

Endocrine radionuclide scintigraphy with fusion single photon emission computed tomography/computed tomography

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Abstract

AIM: To review the benefits of single photon emission computed tomography (SPECT)/computed tomography (CT) hybrid imaging for diagnosis of various endocrine disorders.

METHODS: We performed MEDLINE and PubMed searches using the terms: "SPECT/CT"; "functional anatomic mapping"; "transmission emission tomography"; "parathyroid adenoma"; "thyroid cancer"; "neuroendocrine tumor"; "adrenal"; "pheochromocytoma"; "paraganglioma"; in order to identify relevant articles published in English during the years 2003 to 2015. Reference lists from the articles were reviewed to identify additional pertinent articles. Retrieved manuscripts (case reports, reviews, meta-analyses and abstracts) concerning the application of SPECT/CT to endocrine imaging were analyzed to provide a descriptive synthesis of the utility of this technology.

RESULTS: The emergence of hybrid SPECT/CT camera technology now allows simultaneous acquisition of combined multi-modality imaging, with seamless fusion of three-dimensional volume datasets. The usefulness of combining functional information to depict the bio-distribution of radiotracers that map cellular processes of the endocrine system and tumors of endocrine

origin, with anatomy derived from CT, has improved the diagnostic capability of scintigraphy for a range of disorders of endocrine gland function. The literature describes benefits of SPECT/CT for ^{99m}Tc -sestamibi parathyroid scintigraphy and ^{99m}Tc -pertechnetate thyroid scintigraphy, ^{123}I - or ^{131}I -radioiodine for staging of differentiated thyroid carcinoma, ^{111}In - and ^{99m}Tc -labeled somatostatin receptor analogues for detection of neuroendocrine tumors, ^{131}I -norcholesterol (NP-59) scans for assessment of adrenal cortical hyperfunction, and ^{123}I - or ^{131}I -metaiodobenzylguanidine imaging for evaluation of pheochromocytoma and paraganglioma.

CONCLUSION: SPECT/CT exploits the synergism between the functional information from radiopharmaceutical imaging and anatomy from CT, translating to improved diagnostic accuracy and meaningful impact on patient care.

Key words: Parathyroid adenoma; Neuroendocrine tumor; Single photon emission computed tomography/computed tomography; Single photon emission computed tomography-computed tomography; Thyroid cancer; Pheochromocytoma; Paraganglioma

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Core tip: The emergence of hybrid single photon emission computed tomography (SPECT)/computed tomography (CT) camera technology now allows simultaneous acquisition of multi-modality imaging with seamless fusion of three-dimensional volume datasets; combining functional information from radionuclide scintigraphy and anatomy derived from CT. SPECT/CT imaging exploits the synergism between "function" and "form" for investigation of endocrine disorders, translating to improved diagnostic accuracy and meaningful impact on patient care.

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INTRODUCTION

The history of nuclear medicine imaging has been intimately tied to the investigation of endocrine disorders using radioisotopes labeled to ligands specific for molecular processes within cells of the endocrine system. This approach depicts physiological and pathological biodistributions of these radiotracers, creating "*in vivo* functional maps", that can be used to aid diagnosis and management of thyroid, parathyroid and adrenal disorders. Radionuclide thyroid scintigraphy is the

prototypic test of endocrine dysfunction *via* determination of thyroid trapping and organification of radioiodine. On a molecular level radioiodine uptake measurements with either radioiodine-131 (^{131}I) or radioiodine-123 (^{123}I) are mediated by the sodium-iodide symporter (NIS) expressed on thyroid cells^[1,2]. These radioisotopes are also used following thyroidectomy for staging of well-differentiated thyroid cancers (DTC), and in the case of ^{131}I to ablate normal thyroid remnant tissues and to treat thyroid cancer metastases^[3,4].

Other commonly used endocrine radionuclide studies are parathyroid scintigraphy with ^{99m}Tc -methoxyisobutylisonitrile (sestamibi) for detection of hyperfunctioning parathyroid adenomas, somatostatin receptor scintigraphy (SRS) with radiolabelled somatostatin analogues for imaging of neuroendocrine tumors (NETs) and metaiodobenzylguanidine (MIBG) scans for imaging of chromaffin-cell tumors of the neural crest. Less widely available are adrenal cortical imaging agents, including ^{131}I -6- β -iodomethyl-19-norcholesterol (NP-59) for evaluation of cortisol, aldosterone and androgen secreting adrenal adenomas, and ^{123}I -metomidate (MTO), a selective β 11-hydroxylase inhibitor used to image adrenocortical adenomas and some adrenocortical cancers.

The development of hybrid single photon emission computed tomography (SPECT)/computed tomography (CT) cameras that allow combined multi-modality imaging in a single diagnostic session, with fusion of three-dimensional (3D) volume datasets, represents a significant technological advance in the field of diagnostic imaging^[5,6]. There is growing literature describing the advantages that contemporary SPECT/CT technology affords, when applied to the evaluation of endocrine disorders, improving diagnostic accuracy with subsequent impact on patient management^[7,8].

MATERIALS AND METHODS

We performed a PubMed literature search using the terms: "SPECT/CT", "functional anatomic mapping", "transmission emission tomography", "parathyroid adenoma", "thyroid cancer", "neuroendocrine tumor", "adrenal", "pheochromocytoma", "paraganglioma", and critically reviewed those articles published in English during the years 2003 to 2015 describing the utility of endocrine SPECT/CT scintigraphy. Reference lists from the articles were reviewed to identify additional pertinent articles. We provide a synthesis of the clinical usage and benefits of SPECT/CT and conclude that the combination of function and form, in a synergistic and complementary manner, has improved diagnostic imaging (Table 1). Institutional board review approval was obtained for the figures in this manuscript.

RESULTS

Radionuclide scans are performed after administration

Table 1 Advantages of single photon emission computed tomography/computed tomography for endocrine scintigraphy

Reported benefits of hybrid SPECT/CT imaging	^{99m} Tc-sestamibi parathyroid scan	^{99m} Tc-pertechnetate or ¹²³ I-thyroid scan	¹³¹ I- or ¹²³ I-thyroid cancer scan	¹¹¹ In-DTPA octreotide scan	¹³¹ I-NP-59 adrenal cortical scan	¹³¹ I- or ¹²³ I-MIBG scan
Precise localization of the radioactivity	++++	++	++++	++++	+++	++++
Characterization of the radioactivity	++++	++	++++	++++	+++	++++
Clarification of equivocal radiotracer uptake	++	NA	++++	++++	++	+++
Incremental sensitivity over planar/SPECT	++	NA	+	++	+	+
Incremental specificity over planar/SPECT	++++	NA	++++	++++	+++	+++
Additional information on the non-diagnostic CT	+++	NA	+++	+++	++	+++
Improved interobserver agreement	+++	NA	++	++++	NA	+++
Improved reader confidence	+++	NA	++++	++++	NA	+++
Attenuation correction	+	NA	+	++	NA	++
Staging (TNM) of tumor	NA	NA	++++	++	NA	+
Surveillance and detection of recurrent tumor	NA	NA	++++	++++	NA	++
Preoperative localization of target for resection	++++	NA	+	+	+++	+++
Confirming of radiotracer avidity as a prerequisite to radionuclide based therapy ¹	NA	NA	++++	++++	NA	+++
Exclusion of radiotracer avidity to recommend alternative imaging ²	NA	NA	+++	+++	NA	+++
Correlation to outcomes and prognosis	+++	NA	+++	++	++++	++
Radiation dosimetry (tumor- or organ-specific)	NA	NA	+++	+++	NA	NA
Radionuclide imaging times reduced	NA	NA	++	+++	NA	NA
Ordering of additional CT/MRI imaging reduced	NA	NA	+++	+++	+	+
Change in management	++++	NA	++++	++++	++++	++++
Surgical times reduced	++++	NA	NA	NA	NA	NA
Cost-effectiveness	++	NA	NA	NA	NA	NA

¹e.g., MIBG avidity prior to ¹³¹I-MIBG therapy of metastatic pheochromocytoma, paraganglioma and neuroblastoma; ²e.g., selection of non-iodine-avid thyroid cancer for ¹⁸F-fluorodeoxyglucose PET imaging. SPECT/CT: Single photon emission computed tomography/computed tomography; MRI: Magnetic resonance imaging; ^{99m}Tc-: ^{99m}technetium; ¹²³I-: ¹²³I-radioiodine; ¹³¹I-: ¹³¹I-radioiodine; ¹¹¹In-DTPA Octreotide: ¹¹¹In-diethylene triamine penta-acetic acid-pentetreotide (Octreoscan®); ¹³¹I-norcholesterol (NP-59); ¹³¹I-6-beta-iodomethyl-19-norcholesterol; ¹²³I- or ¹³¹I-MIBG: ¹²³I- or ¹³¹I-metaiodobenzylguanidine; NA: Not applicable or not available; TNM: Tumor node metastasis.

of a radiolabelled ligand, with the resultant gamma photons emitted by radioactive decay detected using Anger gamma cameras equipped with collimated sodium (TI) iodide scintillation crystals. Historically the first images were planar acquisitions, and as such were limited by adjacent radioactivity from overlying tissues, low spatial resolution and paucity of correlative anatomic data. Subsequently, the introduction of SPECT was a major advancement, providing 3D tomography datasets initially by the process of filtered back-projection and more recently with, iterative reconstruction techniques. SPECT imaging markedly improves contrast resolution and eliminates interfering background activity, however continues to suffer from low spatial resolution and paucity of anatomic data.

