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Pitfalls and Limitations of Radionuclide Imaging in Endocrinology

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Several different techniques, radiopharmaceuticals, and imaging modalities are commonly used in nuclear medicine for studies of endocrine organs. Nuclear medicine is used in the management of benign and malignant thyroid, parathyroid, and neuroendocrine disorders. Thus, it is essential to acknowledge pitfalls and the limitations of nuclear medicine imaging for accurate diagnosis and patient management.
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Introduction

Since the very early days of nuclear medicine, radionuclide imaging has been used in endocrinology, with most investigation relating to thyroid disorders. With advancement in technology and discovery of new tracers, nuclear medicine imaging is now an essential part of any diagnostic and decision algorithm in various endocrine disorders. In this review article, we elaborate on the various pitfalls and limitations of nuclear medicine imaging in benign and malignant thyroid, parathyroid, and neuroendocrine disorders.

Pitfalls in Imaging in Benign Thyroid Disease

Thyroid scintigraphy remains an important imaging modality in day-to-day endocrine clinical practice. The common indications for benign thyroid disease are differentiation of Graves' disease and other forms of thyrotoxicosis, for example, from thyroiditis, determination of function of a thyroid nodule, identification of ectopic thyroid tissue, evaluation of congenital hypothyroidism, characterization of a neck or mediastinal mass, etc. The radiotracers used in thyroid imaging are provided in Table 1.

Technical Factors

Inaccurate data input while computing the thyroid uptake function may lead to wrong estimation. For example, if the sensitivity of a collimator or the residual tracer activity within the syringe is wrongly documented, error in thyroid uptake measurement occurs. In addition, tracer extravasation can lead to wrong uptake estimation. In most cases, visual interpretation of the thyroid image may suggest discordant image findings and estimated function.

Patient Movement

Patient movement may lead to blurring of the image or falsely project uptake at 2 different sites (Fig. 1). This is particularly problematic in presence of cold nodules and ectopic thyroid in children. Thus, any patient movement while scanning should be noted and acquisition repeated.

Factors Influencing Thyroid Uptake

Different drugs may affect the uptake of tracer within the thyroid as mentioned in Table 2 (Fig. 2).[1,2] Moreover, the thyroid uptake is influenced by various diseases and food (Table 3).[2,3] Therefore, it is essential to take note of drug and

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Table 1 Characteristics of Radiopharmaceuticals Used in Thyroid Imaging

	^{99m}Tc-Pertechnetate	^{123}I-Iodide	^{131}I-Iodide
Physical half-life ($t_{1/2}$)	6 h	13.2 h	8.1 d
Photon energy	140 keV	159 keV	364 keV
Beta emission and energy	No	No	Yes (606 keV)
Mechanism of uptake	Trapped by the thyroid	Trapped and organified	Trapped and organified
Advantages	Easily available Less expensive Quicker examination Low radiation burden	Good for visualization of retrosternal tissue Better image quality Low radiation burden	Better for therapeutic indications
Disadvantages	No organification	Less readily available	364-keV photons are not optimal for gamma cameras
		Relatively expensive	High-energy beta emissions
	Poor image quality when uptake is low	Delayed imaging at 24 hours is required	Long physical half-life of gamma emissions
	Not good for retrosternal mass characterization	Higher radiation burden compared with ^{99m}Tc-pertechnetate	High radiation dose to the patient limits the amount of activity that can be administered

medical history to avoid incorrect interpretation of a thyroid scan.

Esophageal Activity Mimicking Thyroid Tissue

Esophageal tracer distribution may mimic ectopic thyroid tissue. This may be seen with both ^{99m}Tc-pertechnetate and ^{123}I when used as imaging agents. Usually this is seen just to the left of the midline as the esophagus may be displaced when the neck is hyperextended in the imaging position. Often acquiring additional images after the patient has swallowed water helps in differentiating the esophageal uptake from the thyroid tissue by clearing esophageal activity. If the activity still persists after swallowing water and is strongly suspicious for physiological activity in the esophagus, SPECT/CT may be considered for further clarification.

Cold Nodule

In general, palpable thyroid nodules have been reported in 15% of the population, and solitary nodules present in approximately 3.2% of women and 0.8% of men.[4] The overall likelihood of malignancy in a solitary thyroid nodule is approximately 10%.[5] The role of thyroid scintigraphy is to assess the functional status of a nodule, and relatively hot or cold regions within the thyroid should be noted. A hot nodule is almost always benign and frequently represents a hyperfunctioning adenoma, whereas a solitary cold nodule has a 5%-10% risk of being malignant and requires further evaluation to exclude malignancy.[6]

A photopenic area within the thyroid does not necessarily mean a nodule, which is diagnosed generally by palpation or anatomical imaging. The differential diagnosis of a cold area within the thyroid is discussed (Table 4).[7] It is always important

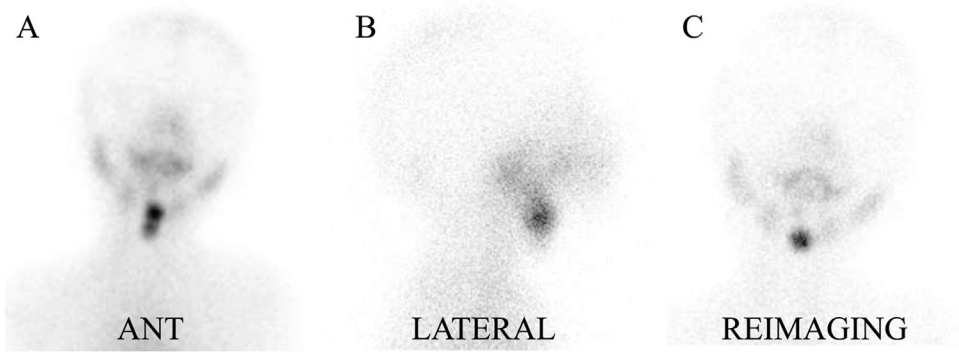

Figure 1 ^{99m}Tc-petechnetate thyroid scan of a child who was under evaluation for thyroglossal cyst showed 2 foci of uptake of tracer in the midline in the anterior image (A). However, the lateral image demonstrated only 1 focus of abnormal uptake (B). The technical staff reported movement of child during image acquisition. Thus, another image of neck was acquired (C), which confirmed single focus of tracer uptake in midline of neck suggestive of functioning thyroid tissue in the thyroglossal cyst. This example illustrates the importance of avoiding and documenting patient movement during image acquisition to prevent false interpretation.

Table 2 Drugs Affecting the Uptake of Tracer Within the Thyroid

	Duration of Effect
Decreased Uptake	
Adrenocorticosteroids	1 Wk
Bromides	1 Wk
Butazolidin	1 Wk
Mercurials	1 Wk
Methimazole	1 Wk
Nitrates	1 Wk
Perchlorate	1 Wk
Penicillin	Variable
Propylthiouracil	1 Wk
Salicylates (large doses)	1 Wk
Sulfonamides	1 Wk
Thiocyanate	1 Wk
Tri-iodothyronine (T3)	2-3 Wk
Thyroxine (T4)	4-6 Wk
Iodine-containing ointments	2-4 Wk
Kelp	4 Wk
Some cough medicines and vitamin preparations	4 Wk
Intravenous contrast agents	1-2 Mo
Oil-based iodinated contrast agents	3-6 Mo
Amiodarone	3-6 Mo
Increased uptake	
Lithium	

to palpate the neck to identify nodules before thyroid scintigraphy. In general, a radionuclide cold or hot marker is used to correlate the palpated nodule with the scintigraphic findings. Sometimes, inaccurate localization may lead to mischaracterization of the nodule, especially in patients with heterogeneous radiotracer distribution within the thyroid.[8]

Further, small cold nodules (less than 1 cm) may be missed owing to poor gamma camera resolution, and pinhole imaging is useful in these cases.[2] Additionally, posterior thyroid nodules may appear falsely warm owing to superimposed normal thyroid uptake. Overlying thyroid tissue and compressive effects in a multinodular thyroid may give falsely warm appearance to a cold nodule in the region of thickened thyroid on a ^{99m}Tc-pertechnetate scan.[9] There may be "discordant" nodules that may concentrate ^{99m}Tc-pertechnetate but fail to organify ^{123}I and may appear warm or hot on ^{99m}Tc-pertechnetate scan but cold on ^{123}I scan.[6] These cases should be further investigated considering these as cold nodules.

Figure 2 ^{99m}Tc-petechnetate thyroid scan of a patient showing impaired tracer uptake in the thyroid as the patient was taking multivitamin sirup containing iodized peptone.

Table 3 Other Causes of Increased or Decreased Uptake on Thyroid Scan

Decreased Uptake	Increased Uptake
Iodine-containing food	Iodine deficiency
Congestive heart failure	Pregnancy
Renal failure	Rebound after stopping levothyroxine and liothyronine therapy
Prior radiation to neck	
Goitrogenic foods like cabbage and turnips	

Characterization of a Mediastinal Mass

A mediastinal mass discovered incidentally on radiologic imaging is often a substernal goiter.[6] Usually, the uptake in the substernal goiter is lower than thyroid bed activity. Thus, ^{99m}Tc-pertechnetate should be avoided while characterizing these masses because of its high mediastinal blood pool activity. ^{123}I is the preferred radiopharmaceutical agent for characterization of a mediastinal mass owing to higher target-to-background activity. SPECT with or without CT is more accurate in such cases.

Causes of Nonvisualization of Thyroid in Neonates

Early detection of congenital hypothyroidism and prompt management are necessary to prevent impairment in normal development and intelligence. Often the neonates with biochemically abnormal thyroid function are referred for a thyroid scintigraphy to diagnose the etiology. Nonvisualization of thyroid tissue in these patients is usually owing to thyroid agenesis. However, nonvisualization could be owing to transient hypothyroidism, secondary to maternal antibodies or mild dyshormonogenesis.[6,10]

Table 4 Differential Diagnosis of Cold Nodule on the Thyroid Scan

Colloid nodule
Simple cyst
Hemorrhagic cyst
Adenoma
Thyroiditis
Abscess
Parathyroid adenoma
Primary thyroid cancer
Metastatic thyroid cancer

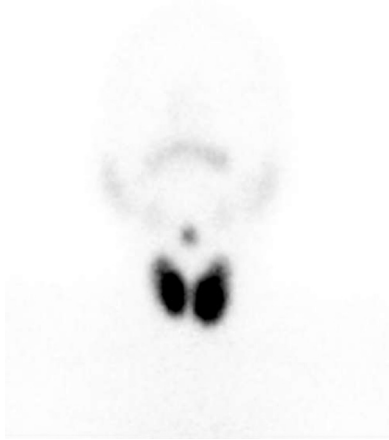

Figure 3 A patient who was under evaluation for thyrotoxicosis underwent a thyroid scan. ^{99m}Tc-petechnetate thyroid scan showed diffusely increased tracer uptake in both thyroid lobes suggestive of diffuse toxic goiter. In addition, there was a prominent focal tracer uptake in the midline suggestive of ectopic lingual thyroid tissue.

Ectopic Thyroid

Ectopic thyroid tissue is an uncommon entity and mostly presents with midline swelling in the neck. A thyroid scan is often performed to differentiate ectopic thyroid tissue from other midline pathology in the neck and detect any ectopic thyroid tissue in the children with hypothyroidism. The thyroid scan also shows the absence or presence of thyroid in its normal location in such patients. However, there may be incidental detection of ectopic thyroid tissue while performing a thyroid scan for other reasons (Fig. 3), and the possibility of such an occurrence should always be considered.

