expected symptoms of thyrotoxicosis. This elevation suppresses TSH and leads to a subsequent phase of hypothyroidism. Ultimately, the patient returns to a euthyroid state. Therefore, subacute thyroiditis is generally considered self-limiting, resolving within weeks to months, and nuclear medicine radioiodine therapies are not indicated.3 Management is usually handled by endocrinologists and/or primary care specialists, and treatment typically focuses on symptom relief.

Granulomatous Thyroiditis (deQuervain’s Thyroiditis). Granulomatous thyroiditis is a type of subacute thyroiditis that follows a viral upper respiratory infection. Although not routinely sampled clinically, granulomas are found on histopathology.2 Patients with deQuervain’s thyroiditis present clinically with pain, fever and thyroid tenderness. A postviral inflammatory response causes inflammation of the thyroid follicles and release of stored thyroid hormones, producing thyrotoxicosis. The inflammation can cause pain and tenderness.3

The inflammation prevents the otherwise normal transport of iodine and peretechnetate into the thyroid cells, resulting in the typical scintigraphy findings of decreased uptake.1,4 Non-steroidal anti-inflammatory drugs can provide symptomatic relief.1

Silent Thyroiditis. Silent thyroiditis is a form of subacute thyroiditis typically found in elderly patients with possible arrhythmias and a nonenlarged thyroid. Patients do not typically present with thyroid pain.2 Silent thyroiditis is thought to be an autoimmune thyroiditis and a variant of Hashimoto’s thyroiditis.1

The pathogenesis of silent thyroiditis is lymphocytic infiltration of the thyroid follicles causing damage and release of thyroid hormones, producing thyrotoxicosis with identical clinical symptoms to Graves’ disease. The episode of hyperthyroidism resolves within weeks. The inflamed follicle cells are unable to organify iodine after the episode of inflammation, causing hypothyroidism and decreased radiotracer uptake on thyroid scintigraphy.5

Postpartum Thyroiditis. Postpartum thyroiditis is another form of subacute thyroiditis manifesting weeks to months after delivery, with patients having a mildly enlarged thyroid gland.2 Postpartum thyroiditis occurs in up to 5% of pregnancies.1

The thyrotoxicosis in postpartum thy-roiditis is mild, typically self-limiting, and resolves within weeks. Histology reveals lymphocytic infiltration of thyroid tissue, similar to silent thyroiditis.5 A transient hypothyroidism follows the episode of thyrotoxicosis in postpartum thyroiditis and can potentially be permanent requiring clinical monitoring.1

Iodine-induced Thyrotoxicosis

Iodine-induced thyrotoxicosis is most commonly secondary to treatment with the antiarrhythmic drug amiodarone, which contains 750mg of iodine per 200mg tablet. A similar process can be seen with iodinated contrast. Radiotracer uptake decreases as the radiotracer competes for uptake with the relatively large pool of stable iodine.1 Amiodarone thyrotoxicosis occurs in 3% of patients treated with amiodarone, and the risk of amiodarone-induced thyrotoxicosis is directly proportional to dosage.6 Treatment is medical and nuclear medicine radioiodine ablation is not indicated.1

Factitious Thyroiditis

Factitious thyroiditis is manifested as elevated serum thyroid hormone
secondary to ingesting exogenous thyroid hormone in euthyroid patients, usually for weight loss. TSH is suppressed and iodine uptake is decreased, resulting in diffusely decreased radiotracer uptake. Treatment is to cease ingestion of exogenous thyroid hormones.\(^1\)

**Struma Ovarii**

Struma ovarii is hyperthyroidism secondary to a rare, typically benign, teratomatous ovarian tumor that secretes thyroid hormones. The excess thyroid hormone suppresses TSH levels and decreases scintigraphic radiotracer uptake. Treatment is tumor excision.\(^1\)

**Diagnosis**

Subacute thyroiditis

**Case-specific Management**

In this case, although the patient presented clinically with symptoms indistinguishable from Graves’ disease, the thyroid uptake and scan did not support this diagnosis. Therefore, other causes of hyperthyroidism that would have decreased thyroid activity on nuclear medicine studies were considered. Among the differentials discussed above, the final diagnosis is largely based on clinical history, as tissue sampling is not routinely performed. In this case, a diagnosis of a subacute thyroiditis was made.

The most important duty of the imager is to recognize and alert the clinician of diagnostic possibilities other than Graves’ disease as the cause of the hyperthyroid state. Nuclear medicine radioiodine therapies for hyperthyroidism are indicated for Graves’ disease and hyperfunctioning nodule(s). Performing a radioiodine therapy in this patient would have been inappropriate given 1) the self-limiting nature of most cases of subacute thyroiditis, making a permanent ablation of the thyroid gland unnecessary; and 2) the extremely low 24-hour thyroid uptake value that would require an unreasonably high dose of I-131 for a successful ablation.