The advantages of hybrid ¹⁸F-fluorodeoxyglucose (FDG) PET/CT led to an interest in the development of

hybrid cameras that combined a conventional gamma camera with an inline CT scanner, with the goal of simultaneous acquisition of SPECT and CT datasets. Co-acquisition of the functional and anatomic data with hybrid scanners removed major barriers of software-based co-registration, such as issues relating to patient positioning between imaging sessions, co-integration of data, and the need for fiducial body markers. Hybrid SPECT/CT cameras were first developed by Lang *et al*^[9] in 1992 with early models using single slice CT scanners. Later models have incorporated multi-slice helical CT with the SPECT/CT usually performed using a so-called “non-diagnostic”, non-intravenous contrast mode with the CT portion contributing an estimated radiation doses of 2-4 mSv to the patient^[5,6,10,11]. SPECT/CT has been successfully applied to radionuclide cardiac imaging, bone scanning, endocrine scintigraphy, lymphoscintigraphy

and liver-spleen imaging^[5,6]. In our experience since 2005, we have found that SPECT/CT has incremental diagnostic value for endocrine scintigraphy, improving diagnostic interpretation and accuracy with meaningful impact on management decisions. The functional and anatomical images are viewed in a tandem side-by-side mode using a localizer tool, or in a “fusion” mode that allows comparative color blending of both 3D datasets as a single image.

An analogy for SPECT/CT for localization of radioactivity is likening its use to global positioning satellite (GPS) technology in the automobile industry. Radionuclide scintigraphy is akin to driving with only a rough idea of the location of the automobile relative to prominent landmarks. Conversely, CT is like a comprehensive street map of a city without an index; finding a specific street or location requires a detailed search by the reader. The combination of imaging modalities in the form of fusion SPECT/CT, a type of “medical GPS”, allows the interpreting physician or radiologist to navigate imaging findings with relative ease. The surgeon who is familiar with cross-sectional modalities such as CT and magnetic resonance imaging (MRI), gains more precise knowledge of the anatomical location of disease targeted for resection, leading to shortened surgical times, shorter hospital stays and faster patient recovery.

The advantages of hybrid SPECT/CT can be broadly categorized as: (1) precise localization of the radioactivity; (2) improved characterization of radioactivity resulting higher specificity, improved sensitivity and overall higher diagnostic accuracy; (3) additional anatomic information derived from the CT component with improved preoperative work-up; (4) CT-based attenuation correction and potential for volumetric dosimetry calculations; (5) increased reader confidence and interobserver agreement; and (6) impact on patient management (*e.g.*, change in treatment plans, shortened surgical operating times)^[7,8].

DISCUSSION

Parathyroid scintigraphy with ^{99m}Tc-sestamibi

Primary hyperparathyroidism presents as hypercalcemia due to excess parathyroid hormone secretion that affects 1 in 2000 males and 2–3 in 500 females, and is due to parathyroid adenoma (85%), hyperplasia (10%) or parathyroid carcinoma (< 1%)^[12]. As a result of routine laboratory screening tests, the majority of patients with primary hyperparathyroidism are asymptomatic at presentation^[13,14]. Secondary hyperparathyroidism occurs in the setting of renal dysfunction often associated with multiple hyperplastic parathyroid glands and when autonomous is referred to as tertiary hyperparathyroidism.

Surgical management of primary hyperparathyroidism with traditional four-gland exploration is curative in greater than 90% of patients^[13,14]. Indications for surgery are serum calcium > 1 mg/dL above the upper limit of normal, GFR < 60 mL/min, age < 50 years,

symptomatic hypercalcemia, or osteoporosis on bone mineral densitometry^[12,15]. The shift to minimally invasive parathyroidectomy has advantages of shorter operation times, decreased length of hospital stays and smaller incision/scar, with similar high cure rates. This technique requires accurate preoperative localization of the parathyroid adenoma, with ^{99m}Tc-sestamibi parathyroid scintigraphy and neck ultrasound being the most commonly used imaging tests. 4D-CT is an emerging imaging modality that is promising, although it does impart higher radiation exposure^[16,17]. Emphasis is for cure at initial surgery due to difficulties related to reoperation in the neck. When surgical procedures fail there may be problems related to multiglandular hyperplasia or ectopic parathyroid locations^[13,14]. The introduction of intra-operative parathyroid hormone monitoring has helped to address some of the issues with these challenging cases, where a 50% decline predicts successful resection of the “culprit” adenoma responsible for hypersecretion of parathyroid hormone.

Parathyroid scintigraphy uses ^{99m}Tc-sestamibi which is accumulated by both thyroid and parathyroid tissues. Dual time-point imaging protocols use the different retention and washout rates between thyroid and parathyroid tissues at early 10–20 min and delayed 2 h time-points to identify parathyroid adenomas^[12,15]. The reported sensitivity varies between 54% to 100% depending on the cohort reported^[18]. Numerous studies confirm incrementally utility and diagnostic value of parathyroid SPECT/CT compared to either planar or planar/SPECT techniques for preoperative localization of parathyroid adenoma using a minimally invasive surgical approach in patients with primary hyperparathyroidism, secondary hyperparathyroidism, ectopic or multiglandular disease, and at reoperation^[19–43]. We performed a meta-analysis of parathyroid SPECT/CT in 12233 patients in 24 studies and found a pooled sensitivity (identification rate) of 86%. Using pooled unpaired analysis there was a step-up in diagnostic sensitivity between planar (70%), SPECT (74%) and SPECT/CT (86%) techniques^[44]. Specificity of parathyroid SPECT/CT could not be analyzed as most studies reported surgically treated cohorts without clinical follow-up of negative studies to determine actual false-negative rates. In a more recent study of 154 patients undergoing dual-phase parathyroid imaging, SPECT/CT detected more lesions (97.8%) compared to planar imaging (87.6%)^[45]. SPECT/CT was superior to planar imaging particularly for the detection of small adenomas and dual-phase imaging was superior to single-phase studies regardless of the imaging technique employed.

In addition to being more sensitive than planar imaging for detection of adenomas, SPECT/CT is better at lateralization and quadrant localization of the parathyroid adenoma. The CT portion may visualize the adenoma in a eutopic position posterior to the thyroid gland, or for ectopic glands, can demonstrate the superior gland located more posteriorly and the inferior gland more located anteriorly^[46] (Figure 1). SPECT/CT excels for the evaluation and preoperative localization of ectopic

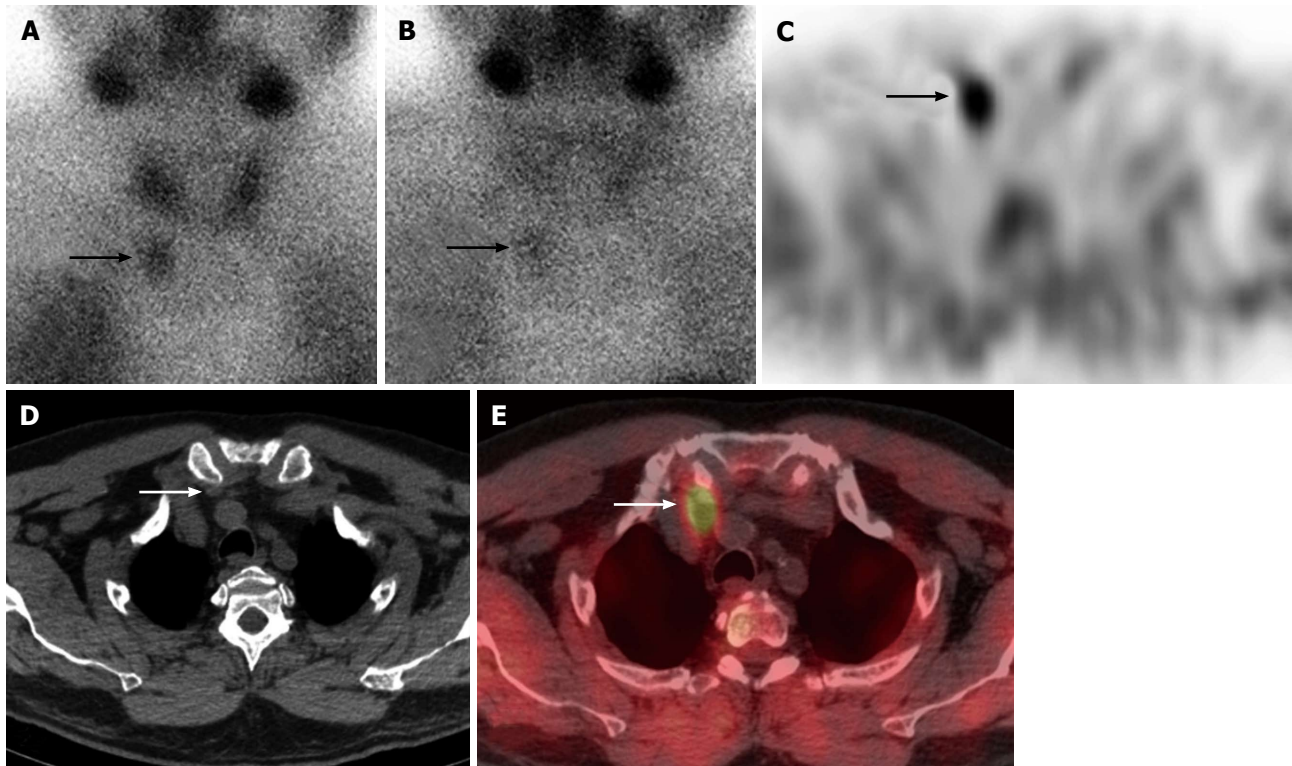


Figure 1 Right inferior parathyroid adenoma in a 60-year-old man. ^{99m}Tc -sestamibi parathyroid scan anterior early 20 min (A) and delayed 2 h planar images (B) show focal radiotracer uptake and retention at the junction of the right lower neck/superior mediastinum (arrows). Axial SPECT, CT and SPECT/CT (C-E) imaging localizes this activity to a soft tissue abnormality in the right lower neck posterior to the sternoclavicular joint (arrows), consistent with ectopic inferior parathyroid adenoma in the lower neck. This was surgically removed via a lower neck incision approach. SPECT: Single photon emission computed tomography; CT: Computed tomography.