Pitfalls in Imaging in Malignant Thyroid Disease

A pretherapy whole-body radioiodine scan (WBS) is usually performed to assess the burden of disease and to determine the radioiodine ^{131}I dose for treatment in patients with differentiated thyroid cancer. There are various causes of false-positive and false-negative WBS findings (Table 5).[11,12] While preparing for WBS, a patient's thyroid stimulating hormone is allowed to increase to >30 mIU/L for optimum radioiodine uptake in the thyroid. WBS may be less sensitive below this level of thyroid stimulating hormone. Further, a high iodine pool may reduce the sensitivity of WBS for detection of disease. Thus, all the patients should be instructed to follow a low-iodine diet.[13]

The role of pretherapy WBS is controversial because of its low effect on further management and concerns over ^{131}I-induced stunning of normal thyroid remnants and metastatic disease.[14,15] The stunning phenomenon is characterized by reduction in uptake of ^{131}I at therapy induced by pretherapy diagnostic ^{131}I activity.[16] Some studies have reported occurrence of stunning mostly with higher activities of ^{131}I and with increasing time between the diagnostic dose and therapy.[17,18] Thus, the American Thyroid Association has recommended the use of ^{123}I (1.5-3 mCi) or low-activity ^{131}I (1-3 mCi) for pretherapy scans, and therapeutic activity should be initiated within 72 hours of the diagnostic activity.[19]

In 10%-26% of patients, a posttherapy WBS shows additional metastatic foci compared with the diagnostic scan, which alters the disease stage in approximately 10% of patients and affects clinical management in 9%-15%.[20,21] This situation arises as the therapeutic dose of ^{131}I is much greater than the smaller dose of ^{131}I used for the pretherapy WBS identifying additional small-volume disease. Moreover, a planar WBS provides poor anatomical information. This is especially true for ^{131}I-WBS, which shows indistinct background activity. Another difficulty in image interpretation is owing to the frequently observed physiological uptake in the salivary glands, liver, esophagus, stomach, and gastrointestinal tract. To overcome the limitations posed by planar images, SPECT/CT is often used when the localization and characteristics of uptake are uncertain. SPECT/CT localizes and characterizes uptake on the planar images, thereby avoiding a false-positive diagnosis (Fig. 4). Also, SPECT/CT can reveal metastatic lesions to unexpected sites.[22] It has been found that posttherapy ^{131}I SPECT/CT data changed clinical management in a significant number of patients, either when used routinely on consecutive patients or when used on selected patients with inconclusive findings.[22]

Parathyroid Imaging

Historically, bilateral neck exploration for localization of all 4 parathyroid glands and removal of glands that are enlarged had been the standard surgical treatment for primary hyperparathyroidism.[23] The current trend is toward minimally invasive surgery, which reduces the time of surgery and hospitalization as well as the risk of hypoparathyroidism. However, success of this depends on accurate preoperative localization of a parathyroid adenoma.[24] Conventionally, parathyroid scintigraphy has been useful in preoperative localization of a parathyroid adenoma. Table 6 outlines different parathyroid scintigraphy

Table 5 Potential False-Positive and False-Negative Causes on the Whole-Body Radiolodine Scintigraphy

False-Positive Causes	False-Negative Causes
External surface contamination through saliva, sweat, and vomit	Loss of differentiation of thyroid cancer cells
Ectopic normal thyroid tissue	Microscopic metastases
Physiological uptake in lacrimal and salivary glands, eutopic or ectopic gastric mucosa, gastrointestinal tract, breast, liver, and urinary tract excretion	Improper patient preparation before WBS (eg, iodine contamination, TSH $<$ 30 mIU/L)
Neoplasms of nonthyroidal origins (gastric adenocarcinoma, meningioma, lung cancers, teratomas, uterine fibromyoma, ovarian adenocarcinoma, and ovarian cystadenoma)	Defective iodine-trapping mechanism

TSH, thyroid stimulating hormone.

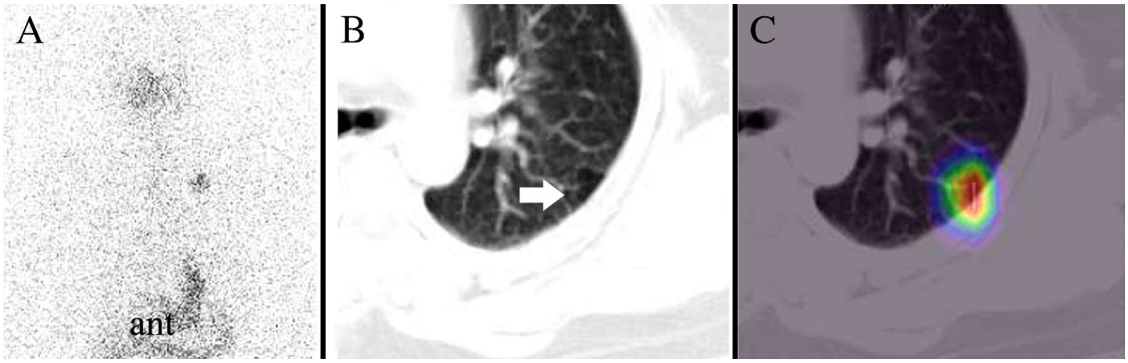

Figure 4 A patient with papillary thyroid cancer previously treated with radioactive iodine underwent diagnostic ^{131}I-radioiodine scan owing to raised serum thyroglobulin. The planar study (A) showed a focus of abnormal tracer accumulation in the left thoracic region, likely owing to lung metastasis. However, SPECT/CT localized tracer uptake within the left lung to a cavity, which is likely infectious. It also showed many nontracer-avid subcentimeter nodules in both lung fields suggestive of poorly differentiated lung metastases and revealed etiology of elevated serum thyroglobulin.

protocols used in preoperative localization of parathyroid adenomas.

Pitfalls in Parathyroid Imaging

"Single-Tracer Dual-Phase" Imaging

The basis of dual-phase ^{99m}Tc-Sestamibi parathyroid scintigraphy is "differential washout" of tracer from the thyroid and parathyroid glands. ^{99m}Tc-Sestamibi localizes in both parathyroid glands and thyroid tissue but usually washes out more rapidly from normal thyroid tissue than from abnormal parathyroid tissue.[25,26]

False Positive

^{99m}Tc-Sestamibi is a nonspecific tracer for parathyroid gland imaging and may lead to false-positive interpretation for a parathyroid adenoma (Table 7). The most common cause of a false-positive study is a solid thyroid nodule (Fig. 5).[27] In such cases, subtraction parathyroid imaging has shown higher specificity to detect abnormal parathyroid tissue.[28] Other false-positive causes are thyroid carcinoma and cervical lymphadenopathy due to lymphoma, metastatic disease, inflammation, and sarcoidosis. Literature evidence also suggests that ^{99m}Tc-Sestamibi uptake can occur in brown tumors related to hyperparathyroidism, although clearly this is rare.[27] ^{99m}Tc-Sestamibi uptake in thymoma, giant lymph node hyperplasia of the mediastinum (Castleman disease), poorly differentiated germ cell tumor, benign and malignant breast disease, bone marrow metastases in chest wall, sternotomy, mediastinal vessels (Fig. 6), axillary lymph nodal metastases or inflammation, and radiotracer extravasation with visualization of axillary lymph nodes may mimic ectopic parathyroid adenoma (Fig. 7).[29-36] However, knowledge of common sites for ectopic parathyroid tissue and use of SPECT/CT are often helpful in avoiding false positives. Asymmetric tracer activity in the submandibular glands is a normal variant and may be misinterpreted as an ectopic undescended adenoma (Fig. 8).[37] The presence of asymmetric tracer uptake in such patients can be confirmed with pertechnetate thyroid imaging. Additionally, parathyroid imaging cannot differentiate between parathyroid carcinoma and parathyroid adenoma.

Dual-phase parathyroid scintigraphy is less sensitive in patients with multigland parathyroid adenoma.[38] However, given the relative rarity of multiglandular adenomas in primary hyperparathyroidism when compared with coexistent thyroid abnormalities, the second focus of uptake on a delayed image should be interpreted cautiously as this may represents a thyroid nodule.[39]

False Negative

^{99m}Tc-Sestamibi retention in the parathyroid is related to the presence of oxyphil cells, which are rich in mitochondria and are sites of intracellular sestamibi sequestration.[40] However,

Table 6 Different Protocols for Parathyroid Scintigraphy

Parathyroid Imaging Protocol	Tracers	Mechanism
Dual-phase parathyroid scintigraphy	^{99m}Tc-Sestamibi	Differential washout of sestamibi from thyroid and parathyroid tissue owing to increased number of mitochondria in the parathyroid adenoma cells
Dual-tracer subtraction imaging	^{99m}Tc-pertechnate-^{123}I and ^{99m}Tc-Sestamibi-Thallium-201	Subtraction of ^{99m}Tc-Sestamibi image from the thyroid scan image

Table 7 False-Positive and False-Negative Causes on Dual-Phase ^{99m}Tc-Sestamibi Parathyroid Scintigraphy

False Positive	False Negative
Solid thyroid nodule	Early washout from the abnormal parathyroid tissue
Lymphoma	Small size of parathyroid adenoma
Metastatic disease	Parathyroid hyperplasia
Inflammation	P-glycoprotein or multidrug resistance–related protein–expressing parathyroid adenomas
Sarcoidosis	Multigland disease
Thymoma	
Castleman disease	
Poorly differentiated germ cell tumor	
Benign and malignant breast disease	
Bone marrow metastases in chest wall	
Sternotomy	
Axillary lymph nodal metastases or inflammation	
Radiotracer extravasation with visualization of axillary lymph node	
Asymmetric tracer activity in the submandibular glands	

retention of tracer does not always occur in parathyroid adenomas, and in 1 study, it was seen in only 60% of parathyroid adenomas.[41] This early washout from the parathyroid adenoma is a potential cause of false-negative result on dual-phase parathyroid scintigraphy (Fig. 9). This may be due to fewer oxyphil cells within the gland and hence fewer mitochondria.[40,42] A SPECT study immediately following early planar acquisitions or subtraction imaging may be helpful in