**Summary**

Because it is common, Graves’ disease is the initial primary diagnostic consideration in patients with thyrotoxicosis. However, clinicians and imagers must be cognizant of other causes of thyrotoxicosis as the treatments are different. Encountering a hyperthyroid patient with depressed findings on scintigraphy suggests a process other than Graves’ disease. Subacute thyroiditis, as well as other rarer causes of thyrotoxicosis, are uncommon but are important disease processes for imagers to be aware of to avoid inappropriate and ineffective radioiodine therapies.

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Hypertrophic Osteoarthropathy

A 56-year-old woman presented for staging after a suspicious lung nodule was discovered. Anterior whole-body planar image from a Tc-99m methyl diphosphonate (MDP) bone scan (A) demonstrates heterogeneous increased linear cortical uptake in the bilateral lower extremities having a “double stripe” or “tram-track” appearance. Fused F-18 fluorodeoxyglucose (FDG) PET/CT (B) demonstrates a hypermetabolic spiculated pulmonary nodule in the posterior left lower lobe. Tissue sampling of the nodule revealed primary bronchogenic carcinoma.

Hypertrophic osteoarthropathy (HOA) is rarely seen in its primary form, pachydermoperiostosis, and more commonly encountered in its secondary form. Although pulmonary infection/inflammation can result in secondary HOA, lung carcinoma is the most common cause.1 However, a wide variety of extra-thoracic processes have also been associated with HOA, including malignancies of the gastrointestinal tract, kidney, liver, and pancreas; cirrhosis; and inflammatory bowel disease. HOA is a benign process and is unrelated to osseous metastases. Despite theories, the precise mechanism of HOA is unknown.2 Scintigraphy findings may improve after treating the underlying condition.1

Although less sensitive compared to bone scintigraphy, HOA can be seen on other imaging modalities including radiographs, CT, and MR, and presents with symmetric periosteal reaction/periostosis in the extremities.2 Nuclear medicine bone scans are common in clinical imaging and are highly sensitive at detecting osseous metastases, but are not specific. It is important for the interpreting physician to be aware of HOA and its imaging appearance on bone scintigraphy to avoid the misdiagnosis of osseous metastatic disease.

References
Liver Hemangioma

A 34-year-old man presented with an incidental liver lesion. CT (A) showed an indeterminate hypodense lesion in the right hepatic lobe. Subsequently, a Tc-99m red blood cell (RBC) SPECT/CT was performed (B and C) for further characterization. Focal radiotracer uptake localized to the lesion, which is most consistent with a liver hemangioma.

A liver hemangioma is a benign hypervascular lesion frequently encountered incidentally. It is important to accurately characterize a lesion as a hemangioma, distinguishing it from other more aggressive lesions, including malignancy.

Although CT and MR characterize the vast majority of liver hemangiomas, Tc-99m RBC scans can confirm lesions that are indeterminate on CT or MR due to atypical features. Although early blood pool imaging is variably performed clinically as it is nonspecific, a hemangioma classically demonstrates relative decreased radiotracer uptake compared to the liver. However, on delayed imaging at 1-2 hours, a hemangioma demonstrates relative increased uptake compared to the liver background. This pattern of uptake is thought to be related to the sluggish flow of blood through the larger vascular channels in the hemangioma.1

The lesion size should be considered before performing this study. Only larger hemangiomas (> 3 cm) can be reliably evaluated by planar imaging. SPECT imaging is more useful with smaller lesions demonstrating a sensitivity of 91% in evaluating hemangiomas > 1.3 cm, but sensitivity decreases when lesions are subcentimeter.2 Hybrid SPECT/CT can improve reader confidence with precise anatomic localization.

References
Crossed Cerebellar Diaschisis

A patient with progressive memory loss presented for neurodegenerative disorder evaluation using F-18 fluorodeoxyglucose (FDG) PET/CT. CT (A) demonstrated a right cerebral infarct in the posterior right temporal and occipital lobes with corresponding hypometabolism noted on PET (B). A second region of hypometabolism is present in the left cerebellar hemisphere (C, D), contralateral to the infarct.

Crossed cerebellar diaschisis (CCD) is an imaging finding encountered in nuclear neuroimaging in which cerebellar hypometabolism or hypoperfusion is noted contralateral to a supratentorial cerebral process, most often infarction. However, a variety of processes have been associated with CCD, including tumors and hemorrhage. CCD can be identified on both SPECT and PET. Regardless of whether it is a perfusion or a metabolism study, the decreased uptake in the contralateral cerebellum is thought to relate to a disruption of the corticopontocerebellar neuronal pathways. This results in a functional abnormality in a region of the brain that is separate from the pathologic process.

CCD is considered an incidental finding and has no known symptoms other than that of the underlying supratentorial process. Variably, it can improve or resolve over time. The interpreting physician must be aware and recognize CCD when encountering decreased cerebellar uptake contralateral to a cerebral process to avoid misdiagnosing additional pathology in the cerebellum.

REFERENCES