parathyroid glands^[40]. This has been universally reported as a major benefit of the technique^[44], particularly for the inferior parathyroid glands that are more likely to migrate during embryological development to ectopic sites including high cervical, intra-thyroidal, intra-thymic, anterior mediastinal and mediastinal locations. Another group of patients that had improved diagnostic accuracy with SPECT/CT were patients with concurrent multinodular thyroid, which often causes false-positive results due to retention of sestamibi in thyroid nodules. SPECT/CT can distinguish eutopic adenomas from false-positive uptake in patients with multinodular goiter^[30,38].

There are a few studies comparing SPECT/CT with neck ultrasound or neck CT. In a comparative study of 38 patients with primary hyperparathyroidism whose work-up included 4D-CT, neck ultrasound and MIBI SPECT/CT, 4D-CT had sensitivity of 92.1%, superior to ultrasound (84.2%), and SPECT/CT (84.2%)^[47]. 4D-CT had better specificity of 95.6%, ultrasound (86.8%) and SPECT/CT (90.4%), although there were no ectopic adenomas included in this cohort. 4D-CT could be cost-effective, given its similar costs to parathyroid scintigraphy, although the main limitation of 4D-CT is the radiation dose exposure, of particular concern in younger patients^[16]. Comparison of parathyroid SPECT/CT to neck ultrasound in 64 patients reported SPECT/CT sensitivity 70.6% and specificity 94.4%, was higher than ultrasound, 60.3% and 72.2% respectively^[48]. In another

study SPECT/CT had a sensitivity of 88.5%, planar scintigraphy 75.4% and ultrasound 77%^[49]. A major limitation of neck ultrasound is the inability to detect ectopic adenomas^[50].

Benefits of SPECT/CT for surgical management of hyperparathyroidism include shorter surgical times, preoperative localization of eutopic retrotracheal and ectopic adenomas and improvement in diagnostic accuracy. At surgery, the adenoma is usually found within a close distance (< 1.9 cm) from the expected location predicted by imaging^[31]. More recently SPECT/CT has been used intraoperatively with a hand-held gamma-probe to locate parathyroid adenomas, similar to the technique to identify lymph nodes in breast lymphoscintigraphy^[51]. SPECT/CT has the potential to avoid false-positive results, with unique cases reported due to an inflamed lymph node, metabolically active brown adipose tissue or from pulmonary emboli, uncommon though important diagnostic pitfalls^[52-55]. The management of patients considering reoperation remains challenging where SPECT/CT continues to demonstrate low sensitivity, necessitating other diagnostic strategies that may include selective venous sampling or, if available, positron emission tomography (PET) imaging^[36].

Thyroid imaging with ^{99m}Tc -pertechnetate and ^{123}I -radioiodine

Thyroid pinhole imaging with either ^{99m}Tc -pertechnetate

or ^{123}I -radioiodine distinguishes hyperthyroidism due to Graves' disease or toxic multinodular goiter, from conditions with decreased thyroid gland uptake, such as subacute thyroiditis^[56,57]. Quantitative assessment of radioactive iodine thyroid uptake at 24 h provides an objective measure of thyroid function^[57,58]. Another indication for thyroid imaging is to identify dominant so-called "cold" or hypofunctioning thyroid nodules to assess thyroid cancer risk. In these settings thyroid scans are usually correlated with high-resolution thyroid ultrasound. A few authors have reported cases of thyroid SPECT/CT to assist the diagnosis of co-existent Graves' disease in the presence of a multinodular thyroid gland (Marine-Lenhart syndrome)^[59].

Thyroid scans are performed in the neonatal period for diagnosis of hypothyroidism to distinguish thyroid gland agenesis from dysmorphogenesis in which the thyroid gland is present, though non-functioning. Thyroid gland ectopia is a rare disorder, the most common site being at or near the tongue base (lingual thyroid), which in 70% of cases is associated with agenesis of the eutopic thyroid^[60,61]. Lingual thyroid may present with hypothyroidism and subsequent thyroid hormone replacement usually results in atrophy of the thyroid tissue. Rarely in adulthood the lingual thyroid may cause obstructive or compressive symptoms such as dysphagia, odynophagia, bleeding, coughing and obstructive sleep apnea^[62,63]. The utility of thyroid imaging in cases of hypothyroidism where ultrasound cannot identify a normal thyroid gland is obvious, and thyroid agenesis should be differentiated from ectopic thyroid tissue (lingual thyroid) that may later be misdiagnosed as a soft tissue neoplasm. SPECT/CT has shown to be of diagnostic value with either $^{99\text{m}}\text{Tc}$ -pertechnetate^[64-66] or ^{123}I radiotracers^[67,68]. An emerging therapy option for obstructive lingual thyroid is radioactive ^{131}I ^[67,69,70]. While the conventional diagnostic planar thyroid scan will guide management of patients with thyroid agenesis, SPECT/CT will allow identification of ectopic thyroid (lingual thyroid) confirming its ability to accumulate radioiodine, a prerequisite for radioiodine therapy. Advantages include avoidance of surgery and associated post-operative bleeding and infection^[67]. SPECT/CT has also been used to evaluate for struma ovarii, thyrotoxicosis due to ectopic thyroid tissue at adnexal sites, and has been reported to detect metastatic peritoneal deposits in a rare strumal malignancy^[71].

Thyroid cancer scintigraphy with $^{99\text{m}}\text{Tc}$ -pertechnetate and ^{123}I -radioiodine

DTC has a favorable prognosis with a greater than 90% 10-year survival for papillary thyroid cancer (PTC) and an 85% 10-year survival for follicular thyroid cancer. Standard management of DTC centers on total or near-total thyroidectomy with central and lateral compartment dissection performed for removal of palpable, enlarged, diseased lymph nodes. Surgery removes the primary tumor, and any possible co-existing multifocal disease,

addresses cervical lymph node involvement and prepares the patient for radioiodine remnant ablation, and whole body radioiodine imaging^[72-74]. Currently, there is a trend towards performing risk stratification of thyroid cancer designed to predict recurrence risk that more readily aids management decisions, rather than simply using prognostic staging classification systems^[75,76]. As thyroid microcarcinomas (tumors size ≤ 1 cm) are becoming increasingly diagnosed, the role of radioiodine in the management of DTC has become somewhat controversial in low-risk patients without extra-thyroidal tumor extension or high-risk histopathological features^[77-79]. There is consensus for the use of ^{131}I in the treatment of regional and distant metastases of DTC^[72,73], however evidence is lacking that it decreases recurrence rates or increases survival in stage I, low-risk disease^[72-74,80,81]. Recently there has been an exploration of reducing the administered doses of ^{131}I for thyroid remnant ablation with excellent efficacy demonstrated using doses at a lower threshold of 1.1 GBq (30 mCi). Further, recombinant human thyrotropin (rhTSH Thyrogen®) stimulation for radioiodine imaging is now an acceptable alternative to endogenous hypothyroidism for diagnostic imaging and to perform thyroid remnant ablation^[82,83], although its use for treatment of iodine-avid metastases is still under investigation.

Radioiodine imaging using planar techniques has sensitivity of between 45% to 75% and excellent specificity of 90% to 100% for detection of thyroid tissues, with post-therapy ^{131}I scans considered to have the highest sensitivity^[84-86]. Planar imaging detects functioning thyroid tissue, but characterization of benign vs malignant etiology is limited by a lack of anatomic information. Focal neck uptake is often indeterminate and identification of iodine-avid metastases may be hampered by their small size, especially in locations where the anatomy has been altered by prior surgery, or in close proximity to sites of physiological radioiodine accumulation. Also, cervical lymph node metastases or other metastatic sites may go undetected on the post-ablation whole-body scan because of the much higher radioiodine avidity in thyroid remnant tissue. ^{131}I SPECT/CT improves diagnostic accuracy by better distinguishing cervical lymph node metastases from remnant thyroid tissue in the neck^[87,88] (Figure 2). SPECT/CT allows reliable diagnosis of lymph node involvement as early as at the time of thyroid remnant ablation, thus opening a new avenue for more accurate staging of patients with DTC, and guiding the most appropriate therapeutic options^[89].