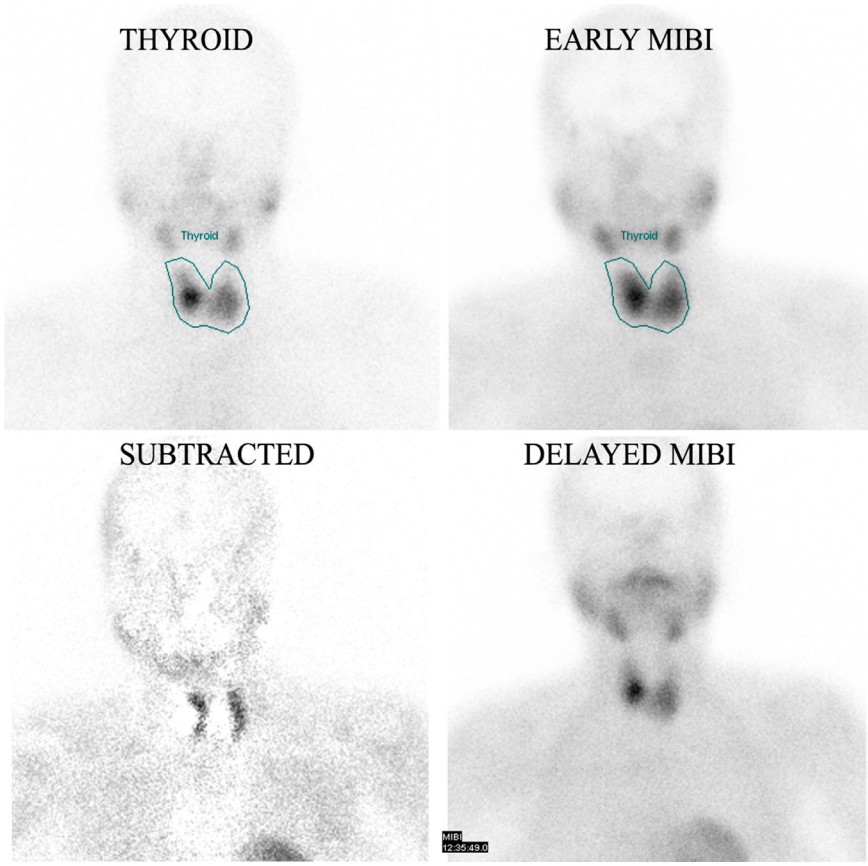

Figure 5 False-positive ^{99m}Tc-petechnetate and ^{99m}Tc-sestamibi subtraction and dual-phase ^{99m}Tc-sestamibi studies of a patient with raised serum parathyroid hormones. The computer-generated subtracted image showed tracer retention in the neck, but this is due to patient movement in between pertechnetate and ^{99m}Tc-sestamibi imaging. Thus, manual registration of both images may be necessary before performing subtraction. The delayed ^{99m}Tc-sestamibi image showed focal tracer retention at the lower pole of the right thyroid lobe, which also showed intense uptake on the thyroid scan, suggestive of a thyroid nodule. A thyroid nodule is the most common cause of false-positive parathyroid adenoma on a dual-phase parathyroid scan.

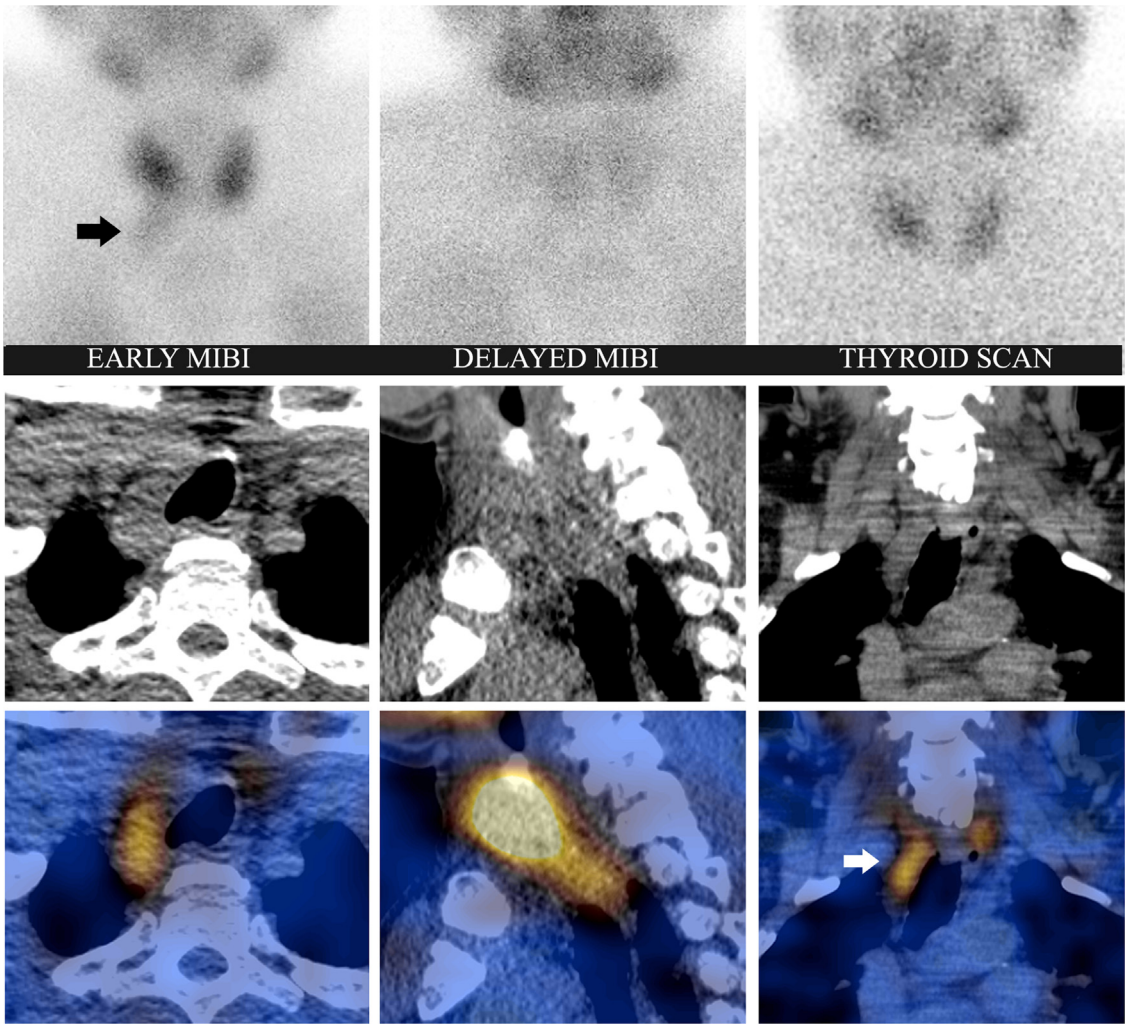

Figure 6 False-positive uptake in the mediastinal vessel: Dual-phase ^{99m}Tc-sestamibi scintigraphy showed low-grade tracer uptake inferior to the right thyroid lobe on the early image, which is not coinciding to the thyroid scan and hence suspicious for a parathyroid adenoma. However, SPECT/CT localizes this abnormal tracer uptake to the mediastinal vessel.

Figure 7 Early ^{99m}Tc-sestamibi image shows uptake in the right axillary region. This was likely owing to lymph node uptake as there was injection-site tracer extravasation in the right hand.

avoiding false-negative results owing to parathyroid adenomas with rapid washout.[43] Small adenomas less than 500 mg are another possible cause of a false-negative test result.[40,44] It has been shown that ^{99m}Tc-sestamibi parathyroid scintigraphy is less sensitive for detecting parathyroid hyperplasia than for detecting parathyroid adenomas. This may be explained by smaller size of parathyroid hyperplasia compared with adenomas. In addition, hyperplasia is usually characterized by a mixture of chief cells and to lesser extent oxyphil cells.[45] Studies have also shown that MIBI uptake correlated with the active growth phase of the cells.[46] In general, parathyroid adenomas that express P-glycoprotein or multidrug resistance–related protein do not accumulate MIBI and show negative finding on parathyroid scintigraphy.[47]

Further, there may be apparent absence of ^{99m}Tc-sestamibi washout from the thyroid in presence of a large parathyroid adenoma. The homogenous tracer uptake in the parathyroid may mimic normal thyroid gland and no differential washout on delayed image, thus leading to erroneous visual interpretation of a normal scan (Fig. 10).[48] SPECT or SPECT/CT

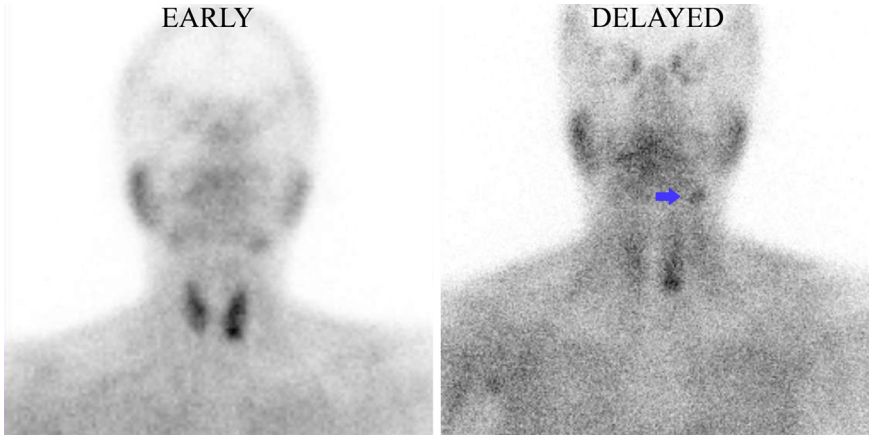

Figure 8 Dual-phase ^{99m}Tc-sestamibi scintigraphy of a patient with raised serum parathyroid level showed differential tracer washout at the lower pole of the left thyroid lobe indicative of a left inferior parathyroid adenoma. There is another focus of uptake in the left submandibular region (arrow) on the delayed image, which correlates to uptake in the left submandibular gland on the early image. Thus, asymmetric tracer activity in the submandibular glands can lead to false-positive interpretation.

imaging is usually helpful in differentiating uptake in the thyroid and a large parathyroid gland. Ectopic parathyroid adenoma can descend up to the level of the aortic arch and can be missed if imaging is limited to the neck. Thus, imaging should extend from the base of the jaw to the base of the heart to look for ectopic parathyroid tissue.

Subtraction Imaging

In the early 1980s, the first nuclear medicine procedure to gain wide acceptance to localize parathyroid adenomas was with thallium-pertechnetate subtraction imaging.[49] Thallium accumulates in both parathyroid and thyroid tissues, whereas pertechnetate accumulates only in the thyroid tissue. Thus, residual tracer activity after subtraction of the pertechnetate image from the thallium image represents abnormal parathyroid tissue. Owing to poor imaging characteristics and high radiation burden of thallium, ^{99m}Tc-sestamibi rapidly replaced thallium for subtraction imaging. In addition, thyroid imaging can be performed with ^{123}I substituting pertechnetate in the subtraction protocol. Subtraction imaging is often helpful in presence of thyroid nodules, avoiding the false-positive result.[50] Moreover, subtraction imaging is useful in recurrent or persistent disease.[51]

There are certain limitations of subtraction imaging. First, patient movement and misregistration of the ^{99m}Tc-Sestamibi and pertechnetate images may lead to an inaccurate result (Fig. 5). Some prefer acquisition of dynamic images during the subtraction study. Thus, frames with excessive movement can be eliminated without discarding the entire data set.[27] Otherwise, correction for patient movement artifacts may be performed by realigning the images between the 2 sets of images. Inserting an intravenous cannula is likely to be helpful to avoid motion during sestamibi injection.[43]

A large multinodular goiter may lead to a false-negative finding on subtraction study as a small parathyroid lesion

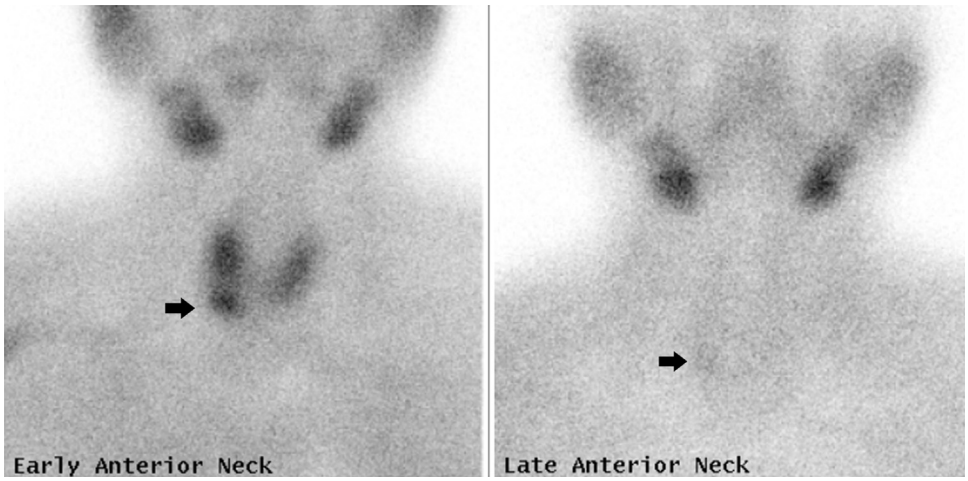

Figure 9 Early washout from a parathyroid adenoma. Dual-phase ^{99m}Tc-sestamibi scintigraphy of a patient with raised serum parathyroid level showed a prominent focus of tracer uptake inferior to the right thyroid lobe on the early image with minimal tracer retention at this site on the delayed study. However, owing to prominent focal uptake, the study was interpreted as suspicious for a parathyroid adenoma inferior to the right thyroid lobe, which was later on confirmed histopathologically.