Reports of ^{131}I - and ^{123}I -SPECT/CT have studied patients prepared with either exogenous rhTSH stimulation or endogenous hypothyroidism, and imaged with diagnostic doses between 37 MBq - 430 MBq (1 mCi - 11 mCi)^[85,86,90-93] and therapeutic doses from 1.1 GBq - 9.7+ GBq (30 mCi - 260+ mCi)^[86,94-109]. Radioiodine SPECT/CT has been used for surveillance of thyroid cancer recurrence, in the immediate post-

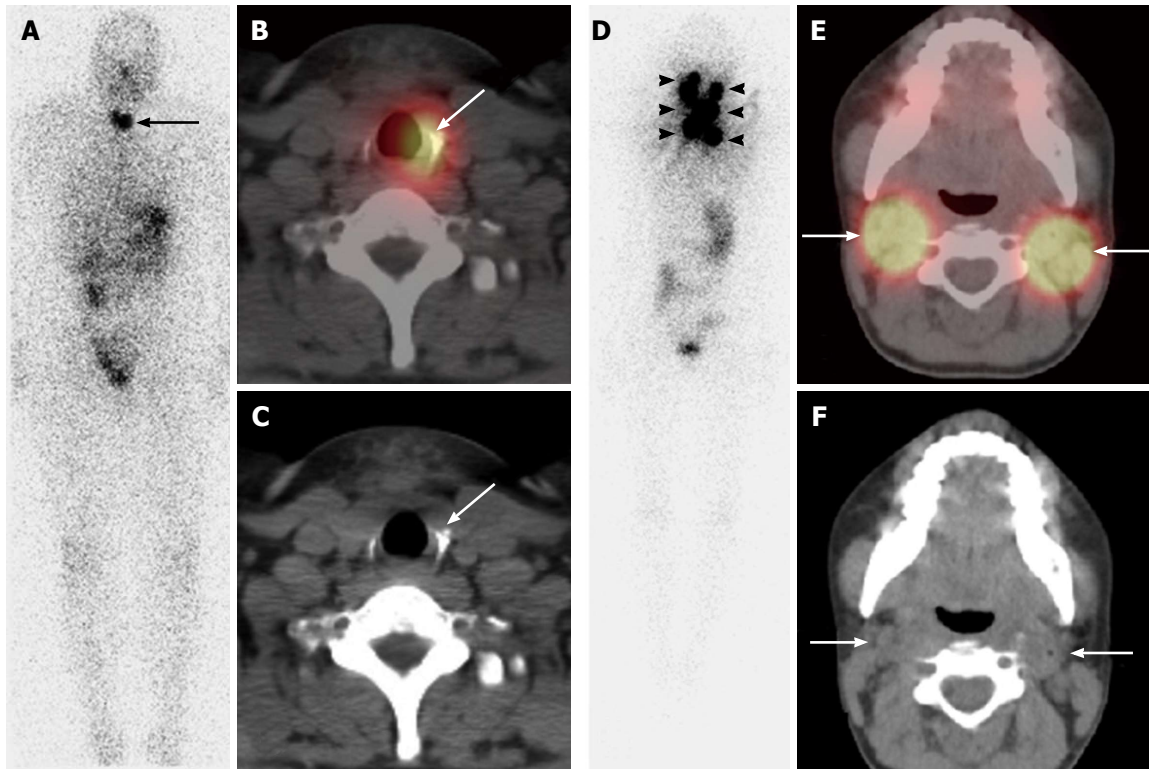


Figure 2 Pre-ablation ^{131}I single photon emission computed tomography/computed tomography scan in a 29-year-old woman with papillary thyroid cancer, the largest lesion measuring 4.2 cm in the right lobe. Post-surgical thyroglobulin was 0.9 ng/mL with a thyrotropin (TSH) of 57 mIU/L. Planar scan (A) depicts two foci of neck activity (long arrow). SPECT/CT (B, C) localized uptake to soft tissue in the left thyroid bed compatible with remnant thyroid tissue (long arrows) and the patient was given a low dose ^{131}I treatment for remnant ablation. Pre-ablation ^{131}I SPECT/CT scan in a 18-year-old woman with multifocal papillary thyroid cancer, the largest lesion measuring 2.0 cm in the left lobe, with capsular invasion; metastatic lymph nodes were resected from the central compartment. Post-surgical thyroglobulin was 223 ng/mL with a TSH of 68 mIU/L. Planar scan (D) depicts multiple foci of neck activity (arrowheads). SPECT/CT (E,F) localized uptake to bilateral bulky iodine-avid lymph nodes in the neck (long arrows), and also the left supraclavicular fossae (not shown). After imaging the patient classified as high risk for recurrence, recommendation was for medium dose ^{131}I therapy. SPECT: Single photon emission computed tomography; CT: Computed tomography.

surgical setting prior to ^{131}I therapy^[85,86,96,110,111], at the time of first radioiodine ablation^[90,91,93] and in post-therapy imaging^[94-99,101,102,105,106,108,109,112-114]. An important advantage of ^{131}I SPECT/CT is that it decreases equivocal findings frequently encountered on planar imaging^[97]. Diagnostic ^{131}I SPECT/CT performed at the time of the first radioiodine ablation correctly classified equivocal findings and had incremental diagnostic value in 41% foci, compared to planar imaging^[91,92]. Thyroid remnant tissue in proximity to the recurrent laryngeal nerves is typically not removed during total thyroidectomy due to concern for nerve damage. Thyroglossal duct remnant is a midline focus in the central neck compartment often near the hyoid bone, representing some residual thyroid tissue along the tract of embryological descent^[93,94]. SPECT/CT allows confident identification of benign uptake within thyroglossal duct and thyroid bed remnants and can distinguish them from nodal regional metastases, even disease within anatomically normal-sized lymph nodes, that are otherwise not easily identified on neck ultrasound after thyroidectomy^[115].

Barwick *et al.*^[110] reported ^{123}I SPECT/CT imaging for thyroid cancer recurrence with a higher sensitivity of 50% and specificity of 100%, compared to SPECT (sensitivity 45% and specificity 89%) and planar imaging

(sensitivity 41% and specificity 68%). They concluded that ^{123}I SPECT/CT primarily led to increase in imaging specificity. Patients with intermediate-to-high risk histopathological features; such as tall cell, columnar or poorly differentiated (insular) thyroid cancer have a greater risk for non-iodine-avid disease, which can be identified even in the face of negative scintigraphy, on the non-contrast enhanced CT portion of the imaging examination. ^{131}I SPECT/CT found sites of non-iodine-avid disease in 21.6% of patients with intermediate-to-high risk stratification of their thyroid cancer^[109]. The identification of non-iodine-avid disease due to loss of sodium iodide symporter expression can occur in between 20%-30% of patients with DTC and implies that radioiodine will be ineffective for imaging and therapy therefore requiring alternative FDG PET/CT imaging and consideration of external beam radiation therapy or reoperation if appropriate.

Whole body screening with ^{131}I SPECT/CT has utility to evaluate for distant metastatic disease^[85,90,91,96-98,106,108,110]. The pattern is usually metastatic spread to the lungs or bone, or rarely to liver, skin, brain or other sites (Figure 3). ^{131}I SPECT/CT exhibits significantly higher sensitivity than $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) bone scans for detecting skeletal thyroid cancer metastases^[113]. ^{131}I

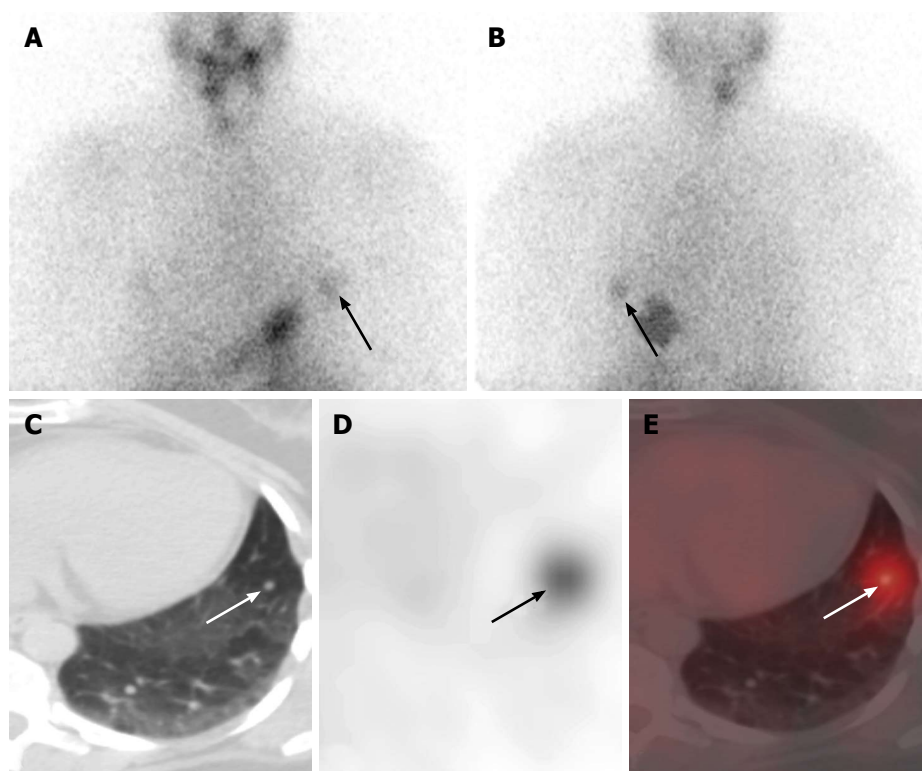


Figure 3 Pre-ablation hypothyroid ^{131}I -radioiodine whole body planar and single photon emission computed tomography-computed tomography scan in a 45-year-old female with papillary thyroid cancer after total thyroidectomy. Anterior (A) and posterior (B) planar images demonstrate a focus of activity in the left thorax (arrow), which is better visualized on the posterior image. Unenhanced axial CT (C), SPECT (D), and SPECT-CT (E) show a 7 mm a radioiodine avid nodule in the lingula (arrow). The utilization of SPECT-CT increases diagnostic certainty in comparison to planar-only imaging evaluation, obviates the need for concurrent diagnostic CT and allows therapeutic evaluation of this nodule after radioactive iodine thyroid treatment. SPECT: Single photon emission computed tomography; CT: Computed tomography.