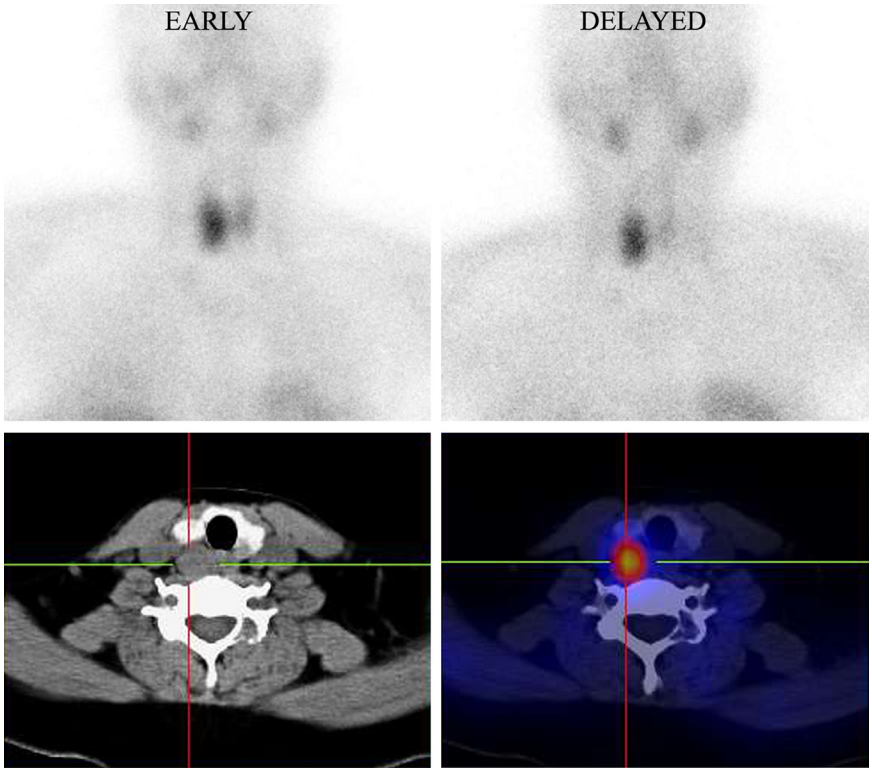

Figure 10 On a dual-phase ^{99m}Tc-sestamibi scintigraphy, there is intense tracer uptake on the right side of the neck with no perceptible tracer washout. Both early and delayed images are nearly identical, with some tracer washout from the left thyroid lobe. On delayed SPECT/CT, the tracer uptake on the right side of the neck corresponds to a large soft tissue lesion posterior to the right thyroid lobe. This case illustrates apparent absence of ^{99m}Tc-Sestamibi washout from the thyroid in presence of a large parathyroid adenoma.

with mismatch in uptake may be masked by the large thyroid mass and such a likelihood is more probable if the parathyroid is located behind the thyroid.[28] Another false-negative cause is oversubtraction.[43] Ideally, progressive incremental subtraction should leave an activity in the thyroid area that is similar to the background of adjacent neck tissues. Further, if the patient is on thyroid hormone within the previous 3-4 weeks or has been administered iodine-containing contrast media recently, a subtraction study cannot be performed. Thus, radiological studies with iodine-containing contrast media should be avoided for 4-6 weeks before the study, and thyroid hormone should be withheld for 3-4 weeks if subtraction scintigraphy is needed in this group of patients.

Planar vs Tomographic Imaging

SPECT imaging provides 3-dimensional information and has superior contrast resolution compared with planar imaging. SPECT parathyroid imaging has shown increased sensitivity over planar imaging (96% compared with 79%) and provides a more precise localization of abnormal parathyroid glands, in particular ectopic parathyroid lesions.[43,52] SPECT also allows determination of depth of ectopic tissue, which is difficult to assess on planar imaging. However, SPECT should be acquired immediately following an early study to avoid false-negative results owing to rapid washout.[43]

SPECT/CT is a relatively newer modality with the added advantage of morphologic information and helps in more precise localization of parathyroid adenomas by providing anatomical information from CT. In patients with mediastinal ectopic parathyroid adenomas and distorted neck anatomy, SPECT/CT may be more informative by giving the exact anatomical localization of the abnormality (Fig. 11).[53,54] It is further useful in intrathyroidal adenomas, as planar parathyroid imaging cannot differentiate between intrathyroidal or eutopic extrathyroidal adenomas.

Neuroendocrine Tumors

Somatostatin Receptor Imaging

Somatostatin receptor (SSR) imaging was introduced in the late 1980s.[55] SSRs are expressed in a number of normal cells including the pituitary, thyroid, spleen, kidney, and peripheral nervous system. In addition, several tumors have been found to express SSRs, with a high incidence and density of receptors found particularly in neuroendocrine tumors (NETs).[56]

The first somatostatin analogue used for imaging of NETs was octreotide. This remains one of the most popular analogues used for imaging, labeled with ^{111}Indium (^{111}In). It has a half-life of 68 hours, and delayed imaging (24 or 48 hours) is usually required to ensure reduction in background

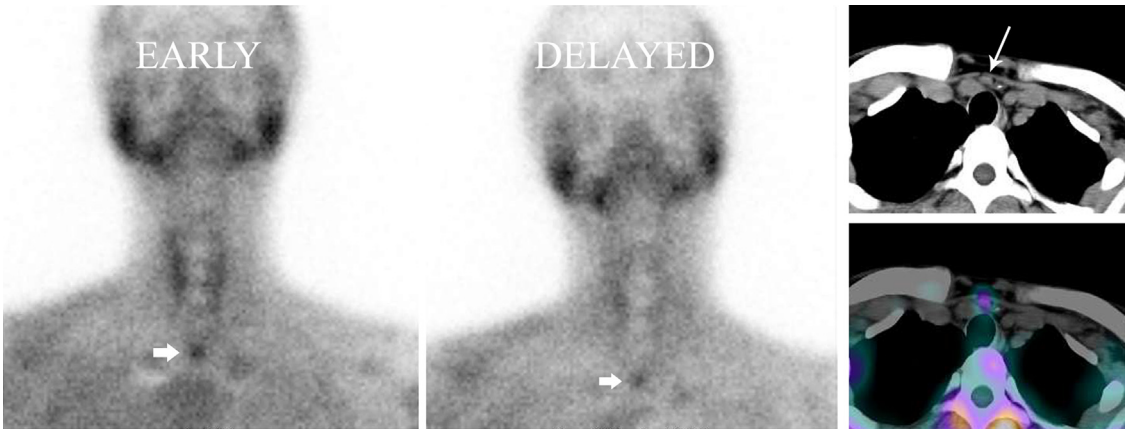

Figure 11 On a dual-phase ^{99m}Tc-sestamibi scintigraphy, a doubtful focus of uptake was noted in the suprasternal region on both early and delayed images. SPECT/CT precisely localized this uptake to a soft tissue nodule in the pretracheal region just above the sternum indicating an ectopic parathyroid tissue. Thus, SPECT/CT is helpful in accurate characterization and precise localization of ectopic parathyroid adenoma.

activity caused by clearance via the renal and hepatobiliary system.^{99m}Tc-labeled SSR have also subsequently been used, with similar success as with ^{111}In-pentetreotide.

Gallium-68 (^{68}Ga) SSR imaging has become increasingly more popular in centers where PET/CT imaging is available. ^{68}Ga has a convenient physical half-life of 68 minutes and decays by positron emission. There is no doubt that ^{68}Ga-DOTA–conjugated peptide imaging represents a significant evolutionary advance over ^{111}In-pentetreotide. The advantages of improved resolution and sensitivity of PET and the stronger binding affinity for the SSR-expressing tumor with DOTATATE (or DOTA-NOC and DOTA-TOC) have been demonstrated.[57]

Normal Distribution of ^{111}In-Pentetreotide

There is rapid clearance of ^{111}In-pentetreotide from the circulation, with only 1% of the radiopharmaceutical present in the bloodstream at 20 hours after tracer administration. Excretion is almost entirely renal, with hepatobiliary excretion and elimination via the feces accounting for 2% of the total administered activity.[58] Thus, delayed imaging can demonstrate variable amount of activity within the bowel. SSRs are expressed in a number of normal cells including the pituitary, thyroid, spleen (intense uptake), kidney, and peripheral nervous system[59] (Table 8). Other organs are shown at different times because of the clearance of ^{111}In-pentetreotide: gallbladder, bowel, renal collecting system, ureters, and bladder.

Normal Distribution of ^{68}Ga-DOTA–conjugated peptides

The normal distribution of ^{68}Ga-somatostatin imaging is similar to those of ^{111}In-pentetrotide with some notable differences (Table 8). ^{68}Ga-DOTA–conjugate peptides are rapidly cleared from the blood. Excretion is almost entirely renal.[60] Apart from physiological uptake in the spleen, kidneys, thyroid, and liver, intense uptake is also seen in the pituitary and adrenal glands. Further low- to moderate-grade uptake is seen in the salivary glands and stomach. All of these organs express SSRs. There is variable normal uptake of tracer within the pancreas with more intense uptake of tracer often seen in the uncinate process of the pancreas. This can often present a diagnostic quandary; particularly in patients with suspected pancreatic neoplasm (eg, suspected gastrinoma or insulinoma). Increased uptake can also be seen in the duodenum owing to tracer excretion (Fig. 12).

Artifacts, False Positives, and False Negatives With SSR Imaging

False Positives. High-grade uptake can be seen in other tumors of neural crest origin and pituitary or medullary thyroid tumors, with low-grade uptake seen in other tumors (Table 9). Other inflammatory or infective conditions may also result in low-grade uptake of tracer (Fig. 13). Intense uptake of tracer can be seen in accessory splenic tissue, which can be misinterpreted as a nodal metastasis (Fig. 14). If there is doubt, a colloid scan can differentiate between tumor and accessory splenic tissue.

Sites of physiological uptake can also be misinterpreted as NET, for example, uptake in the uncinate process of the pancreas or tracer accumulation related to excretion (gallbladder or renal excretion system). Knowledge of the normal distribution or variants is important to not misinterpret these areas of physiological uptake.