SPECT/CT has utility for depicting distant metastatic disease including unusual sites leading to changes in staging and risk stratification^[103,104]. ^{131}I SPECT/CT has been reported to localize unanticipated thyroid cancer metastases to liver, kidney, muscle and trachea^[116-125]. Numerous benign variants and physiological disease mimics are well described and routinely identified on radioiodine scintigraphy^[126-128], estimated to occur in up to 22% of radioiodine scans^[111]. NIS activity or iodide-chloride channels can be found in extra-thyroidal tissues; salivary glands, lactating and non-lactating breasts, and in gastric mucosa^[129]. Other sites of benign radioiodine uptake include the choroid plexus, ciliary body of the eye, lacrimal glands, placenta, thymus and skin^[1,129-133]. Pattern recognition allows most of these normal variants to be correctly diagnosed on planar imaging, though the use of SPECT/CT increases interpretation confidence and resolves diagnostic uncertainty^[134,135]. Case reports confirming this utility of SPECT/CT for evaluation of uncommon benign mimics of disease that include lingual thyroid(s), nasolacrimal duct(s), thymus, renal cysts, menstruating uterus, struma ovarii, and ovarian teratomas^[68,116-125,136-139]. Oral radioiodine uptake that was present in 57% of scans localized to high-density dental material on SPECT/CT. Authors have postulated a novel physiologic mechanism for radioiodine uptake that radioiodine has an affinity for metals in dental amalgam

via a chemical reaction^[140,141].

Management decisions for thyroid cancer are based on accurate staging and risk stratification. The impact of ^{131}I SPECT/CT on tumor node metastasis (TNM) staging was assessed in 320 patients prior to receiving their first radioiodine ablation. In those < 45 years, SPECT/CT disclosed distant sites of metastases in 4% and regional nodal metastases in 44%. In patients 45 years or older, SPECT/CT found distant metastases occurred in 10% and nodal metastases in 28%. The overall change to TNM staging contributed from ^{131}I SPECT/CT was 4% patients < 45 years, and 25% of patients, 45 years or older^[93]. In a study of 308 DTC patients with post-therapy SPECT/CT, evaluation of post-surgical, preablation thyroglobulin thresholds were examined, comparing rhTSH in 123 patients to thyroid hormone withdrawal in 185 patients^[142]. For prediction of residual structural disease a cut-off thyroglobulin level of 2.8 ng/mL for rhTSH and 28 ng/mL for thyroid hormone withdrawal was established. In a study of the incremental detection rate of SPECT/CT over planar images, SPECT/CT found additional disease in 8.6% of cases. Patients with additional disease on SPECT/CT had significantly higher thyroglobulin levels (4.3 ng/mL) compared to those without additional SPECT/CT findings (1.6 ng/mL)^[143].

^{123}I or ^{131}I SPECT/CT was studied in a pediatric population and accurately localized radioactivity foci in

the neck including benign variants. It changed clinical decision-making by determining that ^{131}I therapy was unnecessary in two children^[144]. This avoidance of unnecessary ^{131}I radiation exposure is important in those cases where SPECT/CT imaging has reliably excluded residual or metastatic disease^[145,146]. Authors have found that lymph nodes > 1.0 cc are less likely to be effectively treated by radioactive iodine therapy without surgical intervention^[99]. The presence of ^{131}I uptake on post-therapy SPECT/CT better predict short-term outcome and failure of ^{131}I therapy than planar imaging^[94]. A study of 170 patients found that post-therapy SPECT/CT was the only independent prognostic indicator of treatment failure at 2 years^[95]. SPECT/CT can be used to provide more accurate tumor dosimetry by better defining the volume of metastatic disease. This approach to select a calculated delivered radiation tumor-absorbed dose has been used to treat a large skull metastasis from follicular-variant PTC^[147] and in a patient with diffuse bone metastases^[148].

SRS imaging of NETs with ^{111}In - and $^{99\text{m}}\text{Tc}$ -labeled analogues

NETs are rare neoplasms derived from the amine precursor uptake and decarboxylase system, that have potential for hypersecretion of hormones and malignancy risk^[149,150]. They have heterogenous biological behavior and prognosis. After diagnosis the management of NETs depends upon histopathological classification by differentiation and grade. Differentiation is used to confirm neuroendocrine origin and cell type. Ki-67 indices and mitotic rates are used to determine the grade and malignant potential of the NET. These data when combined with staging schema such as American Joint Committee on Cancer staging systems more closely reflect prognosis, and guide imaging strategies and management decisions. First-line treatment is surgical excision of the primary tumor and solitary metastatic lesions, with chemotherapy and systemic treatments reserved for widespread distant disease. As surgical resection remains the only curative treatment, accurate pre-operative staging is of paramount importance.

Depending on their classification, NETs present a clinical challenge for therapy, with anatomic and functional imaging offering complementary and unique advantages that can affect management and potentially reduce morbidity and/or mortality. Although standard imaging techniques (CT and MRI) can be useful in a search for disease, in many situations NETs are small and inconspicuous. SRS depicts NETs *via* overexpression of somatostatin receptors (SSTR) expression by these tumors, particularly SSTR2. ^{111}In -DTPA-pentetreotide is the most commonly used somatostatin analogue which has the highest sensitivity and specificity for carcinoid tumors that present with a syndrome of flushing, hypotension and other symptoms of tryptophan excess. Sensitivity of ^{111}In -DTPA-pentetreotide scintigraphy is notably lower in poorly differentiated NETs and also in

insulinomas that do not express SSTR2. Overall SRS for NET staging has a sensitivity (80%-100%) that exceeds that of CT^[151,152]. ^{111}In -DTPA-pentetreotide may be used to image pheochromocytoma and paragangliomas, although MIBG is preferred due to higher specificity. ^{111}In -DTPA-pentetreotide is also useful for imaging of head and neck paragangliomas, which are of parasympathetic origin, including carotid body tumors and glomus vagale and jugulare.

Studies have reported that ^{111}In -DTPA-pentetreotide SPECT/CT imaging provides incremental diagnostic value over planar and SPECT imaging, achieved through superior lesion localization, identification of physiologic radioactivity distributions, and additional anatomic information derived from the non-diagnostic CT portion^[153-165]. Numerous studies have found that ^{111}In -DTPA-pentetreotide SPECT/CT fusion images had superior diagnostic accuracy compared to side-by-side analysis or software co-registration^[153,155-158,161,162,165]. Typically, physiological sites of uptake in pituitary, thyroid, liver, spleen, gastrointestinal and genitourinary sites (kidneys and bladder) can be distinguished from benign inflammatory processes, infections, sarcoidosis and other granulomatous diseases that may be a source of false-positives. In a study of 107 patients ^{111}In -DTPA-pentetreotide SPECT/CT had an overall sensitivity of 87.8% and specificity of 96.6%, compared to planar imaging, correctly characterizing and reducing the number of equivocal findings from 14 (13%) to 1 (1%)^[166]. SPECT/CT was able to detect lesions unsuspected on planar and SPECT, and had an overall, low rate of false-positive findings (only 12 of 160 lesions) (Figure 4). Additional benefits of the SPECT/CT are improved interobserver variation, reader confidence, and the ability to perform shorter imaging protocols at 24-h time-points obviating the need for later 48 h imaging^[162,167].

A comparative study of $^{99\text{m}}\text{Tc}$ -HYNIC octreotate SPECT/CT and ^{111}In -DTPA-pentetreotide SPECT/CT was performed in 14 patients with NETs. $^{99\text{m}}\text{Tc}$ -HYNIC detected 40/43 (93%) lesions compared to ^{111}In -DTPA-pentetreotide 36/43 (83%), although this did not reach statistical significance. This study found $^{99\text{m}}\text{Tc}$ -HYNIC octreotate has better image quality, lower radiation dose and a trend towards better diagnostic performance^[168]. In a study looking at the ability of SRS to detect primary NETs with ^{68}Ga -DOTATOC PET/CT in 52 patients was compared to ^{111}In -DTPA-pentetreotide SPECT/CT in 71 patients. PET/CT was able to detect the primary tumor in 15 patients (29%) compared to only 4 (8%) with SPECT/CT^[169]. Another comparative study of ^{68}Ga -DOTATATE PET, $^{99\text{m}}\text{Tc}$ -HYNIC-octreotide and whole body MRI found that PET had sensitivity of 96%, compared to SPECT/CT 60% and diffusion weighted MRI of 72%^[170]. The specificities for PET, SPECT/CT and MRI were 97%, 99% and 100% respectively. Therefore ^{68}Ga -DOTA peptide PET is preferable to SRS with SPECT/CT whenever available. An interesting study comparing ^{111}In -DTPA-pentetreotide SPECT/CT with FDG PET/CT

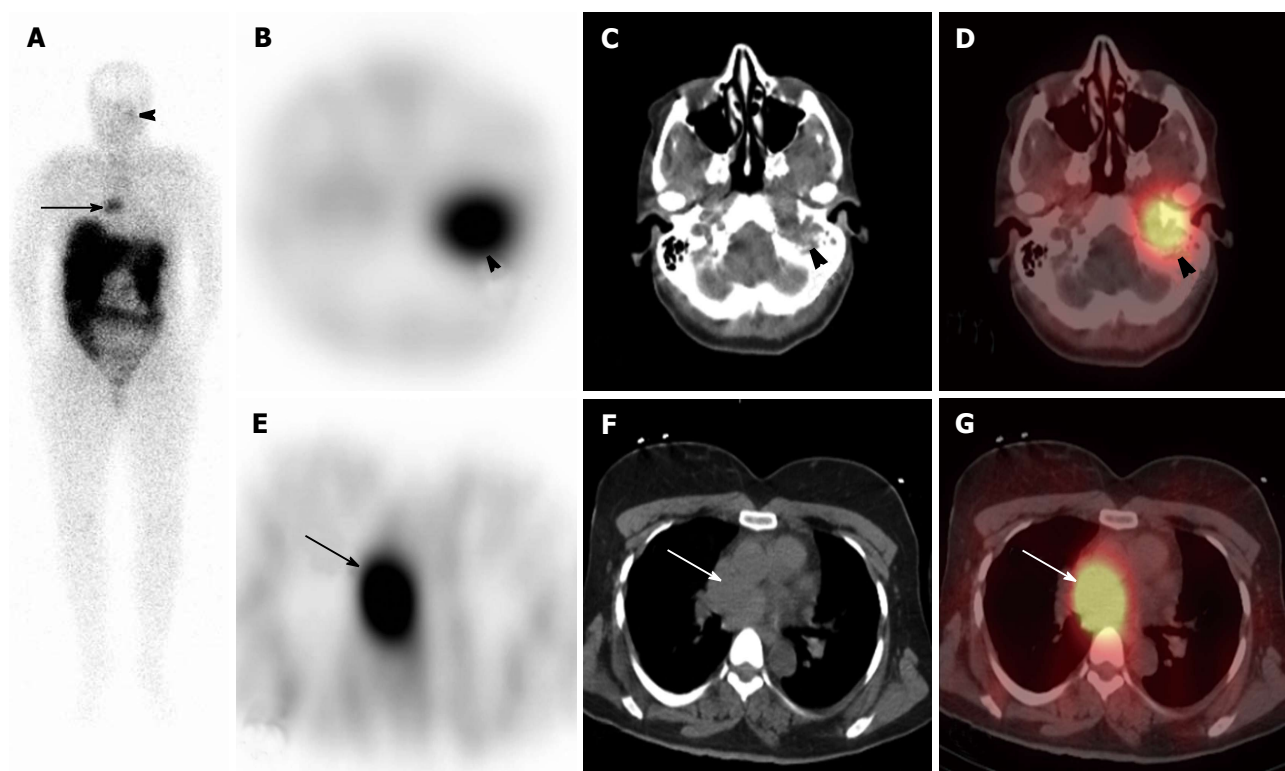


Figure 4 ^{111}In -DTPA-pentetreotide scan in a 45-year-old woman with paraganglioma and glomus tumor, to evaluate for octreotide-avidity. On anterior (A) whole body planar images, there are 2 foci of uptake overlying the left skull base (arrowhead) and the mediastinum (arrows). On Axial SPECT, CT and SPECT/CT (B-D) the skull base radiotracer uptake localizes to a known glomus jugulare tumor adjacent to the left temporal bone and on thoracic axial SPECT, CT and SPECT/CT (E-G) the thoracic radioactivity is within a soft tissue mass in the middle mediastinum, located posterior to the ascending aorta. There is no abnormal radiotracer accumulation below the diaphragm. SPECT: Single photon emission computed tomography; CT: Computed tomography.

in 15 patients with 45 metastatic lesions reported an inverse relationship between the SRS uptake and FDG uptake, supporting the hypothesis that more proliferative metastatic disease is less differentiated with respect to somatostatin receptor expression, though conversely having greater dependence upon glucose metabolism^[171].

Quantitative SPECT/CT allows tumor dosimetry calculations in patients receiving radiolabeled therapies for metastatic NETs^[172,173]. Automated dosimetry tested in 17 patients allowed calculation of absorbed doses to solid organs, the liver, kidneys and spleen^[174]. Using SPECT/CT derived dosimetric calculations, the greatest exposure to the kidneys occurred at 1-2 h, allowing shortening of reno-protective amino-acid infusion times^[175].

Adrenal cortical imaging with ^{131}I -norcholesterol and MTO

Adrenal cortical scintigraphy has usually been performed in 2 settings: (1) for preoperative evaluation of hyperfunctioning adrenal adenomas in which surgery is being contemplated; and (2) for characterization of incidentally discovered adrenal masses. In this setting of adrenocorticotrophic hormone (ACTH)-independent Cushing's disease, Conn's syndrome or rarely hyperandrogenism, with biochemically proven adrenocortical hypersecretion, ^{131}I -6-beta-iodomethyl-19-norcholesterol NP-59, a cholesterol precursor of LDL (a component of the corticosteroid synthesis pathway) has been used to lateralize

the responsible adrenal adenoma^[176-180]. It is important in ACTH-independent Cushing's syndrome to distinguish a hypersecretory adenoma that is surgically curable from bilateral adrenal macrohyperplasia that responds poorly to surgical resection. Similarly hyperaldosteronism presenting with hypokalemia and hypertension with lateralizing signs on dexamethasone suppression ^{131}I -NP-59 scintigraphy will have excellent sensitivity for diagnosis of aldosteronoma and subsequent surgical cure^[177-179], whereas marohyperplasia will not be cured by surgery. Despite the exquisite detail provided by morphological imaging, CT performs less perfectly for this indication because of non-functioning adenomas that confound diagnosis, which are anatomically abnormal but may not be the source of hyperfunction.

SPECT/CT used with the NP-59 scan allows direct evaluation of the hyperfunctioning cortisol secreting tumor to lateralize disease before surgery predicting successful response to adrenalectomy^[181] (Figure 5). In 49 patients with primary hyperaldosteronism undergoing surgery, two semi-quantitative parameters derived from NP-59 SPECT/CT, the adrenal: Liver ratio and the lesion to contralateral gland ratio both predicted surgical cure and correctly distinguished adenoma from macrohyperplasia^[182]. Similar findings were reported for SPECT/CT in stage 1, atypical hyperaldosteronism^[183]. Currently, NP-59 is not available in North America, although it continues to be commercially available in Europe and Asia.