False Negatives

False negatives also occur. Uptake of SPECT and PET SSR imaging agents is present in most patients (>80%) with gastroenteropancreatic NETs, with the major exceptions being insulinomas (with a reduced sensitivity of 50%-70% either because of the small size of the tumors or poor SSR-2 receptor expression) and poorly differentiated NETs (because of a lower expression of SSRs) (Fig.15).[61] Reduced uptake in the spleen and liver can occasionally be seen owing to unlabeled octreotide, which may result in better visualization of hepatic metastases (better target: background). However, it has also been reported that unlabeled octreotide may reduce visualization of hepatic metastases.[62-64]

Table 8 Normal Distribution in SSR Imaging

Organ	Uptake or Excretion of ^{111}In-Pentetreotide	Uptake or Excretion of ^{68}Ga-DOTA–Conjugate Peptides	Mechanism of Uptake
Spleen	2.5% At 24 h	Intense uptake	Receptor binding
Thyroid	Variable usually low-grade diffuse	Usually present	Receptor binding
Liver	2% At 24 h	Moderate uptake	No hepatic SSR, but likely related to hepatic peptide metabolism
Pituitary	Rare	Invariably present	Receptor binding
Adrenal glands	Faint uptake rare	Intense uptake usually present	Receptor binding
Gallbladder	Variable	Usually absent	Excretion
Bowel	Variable	Variable, gastric and duodenal activity can be intense	Excretion
Kidneys	Variable—low to intense	Usually moderate to intense	Reabsorption by renal tubular cells after glomerular filtration
Renal collecting system, ureters, and bladder	Variable	Variable	Excretion
Pancreas	Low-grade uptake in uncinate sometimes present	Uptake in the uncinate process can be intense	Receptor binding with islet cells.

Artifacts

Areas of high physiological uptake (eg, spleen) or intense accumulation related to excretion (eg, gallbladder) may mask potential pathology in this area. It is thus necessary to alter the windowing so that potential lesions in these organs can be unmasked. Similarly, intense tumoral uptake may mask a second adjacent lesion, and thus altering the windowing may help to identify a second lesion (Fig. 16).

Physiological uptake in the uncinate process of the pancreas can be a particular problem, masking an underlying tumor

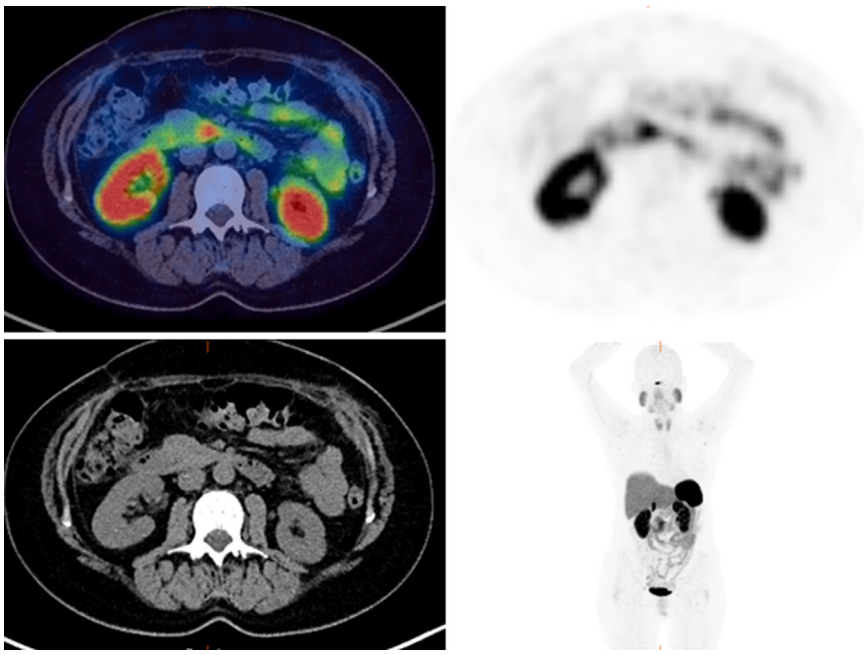

Figure 12 A 60-year-old patient who underwent a distal pancreatectomy in September 2013 for pancreatic NET. A subsequent CT demonstrated an area of arterial enhancement in segment 4A of the liver. ^{68}Ga-DOTATATE did not demonstrate any abnormal uptake in the liver. There is, however, intense uptake in the duodenum, which represents physiological uptake. Learning Point: Variable uptake can often be seen owing to variable excretion and receptor expression in normal cells. Any focal uptake however should be followed up.

Table 9 Other Conditions That Demonstrate Uptake on SSR Imaging

High-Grade Uptake	Low-Grade Uptake
Tumors	
(1) Sympathoadrenal system tumors, for example, pheochromocytoma, paraganglioma, neuroblastoma, and ganglioneuroma	Breast carcinoma, melanoma, lymphomas, some prostate carcinomas, non–small cell lung cancer, sarcomas, renal cell carcinoma, and differentiated thyroid carcinoma
Medullary thyroid carcinoma	
(2) Pituitary Adenoma	
(3) Merkel Cell Carcinoma	
(4) Small cell lung cancer	
Other	
(1) Accessory splenic tissue	(1) Sarcoidosis and other granulomatous diseases
(2) Gallbladder (variable)	(2) Autoimmune disease
(3) Urinary contamination	(3) Postradiotherapy
	(4) Bacterial Infection
	(5) Post-surgical
	(6) Cerebrovascular accident
	(7) Inflamed joints in active rheumatoid arthritis express somatostatin receptors, preferentially located in the proliferating synovial vessels

(particularly in ^{68}Ga-DOTA–conjugate peptide imaging, with more avid uptake in the uncinate process often seen). Any focal (rather than diffuse) uptake within the uncinate process should, however, be considered suspicious.

Metaiodobenzylguanidine Imaging

Metaiodobenzylguanidine (MIBG) is an alkylguanidine (catecholamine analogue) and is concentrated by an active amine uptake mechanism in the cell membrane of sympathomedullary tissues and stored within the cytoplasmic catecholamine storage vesicles. The uptake and persistent storage in the neurosecretory granules allows imaging with radioiodinated MIBG.[65,66] MIBG has been labeled with ^{123}I and ^{131}I, with the former having advantages of better imaging characteristics.

Normal Distribution

^{123}I-MIBG is normally seen in the liver, lungs, heart, spleen, salivary glands, and thyroid (if inadequate thyroid blockade). Low-grade symmetrical uptake is commonly also seen in the adrenal glands.[67] The primary excretory route is through the

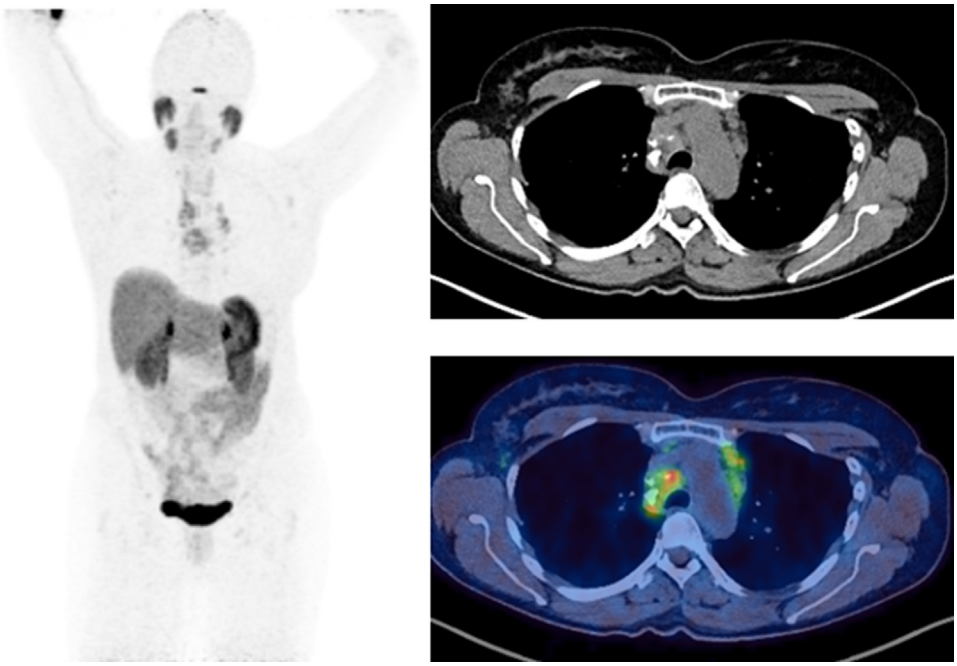

Figure 13 A 61-year-old woman with resected pancreatic NET had a surveillance ^{68}Ga-DOTATATE scan. ^{68}Ga-DOTATATE PET/CT demonstrates moderately intense uptake in calcified nodes: on review had been stable on serial CTs for 2 years. A biopsy of subcarinal node confirmed granulomatous disease, that is, sarcoidosis. Learning point: All areas of avid uptake are not necessarily NET. Review of previous imaging may be helpful in differentiating benign from malignant disease.

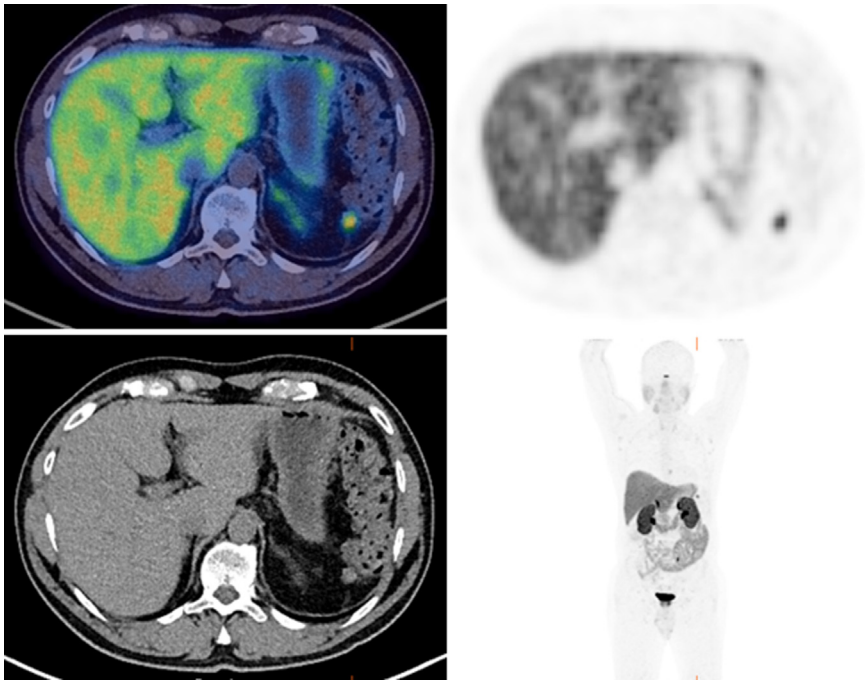

Figure 14 A 61-year-old man underwent follow-up ^{68}Ga-DOTATATE PET/CT imaging 6 months after a distal pancreatectomy and splenectomy for a well-differentiated NET found in the distal pancreas. There is focal uptake of tracer in a nodule in the left upper quadrant. This represents a small focus of accessory splenic tissue and not a metastasis. Learning point: Accessory splenic tissue is common after splenectomy: if any doubt, consider a colloid scan (which will not have uptake in NET but have uptake in splenic tissue).