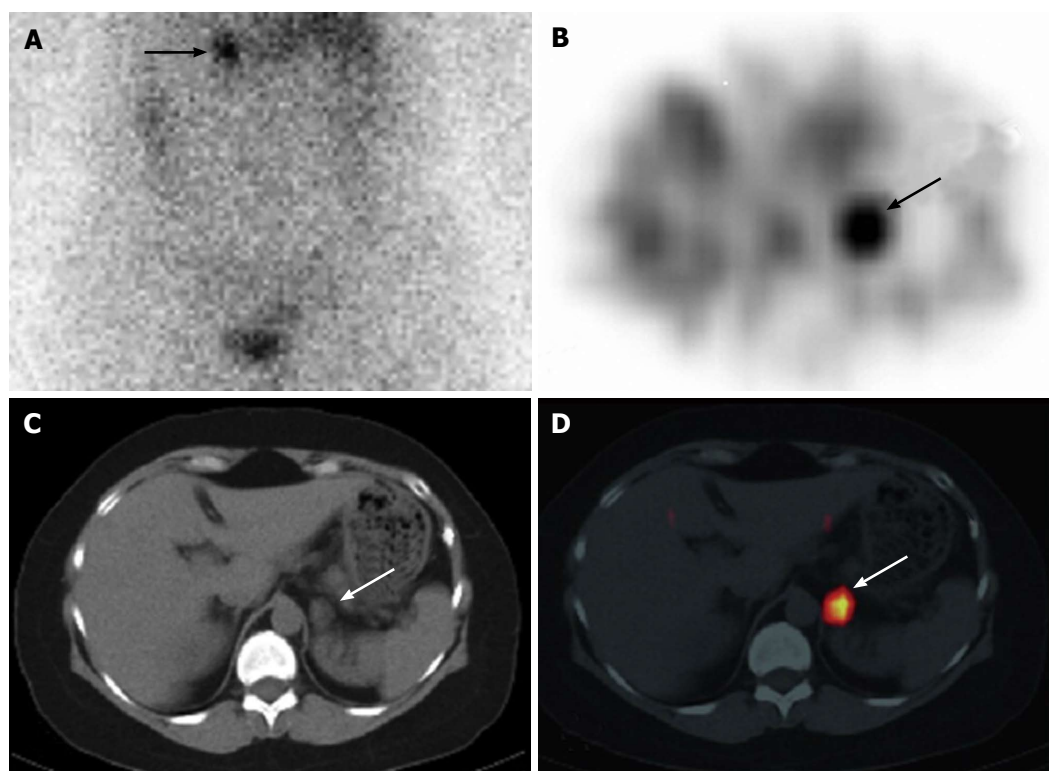


Figure 5 A 55-year-old woman with Cushing syndrome underwent ^{131}I -NP-59 single photon emission computed tomography/computed tomography scan for localization of Cushing's adenoma. Planar posterior (A) abdominal image on day 5 post injection of ^{131}I -NP-59 SPECT/CT demonstrates focal uptake in the left adrenal region (arrow). Transverse SPECT (B), CT images (C) and fused SPECT/CT (D) localize activity to a 1.5 cm \times 1.8 cm nodule arising from the left adrenal gland (arrows). Findings are compatible with a hyperfunctional left adrenal adenoma. Imaging courtesy of "Adrenal Cortical Imaging with I-131 NP-59 SPECT-CT". (By Wong *et al.*^[161], with permission). SPECT: Single photon emission computed tomography; CT: Computed tomography.

Incidentally detected adrenal nodules are being discovered more frequently owing to widespread use of cross-sectional imaging for evaluation of disease outside the adrenal gland. The wide range of pathologies, include malignant (adrenal metastases, adrenocortical cancer) or benign (cortical adenoma, pheochromocytoma, inflammatory diseases, myelolipoma, macrohyperplasia and hemorrhage) processes. The most common benign etiology is a non-functioning adrenocortical adenoma. Unenhanced CT with Hounsfield units < 10 and size < 4 cm are highly predictive of adenoma with sensitivity of around 70% and specificity of $> 95\%$. NP-59 scintigraphy has been used to distinguish benign cortical adenoma, from adrenocortical cancer, when the mass is inconclusive on adrenal washout CT protocol or chemical-shift MRI. Adrenocortical cancer is usually "cold" due to less-avid uptake per gram of tissue^[177]; although rare false-positive have been documented. To our knowledge no SPECT/CT studies for this indication have been published. Evaluation of hyperfunctioning adenomas has also been performed with ^{11}C -metomidate (MTO), a selective inhibitor of $\beta 11$ -hydroxylase. ^{11}C MTO PET and PET/CT distinguishes tissue of adrenocortical origin with high specificity, although it is not well suited to distinguish adenoma from adrenocortical cancer.

Recently efforts have been made to radiolabel MTO with ^{123}I ^[184]. The half-life of 13 h for ^{123}I is more practical compared to the positron emitting ^{11}C half-life of 20 min

allowing SPECT/CT imaging, outside of the research setting. ^{123}I MTO SPECT/CT was used to prospectively study a pilot set of 12 patients with adrenocortical cancer, and found to have a low diagnostic sensitivity, although there was a subset of adrenocortical cancer metastases that did have increased MTO uptake^[185]. This was confirmed in 55 patients with adrenocortical cancer with M1 disease, 22 of whom had functioning disease. ^{123}I MTO SPECT/CT detected just over a third, 16/430 lesions, with the scan being positive in only 34/54 patients, sensitivity of 59%. Planar imaging performed worse than SPECT, with SPECT/CT the being most accurate modality. The subset of 21 patients with metastatic adrenocortical cancer that displayed MTO uptake went on to have ^{131}I radiolabeled-MTO therapy with some encouraging early responses^[186]. Therefore ^{123}I MTO SPECT/CT may have a role for confirming MTO-avidity in M1 adrenocortical cancer patients and allowing the option of a radionuclide based systemic therapy.

Chromaffin tumor imaging of pheochromocytoma, paraganglioma and neuroblastoma with ^{123}I - and ^{131}I -MIBG

Pheochromocytoma is a sympathicoadrenal medullary tumor derived from chromaffin cells of the neural crest. It presents with symptoms of biological catecholamine excess, hypertension, chest pain, anxiety and abdominal discomfort. It may be discovered incidentally (3% of adrenal

“incidentalomas”) or as a secondary cause of hypertension (3%-5% of cases)^[187,188]. Biochemical diagnosis is made with elevated serum and urinary catecholamines and metanephrines. Chromaffin tumors that are extra-adrenal in location are termed paragangliomas and may be found anywhere in the sympathetic nervous system, most commonly at intra-abdominal sites (organ of Zuckerkandl) and less commonly in the thorax^[187,188]. Up to 25% of pheochromocytomas and paragangliomas are hereditary with associated genetic syndromes that include multiple endocrine neoplasia (MEN) type 2B, neurofibromatosis Type 1, von Hippel-Lindau syndrome, familial succinate dehydrogenase (SDH-B, C, D) syndromes and Carney's triad. Genetic testing and counseling should be considered in younger patients and when there is bilateral adrenal, multifocal or malignant disease as these are more commonly found in syndromic tumors.

Surgical management of sporadic, benign pheochromocytoma is curative and preoperative diagnosis has important implications for surgery and anesthesiology. Cross-sectional imaging with either CT or MRI has a high sensitivity (> 90%) for the detection of adrenal medullary tumors, with a lower specificity (around 80%). MIBG scintigraphy is based upon a false neurotransmitter analog of noradrenaline, with ¹³¹I MIBG and ¹²³I MIBG imaging having pooled sensitivity of 93%-100% for detection of pheochromocytoma and 90% for paraganglioma^[189]. Due to its high specificity MIBG has been used for confirmation that an adrenal mass detected on either CT or MRI is a pheochromocytoma. As a whole-body imaging technique MIBG can screen for contralateral disease, extra-adrenal tumors, occult metastases, and help guide suitability for surgical resection. Although the use of MIBG scans has been suggested in patients with genetic predispositions to screen for co-existing paraganglioma or metastases, MIBG scans have been reported to have lower sensitivity for detection of these entities, requiring alternative metabolic imaging with FDG PET/CT.

SPECT/CT use with ¹²³I-MIBG scans has been promising for imaging pheochromocytoma and paraganglioma^[190]. Several small early studies of SPECT/CT reported incremental diagnostic accuracy compared to planar imaging^[191-193]. ¹²³I-MIBG SPECT/CT compared favorably to CT and led to changes in patient management^[191-193]. SPECT/CT had a distinct advantage for evaluation of focal radioactivity in close proximity to the liver or spleen, correctly confirming physiologic patterns of uptake or excretion and allowing accurate anatomic localization of focal areas of avid MIBG uptake^[191,192]. Strengths of SPECT/CT compared to planar and SPECT, were improved detection of local recurrences, small extra-adrenal pheochromocytomas, multifocal tumors, and metastatic disease^[193] (Figure 6).

More recently, in 126 adrenal lesions evaluated with ¹²³I MIBG SPECT/CT, there was incremental step-up in sensitivity between planar (63.3%), SPECT (86.6%) and SPECT/CT (90%) modalities^[194]. Specificity remained high on all modalities; planar 100%, SPECT 96.8%

and SPECT/CT of 100%. The interobserver agreement between 2 readers was also higher with SPECT/CT; Cohen's kappa value for planar was 0.815, SPECT was 0.826 and SPECT/CT was 0.966. In particular, SPECT/CT was helpful in reducing false-positive interpretations from known pitfalls such as compensatory post-resection uptake from the contralateral adrenal and sympathetic innervation at sites of brown fat. Recently ¹²³I MIBG SPECT/CT was compared to MRI concluding that the highest diagnostic sensitivity occurred with a combination of both SPECT/CT and MRI modalities^[195].

Similar to SRS, there are several alternative PET radioisotopes, namely ⁶⁸Ga-DOTA peptides, ¹⁸F-DOPA, ¹⁸F-dopamine, ¹¹C-hydroxyephedrine and FDG PET that can also be used for imaging of pheochromocytoma and paraganglioma. ⁶⁸Ga-DOTATOC PET/CT was compared to ¹²³I MIBG SPECT in 11 patients with either pheochromocytoma or neuroblastoma^[196]. PET had a sensitivity of 94.4% compared to 76.9% with ¹²³I -MIBG SPECT. A comparative between ⁶⁸Ga-DOTATOC PET and ¹²³I MIBG SPECT/CT study in 12 patients with extraadrenal paraganglioma found 100% sensitivity for PET compared to only 20% for MIBG^[197]. PET found more lesions in 100% patients and MIBG in only 6.9%. PET was better for head and neck sites and also for detection of bone lesions^[198]. A comparative study between ¹⁸F-DOPA PET and ¹²³I MIBG SPECT/CT in 12 patients with recurrent paraganglioma found 98% sensitivity for PET compared to only 38% for MIBG^[197]. ¹⁸F-DOPA found more lesions in 8 patients and MIBG found more lesions in 2 patients. Despite the lower sensitivity in these studies, MIBG imaging retains a unique role in patients being considered for ¹³¹I-MIBG radionuclide therapy.