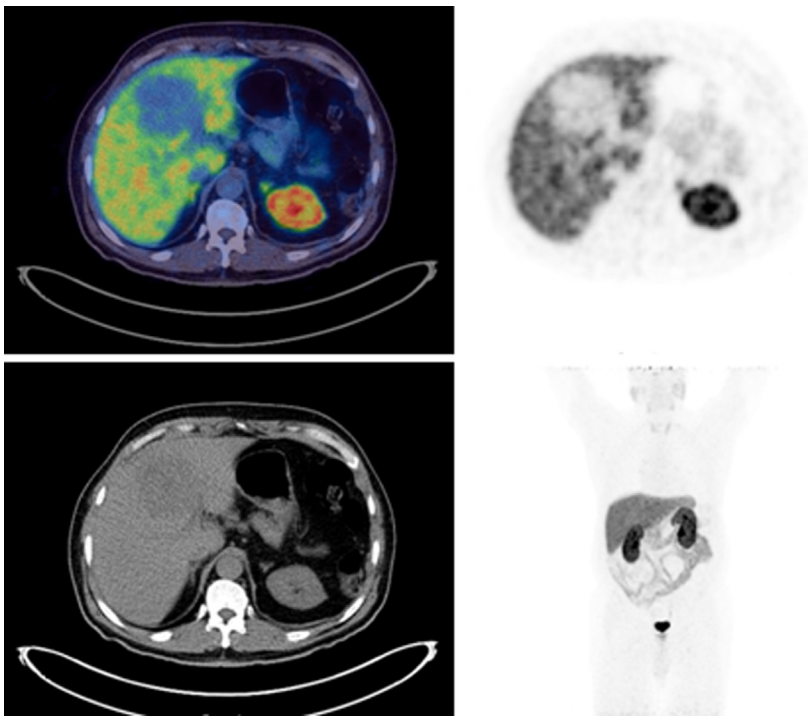

Figure 15 A 56-year-old man with new diagnosis of metastatic NET for staging. The ^{68}Ga-DOTATATE study demonstrates no abnormal uptake. In fact, the large liver metastasis is photopenic. Biopsy of this liver lesion revealed a high-grade neuroendocrine carcinoma with Ki-67 proliferative activity at 30%. Learning point: High-grade or poorly differentiated NETs often show negative finding on SSR imaging. Consider ^{18}F-FDG-PET/CT to more accurately stage these patients.

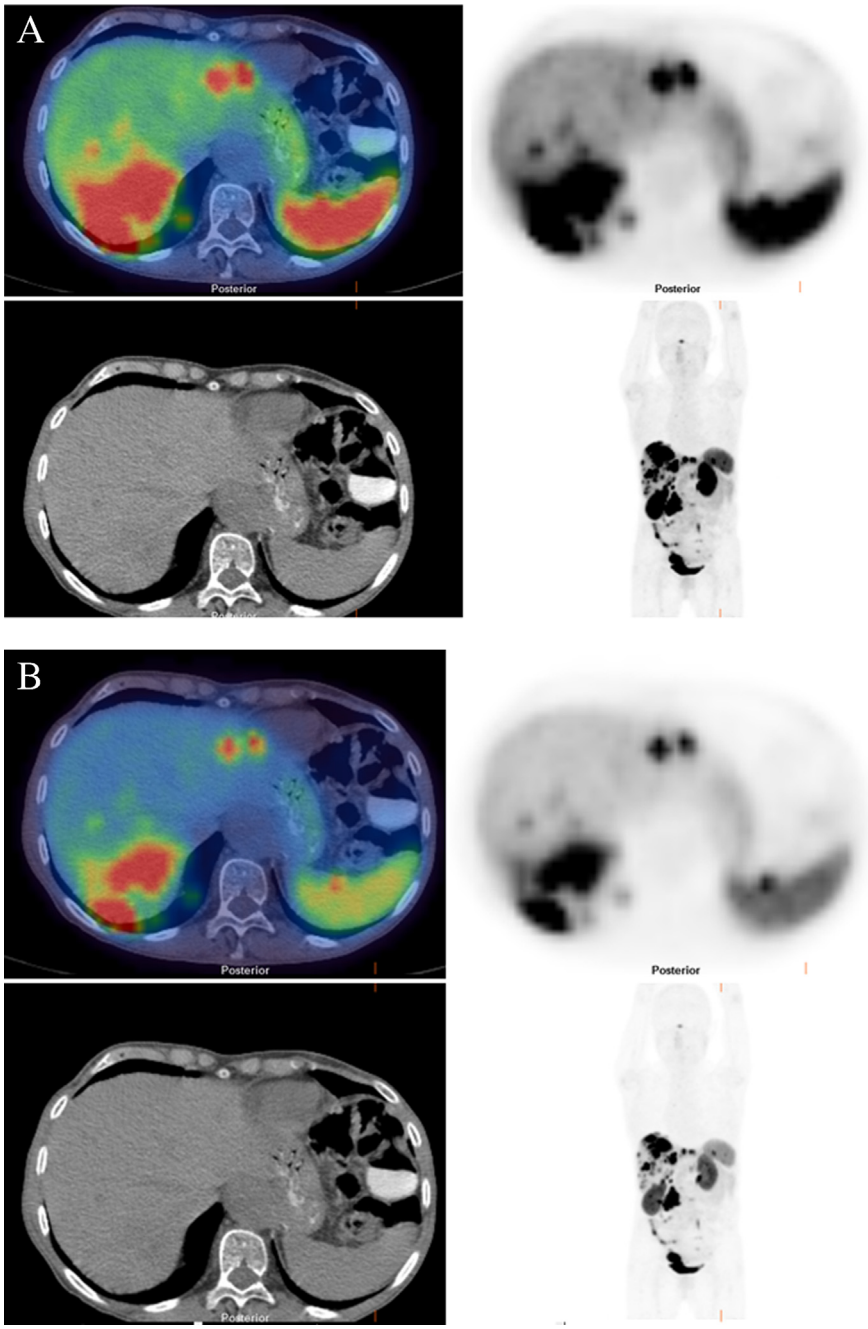

Figure 16 A 66-year-old female patient with metastatic midgut NET was referred for ^{68}Ga-DOTATATE PET/CT for staging. Imaging demonstrates avid uptake in a mesenteric mass and within multiple liver metastases. On the first more intensely windowed PET image (A), no obvious abnormal uptake is seen in the spleen. However, when the window is altered to less intense (B), it can clearly be seen that there is focal uptake in the spleen indicative of a splenic metastasis. Learning point: Altering the windowing is essential in areas of high physiological background or adjacent to a tumor with high-grade uptake.

kidneys, with 50% excreted unaltered by the kidneys within 24 hours.[68] There is also a very small amount of hepatobiliary clearance (<2% up to day 4) and thus uptake can be seen in the renal excretory system or bowel.

Artifacts, False Positives, and False Negatives

^{123}I-MIBG has excellent accuracy for pheochromocytomas (sensitivity of 83%-100% and specificity of 95%-100%). The diagnostic accuracy in paragangliomas (PGLs) is less (50%-75%).[69] MIBG may be inadequate in genotypic abnormalities, for example SDHB mutations and VHL.[70] In particular, ^{123}I-MIBG has a low sensitivity for head and neck PGLs (Fig. 17). In patients with metastatic disease, ^{123}I-MIBG can underestimate the extent of disease, which can affect patient management.

Other false negatives may be related to small lesions, lesion close to an area of high physiological uptake, tumor lesions that

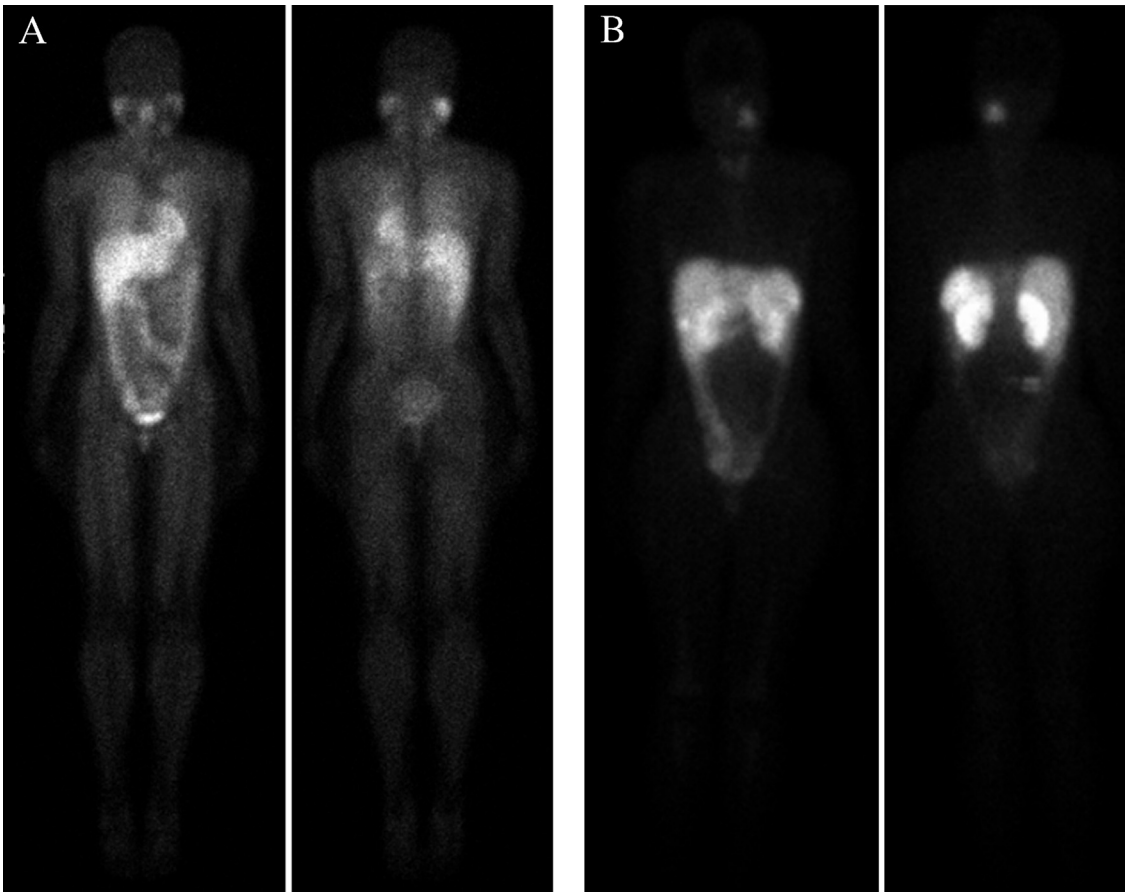

Figure 17 A 32-year-old woman with unresectable left neck paraganglioma was referred to assess suitability for ^{131}I-MIBG therapy. The ^{123}I-MIBG study finding was negative. No abnormal uptake in the neck or elsewhere was seen (A). However, the ^{111}In-pentetreotide scan demonstrated avid uptake in the left neck and within a liver lesion (B). Learning point: ^{123}I-MIBG has a low sensitivity for head and neck paragangliomas.

do not concentrate ^{123}I-MIBG (eg, high-grade tumors and necrotic tumors), and if patients are on interfering drugs.

Several drugs can potentially interfere with ^{123}I-MIBG uptake and result in false-negative results. Where feasible, these drugs should be withheld before ^{123}I-MIBG scan. This may not be possible in certain situations, for example, alpha-blockers should not be stopped in pheochromocytomas, and it may not be practical to stop amiodarone in patients with arrhythmias. Drugs that can interfere with ^{123}I-MIBG uptake and the mechanism of interference are as follows:

1. Type 1 Na^+ dependent uptake or transport mechanism, for example, amiodarone, labetalol, antipsychotics, tricyclic antidepressants, tricyclic-related antidepressants (eg, venlafaxine and mirtazapine), sedating antihistamines, cocaine, and opioids
2. Calcium-mediated mechanism, that is, calcium channel blockers
3. Drugs causing depletion of content in storage vesicles, sympathomimetics: β-2 stimulants (salbutamol), adrenoreceptor stimulants (pseudoephedrine), inotropic drugs (eg, dobutamine), and vasoconstrictor sympathomimetics (eg, phenylephrine), amiodarone, labetalol, and amphetamines
4. Inhibition of uptake by active transport into vesicles, that is, reserpine and guanethidine
5. Unknown, for example, caffeine and α-blockers

False positives may result in patients with diffuse physiological uptake (eg, hyperplastic adrenal gland after contralateral adrenalectomy).

There can be artifact caused by ^{123}I-MIBG SPECT reconstruction (Fig. 18). This reconstruction artifact is caused by septal penetration of high-energy photons that are part of the ^{123}I decay scheme. This can particularly affect areas of high physiological uptake, for example, liver, which may potentially cause misinterpretation of artifact as tumor.

^{18}F-Dihydroxyphenylalanine Imaging

^{18}F-Dihydroxyphenylalanine (^{18}F-DOPA) enters the catecholamine metabolic pathway of endogenous L-DOPA, in both the brain and peripherally. As NETs demonstrate increased activity of L-DOPA decarboxylase, they show a high uptake of ^{18}F-DOPA. ^{18}F-DOPA is useful in imaging pheochromocytomas and PGLs with studies showing superiority to ^{123}I-MIBG imaging.[71,72] In a recent meta-analysis of 11 studies, the pooled sensitivity and specificity (per lesion-based analysis) was 79% and 95%, respectively.[73] It is useful in head and neck

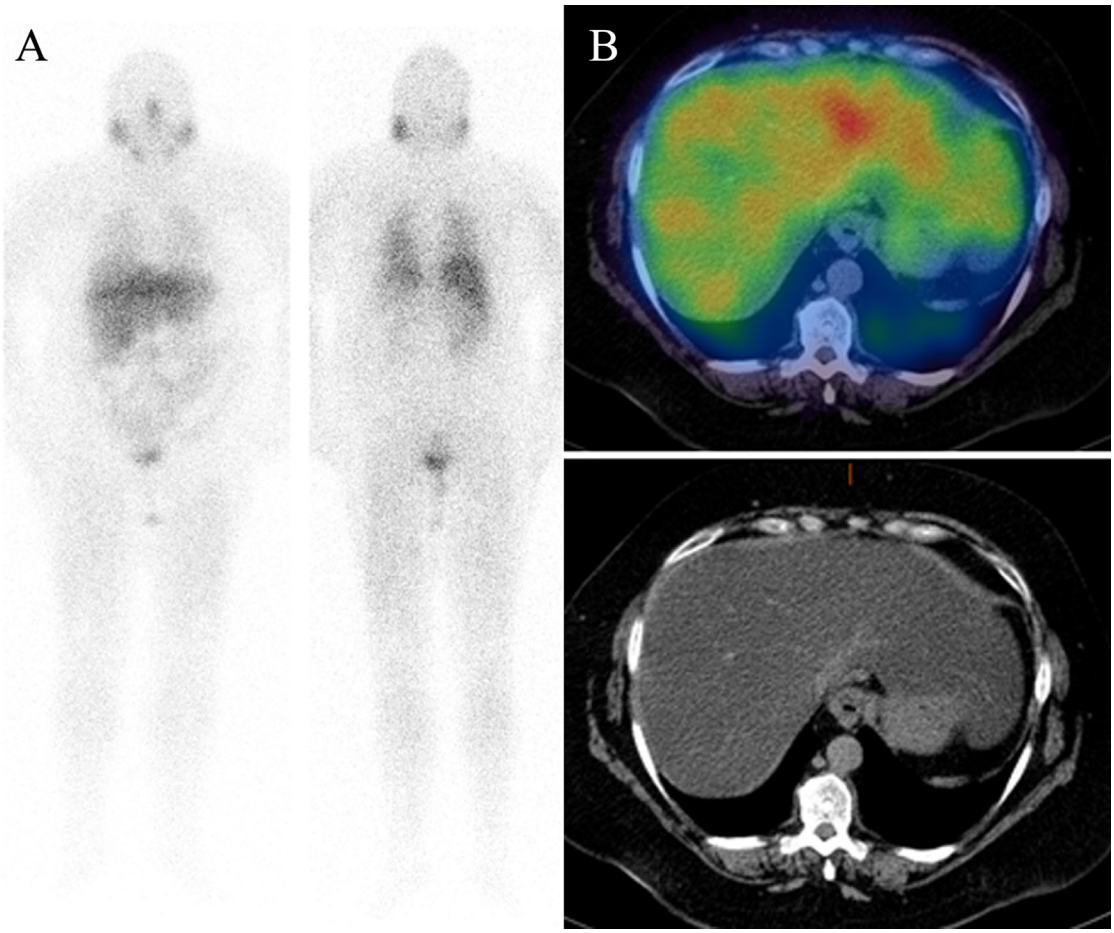

Figure 18 MRI scan of a 60-year-old woman showed a 1.4-cm adenoma in the left adrenal gland. 24-hour urine catecholamines showed increased urine noradrenaline on 2 occasions. ^{123}I-MIBG study demonstrates normal uptake in the adrenals (A). There is, however, very heterogeneous uptake in the liver, particularly in the left lobe (B). This appearance is related to artifact caused by ^{123}I-MIBG SPECT reconstruction. This artifact is related to septal penetration of high-energy photons that are part of the ^{123}Iodine decay scheme. Learning point: Heterogeneous uptake in the liver should not be misinterpreted as metastatic disease. Correlation with diagnostic cross-sectional imaging is usually helpful.

PGLs (sensitivity >90%). This is in part owing to the high tumor: background ratio, with absence of physiological uptake in adjacent structures.[74]

Normal Distribution of ^{18}F-DOPA

There is physiological uptake in the basal ganglia, pancreas (usually in uncinate process but also less intensely in body-tail), liver, and duodenum. Excretion is primarily via the renal route. ^{18}F-DOPA in the plasma is converted into ^{18}F-dopamine in the proximal renal tubule and in the urine (50% excreted within 1 hour). There is also variable but sometimes-significant hepatobiliary excretion. This can result in very intense and variable uptake in the gallbladder, biliary tracts, kidneys, ureters, and bladder.[75] No significant uptake is seen in the adrenal glands, which is an advantage over ^{123}I-MIBG, particularly in patients with multiple endocrine neoplasia type 2.

Artifacts, False Positives, and False Negatives

As increased amino acid transport has been found in macrophages, false positives may result in patients with inflammation (eg, infection and postoperative changes). False negatives in imaging PGL and pheochromocytomas may be seen in small tumors and abdominal SDHx-related PGLs.[76] In the setting of metastatic disease, ^{18}F-DOPA has reduced accuracy in SDHB mutation tumors.[77]

Carbidopa is an amino acid decarboxylase inhibitor, and it inhibits the conversion of L-DOPA to dopamine in extracerebral tissues. This has been reported to increase tumor uptake.[78] However, Carbidopa premedication should not be administered in suspected insulinomas or B-cell hyperplasia, as it causes reduced uptake in the whole pancreas, which could mask the abnormality, leading to a false negative.[79]

Conclusion

In summary, there are various "pearls" and "pitfalls" in nuclear endocrinology imaging. "Pearls" may be wonderful to behold, but it is important to be familiar with the "pitfalls" to avoid an incorrect diagnosis and to improve report quality.