Neuroblastoma is a rare malignant tumor of childhood originating from the neural crest with frequent metastases to the bones, adrenals, lungs and lymph nodes. A meta-analysis of MIBG scans for neuroblastoma demonstrated sensitivity of 97% and specificity of 100%^[189]. The use of SPECT/CT has not been described extensively in the pediatric patient group due to concerns for radiation exposure. In cases of metastatic stage IV disease on the MIBG scan, further evaluation of sites of uptake with SPECT/CT would not be required. However, authors describing small series of SPECT/CT in neuroblastoma recommend that these concerns should be balanced against the useful diagnostic information from CT scans in guiding appropriate management of a life-threatening malignancy^[199-201]. Furthermore, MIBG imaging to confirm uptake and trapping of this radiotracer *via* the noradrenaline receptor is a prerequisite when contemplating systemic therapeutic ¹³¹I MIBG therapy.

Miscellaneous applications and future directions

Medullary thyroid cancers (MTC) are derived from parafollicular (C cells) of neural crest origin, comprising 3%-12% of all thyroid cancers. MTC requires aggressive surgical management as after initial resection up to 40% of patients will have residual or recurrent disease, as indicated by elevated serum calcitonin or carcinoembryonic

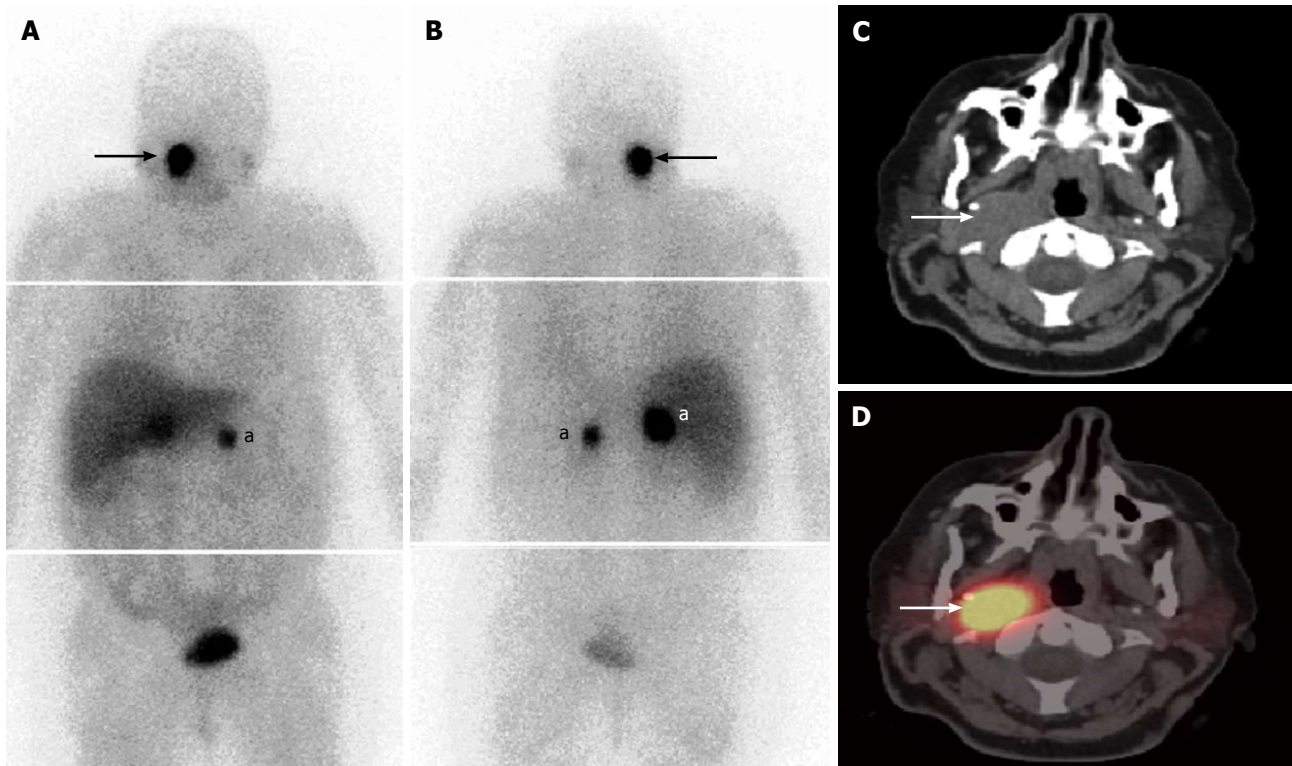


Figure 6 Fifty-three-year-old woman with uncontrolled hypertension and catecholamine hypersecretion, suspected for pheochromocytoma^[123]. I-MIBG composite (A) anterior and (B) posterior whole-body images at 24 h post-injection show bilateral focal intense activity in the region of the adrenal glands (a), with unexpected MIBG avid mass in the right side of the neck (arrows). Axial fused SPECT/CT and CT (C, D) images clearly depict a right neck soft tissue mass with intense MIBG uptake (arrows). This indicates the presence of an extra-adrenal head and neck paraganglioma. SPECT: Single photon emission computed tomography; CT: Computed tomography; MIBG: Metaiodobenzylguanidine.

antigen tumor biomarkers^[202]. Molecular imaging techniques used for MTC include; ^{99m}Tc(V)DMSA (sensitivity 50%-80%), ²⁰¹Tl-thallium (19%), ^{99m}Tc-sestamibi (47%), ¹²³I- or ¹³¹I-MIBG (25%-30%), ¹¹¹In-DTPA-pentetreotide (50%-75%)^[203] and ^{99m}Tc-EDDA/HYNIC-TOC (80%)^[204]. To our knowledge, due to the rarity of MTC, no dedicated cohorts have been studied with SPECT/CT, although it is potentially useful^[8,205]. ¹¹¹In-DTPA-pentetreotide SPECT/CT was able to depict a paratracheal MTC recurrence in one case^[206]. Another report described a patient MEN2B in whom ^{99m}Tc(V)DMSA SPECT/CT was used to demonstrate bone metastases^[207]. SPECT/CT may have a limited role for staging of MTC as the investigation of elevated calcitonin usually requires multimodality imaging with CT, MRI, CT angiography and FDG PET/CT or ¹⁸F-DOPA PET/CT, when available, which have higher sensitivity compared to SPECT/CT techniques.

A novel use of SPECT/CT has been to guide aspiration biopsy in DTC, when the ultrasound fine-needle aspiration biopsy is negative for malignant cells but the lymph node aspirate is positive for thyroglobulin^[208,209]. ^{99m}Tc-sestamibi SPECT/CT has been in DTC to predict nodal metastatic status prior to surgery^[210]. Graves' eye disease is another area where SPECT/CT could have diagnostic value, with localization of ^{99m}Tc-EDDA/HYNIC-TOC to the orbits on SPECT/CT being positively related to the disease activity. SPECT/CT may be a feasible technique to assess treatment response to corticosteroids

in Graves orbitopathy^[211]. Novel preoperative ^{99m}Tc-folate SPECT/CT was used to investigate nonfunctioning pituitary adenomas^[212].

Future use of these interesting novel applications of SPECT/CT remains to be elucidated. Hybrid SPECT/CT is a rapidly emerging, combined dual-modality imaging technique with incremental diagnostic utility over its individual components when applied to nuclear medicine imaging of endocrine disorders. SPECT/CT exploits the synergism between the functional information provided by radiopharmaceutical imaging and the anatomic data available from CT, translating to improved diagnostic accuracy and meaningful impact on patient care.

COMMENTS

Background

Radionuclide scintigraphy has played an integral role in the investigation of endocrine disorders providing unique diagnostic functional information. These are often combined with traditional anatomic imaging modalities such as ultrasound, computed tomography (CT) and magnetic resonance imaging to arrive at the correct clinical diagnosis. The introduction of novel hybrid imaging single photon emission computed tomography (SPECT)/CT cameras allows multimodality imaging during the same imaging session, via co-registration of three-dimensional volume datasets.

Research frontiers

Following the success of hybrid imaging with PET/CT cameras for cancer staging, there had been growing interest in SPECT/CT with the first hybrid camera developed in 1992. Since then, there has been increasing utilization

of this technology for a wide range of radionuclide studies, with accumulating evidence during the 2000's for improved diagnostic performance when applied to endocrine scintigraphic studies.

Innovations and breakthroughs

The ability to localize the exact site of origin of a radioactivity focus *via* SPECT/CT now allows the interpreting radiologist or clinician to precisely characterize this radioactivity to a degree previously not possible.

Applications

SPECT/CT has improved preoperative parathyroid adenoma detection and localization, particularly ectopic locations which are challenging to resect. It has improved the staging of neuroendocrine tumors with somatostatin receptor scintigraphy and pheochromocytoma/paraganglioma using metaiodobenzylguanidine scans. It has advantages for radioiodine imaging of thyroid cancer and for adrenal scintigraphy.

Terminology

SPECT/CT refers to imaging performed on a hybrid gamma camera with an in-line CT. This produces co-registered scintigraphic and CT images that can be viewed with a localizing software tool or in "fusion" mode.

Peer-review

In this systematic review, the authors have presented a thorough and critical analysis of the utility of SPECT/CT for investigation of endocrine disorders. The improved accuracy of endocrine scintigraphic imaging translates to meaningful changes in patient management and improved clinical care.

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