References

1. Donohoe KJ, Balon HR, Christian PE, et al. Society of nuclear medicine procedure guideline for thyroid scintigraphy. September 10, 2006
2. Endocrine system. In: Ziessman HA, O'Malley JP, Thrall JH, (eds): Nuclear Medicine: The Requisites (ed 4). Philadelphia, PA: Saunders; 2014
3. Meller J, Becker W: The continuing importance of thyroid scintigraphy in the era of high-resolution ultrasound. Eur J Nucl Med Mol Imaging 2002;29:S425-S438
4. Tunbridge WMG, Evered DC, Hall R, et al: The spectrum of thyroid disease in a community: The Wickham Survey. Clin Endocrinol 1977;7:481-493
5. Rojeski MT, Gharib H: Nodular thyroid disease: Evaluation and management. N Engl J Med 1985;313:428-436
6. Smith JR, Oates E: Radionuclide imaging of the thyroid gland: Patterns, pearls, and pitfalls. Clin Nucl Med 2004;29:181-193
7. Freitas JE, Freitas AE: Thyroid and parathyroid imaging. Semin Nucl Med 1994;24:234-245
8. Sarkar SD: Benign thyroid disease: What is the role of nuclear medicine? Semin Nucl Med 2006;36:185-193
9. Douglass SR: Evaluation of the thyroid nodule. J Nucl Med 1991;23:2181-2192
10. Sfakianakis GH, Ezuddin SH, Sanchez JE, et al: Pertechnetate scintigraphy in primary congenital hypothyroidism. J Nucl Med 1999;40:799-804
11. Ma C, Kuang A, Xie J, et al: Possible explanations for patients with discordant findings of serum thyroglobulin and 131I whole-body scanning. J Nucl Med 2005;46:1473-1480
12. Shapiro B, Rufini V, Jarwan A, et al: Artifacts, anatomical and physiological variants, and unrelated diseases that might cause false-positive whole-body 131-I scans in patients with thyroid cancer. Semin Nucl Med 2000;30:115-132
13. Intenzo CM, Dam HQ, Manzone TA, et al: Imaging of the thyroid in benign and malignant disease. Semin Nucl Med 2012;42:49-61
14. Muratet JP, Giraud P, Daver A, et al: Predicting the efficacy of first iodine-131 treatment in differentiated thyroid carcinoma. J Nucl Med 1997;38:1362-1368
15. Leger AF, Pellan M, Dagousset F, et al: A case of stunning of lung and bone metastases of papillary thyroid cancer after a therapeutic dose (3.7 GBq) of ^{131}I and review of the literature: Implications for sequential treatments. Br J Radiol 2005;78:428-432
16. Lundh C, Lindencrona U, Postgård P, et al: Radiation-induced thyroid stunning: Differential effects of ^{123}I, ^{131}I, ^{99m}Tc, and ^{211}At on iodide transport and NIS mRNA expression in cultured thyroid cells. J Nucl Med 2009;50:1161-1167
17. Park HM, Park YH, Zhou XH: Detection of thyroid remnant/metastasis without stunning: An ongoing dilemma. Thyroid 1997;7:277-280
18. Hilditch TE, Dempsey MF, Bolster AA, et al: Self-stunning in thyroid ablation: Evidence from comparative studies of diagnostic 131I and 123I. Eur J Nucl Med Mol Imaging 2002;29:783-788
19. Cooper DS, Doherty GM, Haugen BR, et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-1214
20. Fatourechi V, Hay ID, Mullan BP, et al: Are posttherapy radioiodine scans informative and do they influence subsequent therapy of patients with differentiated thyroid cancer? Thyroid 2000;10:573-577
21. Sherman SI, Tielens ET, Sostre S, et al: Clinical utility of posttreatment radioiodine scans in the management of patients with thyroid carcinoma. J Clin Endocrinol Metab 1994;78:629-634
22. Avram AM: Radioiodine Scintigraphy with SPECT/CT: An important diagnostic tool for thyroid cancer staging and risk stratification. J Nucl Med Technol 2014;42:170-180
23. Clark OH: How should patients with primary hyperparathyroidism be treated? J Clin Endocrinol Metab 2003;88:3011-3014
24. Russell CF, Laird JD, Ferguson WR: Scan-directed unilateral cervical exploration for parathyroid adenoma: A legitimate approach? World J Surg 1990;14:406-409
25. Taillefer R, Boucher Y, Potvin C, et al: Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study). J Nucl Med 1992;33:1801-1807
26. O'Doherty MJ, Kettle AG, Wells PC, et al: Parathyroid imaging with technetium-99m-sestamibi: Preoperative localization and tissue uptake studies. J Nucl Med 1992;33:313-318
27. Palestro CJ, Tomas MB, Tronco GG: Radionuclide imaging of the parathyroid glands. Semin Nucl Med 2005;35:266-276
28. Rink T, Schroth HJ, Holle LH, et al: Limited sensitivity of parathyroid imaging with ^{99m}Tc-sestamibi/^{123}I subtraction in an endemic goiter area. J Nucl Med 2002;43:1175-1180
29. Kao CH, Wang SJ, Yeh SH: Tc-99m MIBI uptake in breast carcinoma and axillary lymph node metastases. Clin Nucl Med 1994;19:898-900
30. Shih WJ, Han JK, Coupal J, et al: Axillary lymph node uptake of Tc-99m MIBI resulting from extravasation should not be misinterpreted as metastasis. Ann Nucl Med 1999;13:269-271
31. Palmnedo H, Schomburg A, Grunwald F, et al: Technetium-99-m MIBI scintimammography for suspicious breast lesions. J Nucl Med 1996;37:626-630
32. Hassan IM, Sahweil A, Constatinides C, et al: Uptake and kinetics of technetium-99m-hexakis-2-methoxy isobutyl isonitrile in benign and malignant lesions in the lungs. Clin Nucl Med 1989;14:333-340
33. Aktolun C, Bayhan H, Kir M: Clinical experience with Tc-99m MIBI imaging in patients with malignant tumors: Preliminary results and comparison with T1-201. Clin Nucl Med 1992;17:171-176
34. Aktolun C, Bayhan H, Celasun B, et al: Unexpected uptake of technetium-99m-hexakis-2-methoxy-isobutylisonitrile in giant lymph node hyperplasia of the mediastinum (Castleman's syndrome). Eur J Nucl Med 1991;18:856-859
35. Du Y, Long Y, Ma R: Tc-99m MIBI uptake by a male breast lymphoma accompanied by diffuse bone marrow metastases. Clin Nucl Med 1999;24:454-455
36. Lee JD, Kim SM, Park CH: Tc-99m MIBI uptake in the sternum. Clin Nucl Med 1992;17:819
37. Campeau RJ, Reuther WL, Wayne J: False-positive Tc99m sestamibi examination for parathyroid adenoma in a case of asymmetrical salivary gland enlargement. Clin Nucl Med 1999;24:723-724
38. Ruda JM, Hollenbeak C, Stack BC Jr: A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg 2005;132:359-372
39. Katz SC, Wang GJ, Kramer EL, et al: Limitations of technetium 99m sestamibi scintigraphic localization for primary hyperparathyroidism associated with multiglandular disease. Am Surg 2003;69:170-175
40. Melloul M, Paz A, Koren R, et al: 99m Tc-MIBI scintigraphy of parathyroid adenomas and its relation to tumour size and oxyphil cell abundance. Eur J Nucl Med 2001;28:209-213
41. Lorberboym M, Minski I, Macadziob S, et al: Incremental diagnostic value of preoperative 99mTc-MIBI SPECT in patients with a parathyroid adenoma. J Nucl Med 2003;44:904-908
42. Hetrakul N, Civelek AC, Stagg CA, et al: In-vitro accumulation of technetium 99m sestamibi in human parathyroid mitochondria. Surgery 2001;130:1011-1018
43. Perez-Monte JE, Brown ML, Shah AN, et al: Parathyroid adenomas: Accurate detection and localization with Tc-99m sestamibi SPECT. Radiology 1996;201:85-91
44. Nichols KJ, Tomas MB, Tronco GG, et al: Optimizing the accuracy of preoperative parathyroid lesion localization. Radiology 2008;248:221-232
45. Hindié E, Ugur O, Fuster D, et al: Parathyroid Task Group of the EANM. 2009 EANM parathyroid guidelines. Eur J Nucl Med Mol Imaging 2009;36:1201-1216
46. Torregrossa JV, Fernandez-Cruz L, Canalupo A, et al: 99m Tc-Sestamibi scintigraphy and cell cycle in parathyroid glands of secondary hyperparathyroidism. World J Surg 2000;24:1386-1390
47. Sun SS, Shiau YC, Lin CC, et al: Correlation between P-glycoprotein (P-gp) expression in parathyroid and Tc-99m MIBI parathyroid image findings. Nucl Med Biol 2001;28:929-933
48. Staudenherz A, Telfeyan D, Steiner E, et al: Scintigraphic pitfalls in giant parathyroid glands. J Nucl Med 1995;36:467-469

49. Ferlin G, Borsato N, Camerani M, et al: New perspectives in localizing enlarged parathyroids by technetium-thallium subtraction scan. J Nucl Med 1983;24:438-441
50. Hindie E, Melliere D, Jeanguillaume C, et al: Parathyroid imaging using simultaneous double-window recording of technetium-99m-sestamibi and iodine-123. J Nucl Med 1998;39:1100-1105
51. Weber CJ, Vansant J, Alazraki N, et al: Value of technetium 99m sestamibi iodine 123 imaging in reoperative parathyroid surgery. Surgery 1993;114:1011-1018
52. Slater A, Gleeson FV: Increased sensitivity and confidence of SPECT over planar imaging in dualphase sestamibi for parathyroid adenoma detection. Clin Nucl Med 2005;30:1-3
53. Gayed IW, Kim EE, Broussard WF, et al: The value of 99m-Tc-sestamibi SPECT/CT over conventional SPECT in the evaluation of parathyroid adenomas and hyperplasia. J Nucl Med 2005;46:248-252
54. Krausz Y, Bettman L, Guralnik L, et al: Technetium-99m-MIBI SPECT/CT in primary hyperparathyroidism. World J Surg 2006;30:76-83
55. Krenning EP, Bakker WH, Breeman WA, et al: Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. Lancet 1989;1:242-244
56. Reubi JC: Regulatory peptide receptors as molecular targets for cancer diagnosis and therapy. Q J Nucl Med 1997;41:63-70
57. Antunes P, Ginj M, Zhang H, et al: Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? Eur J Nucl Med 2007;34:982-993
58. Bombardieri E, Ambrosini V, Aktolun C, et al: ^{111}In-pentetreotide scintigraphy: Procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging 2010;37:1441-1448
59. Reubi JC, Waser B, Schaer JC, et al: Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype- selective ligands. Eur J Nucl Med 2001;28:836-846
60. Hofmann M, Maecke H, Börner R, et al: Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: Preliminary data. Eur J Nucl Med 2001;28:1751-1757
61. De Herder WW, Kwekkeboom DJ, Valkema R, et al: Neuroendocrine tumors and somatostatin: Imaging techniques. J Endocrinol Invest 2005;28:132-136
62. Kwekkeboom DJ, Kam BL, van Essen M, et al: Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer 2010;17:R53-R73
63. Kwekkeboom DJ, Krenning EP, Scheidhauer K, et al: ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Somatostatin receptor imaging with 111In-Pentetreotide. Neuroendocrinology 2009;90:184-189
64. Wieland DM, Brown LE, Tobes MC: Imaging the primate adrenal medulla with ^{123}I and ^{131}I metaiodobenzylguanidine. Concise communication. J Nucl Med 1981;22:358-364
65. Solanki KK, Bomanji J, Moyes J, et al: A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobezylguanidine (MIBG). Nucl Med Commun 1992;13:513-521
66. van der Harst E, de Herder WW, Bruining HA, et al: [(123)I]metaiodobenzylguanidine and [(111)In]octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metab 2001;86:685-693
67. Furuta N, Kiyota H, Yoshigoe F, et al: Diagnosis of pheochromocytoma using [^{123}I]-compared with [^{131}I]-metaiodobenzylguanidinescintigraphy. Uptake may also be seen in brown adipose tissue, particularly in children. Int J Urol 1999;6:119-124
68. Bombardieri E, Giammarile F, Aktolun C, et al: ^{131}I/^{123}I-metaiodobenzylguanidine (mIBG) scintigraphy: Procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging 2010;37:2436-2446
69. Taïeb D, Timmers HJ, Hindié E, et al: EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging 2012;39:1977-1995
70. Fonte JS, Robles JF, Chen CC, et al: False-negative ^{123}I-MIBG SPECT is most commonly found in SDHB-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease. Endocr Relat Cancer 2012;19:83-93
71. Mackenzie IS, Gurnell M, Balan KK, et al: The use of 18-fluoro-dihydroxyphenylalanine and 18- fluorodeoxyglucose positron emission tomography scanning in the assessment of metaiodobenzylguanidine-negative phaeochromocytoma. Eur J Endocrinol 2007;157:533-537
72. Rufini V, Treglia G, Castaldi P, et al: Comparison of 123I-MIBG SPECT-CT and 18F-DOPA PET-CT in the evaluation of patients with known or suspected recurrent paraganglioma. Nucl Med Commun 2011;32:575-582
73. Treglia G, Cocciolillo F, de Waure C, et al: Diagnostic performance of ^{18}F-dihydroxyphenylalanine positron emission tomography in patients with paraganglioma: A meta-analysis. Eur J Nucl Med Mol Imaging 2012;39:1144-1153
74. King KS, Chen CC, Alexopoulos DK, et al: Functional imaging of SDHx-related head and neck paragangliomas: Comparison of ^{18}F-fluorodihydroxyphenylalanine, ^{18}F-fluorodopamine, 18F-fluoro-2-deoxy-D-glucose PET, ^{123}I- metaiodobenzylguanidinescintigraphy, and ^{111}In-pentetreotide scintigraphy. J Clin Endocrinol Metab 2011;96:2779-2785
75. Chondrogiannis S, Marzola MC, Al-Nahhas A, et al: Normal biodistribution pattern and physiologic variants of 18F-DOPA PET imaging. Nucl Med Commun 2013;34:1141-1149
76. Imani F, Agopian VG, Auerbach MS, et al: ^{18}F-FDOPA PET and PET/CT accurately localize pheochromocytomas. J Nucl Med 2009;50:513-519
77. Fottner C, Helisch A, Anlauf M, et al: 6-^{18}F-fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to ^{123}I-metaiodobenzylguanidine scintigraphy in the detection of extraadrenal and hereditary pheochromocytomas and paragangliomas: Correlation with vesicular monoamine transporter expression. J Clin Endocrinol Metab 2010;95:2800-2810
78. Timmers HJ, Hadi M, Carrasquillo JA, et al: The effects of carbidopa on uptake of 6-^{18}F-fluoro-L-DOPA in PET of pheochromocytoma and extraadrenal abdominal paraganglioma. J Nucl Med 2007;48:1599-1606
79. Jager PL, Chirakal R, Marriott CJ, et al: 6-L-^{18}F-Fluorodihydroxyphenylalanine PET in neuroendocrine tumors: Basic aspects and emerging clinical applications. J Nucl Med 2008;49:573-586