



# Single-Photon Emission Computed Tomography/Computed Tomography in Endocrinology

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The introduction of fusion of functional and anatomical imaging modalities into the field of endocrinology led to a major breakthrough in diagnosis, staging, and follow-up of patients with endocrine tumors. The management of endocrine tumors is based on a wide variety of conventional techniques, including computed tomography, ultrasound, or magnetic resonance imaging, and on scintigraphic functional techniques, associated with unique uptake and transport mechanisms and with the presence of high density of membrane receptors on some of these tumors. Anatomical modalities provide accurate detection and localization of morphological abnormalities, whereas nuclear medicine studies reflect the pathophysiological status of the disease process. Lack of structural delineation and relatively low contrast hamper the precise anatomical localization of the abnormal functional findings in the presence of potential concurrent foci related to the physiological biodistribution of the radiotracer or to processes unrelated to the evaluated disease entity. The notion that anatomical high-resolution and functional imaging data act as complementary methods led to various combination techniques of these modalities. However, coregistration of the functional and anatomical data after the acquisition of the 2 imaging modalities on separate machines, in different sessions, fails to provide accurate alignment of data, and the mathematical modeling is too cumbersome to be used on a routine basis. In contrast, hybrid imaging devices of single-photon emission computed tomography/computed tomography in a single gantry enable the sequential acquisition of the two modalities, with subsequent merging of data into a composite image display. These hybrid studies have led to a revolution in the field of imaging, providing clinically relevant information that is not apparent on separate images. The present review evaluates the contribution of the integrated single-photon emission computed tomography/computed tomography technology to image analysis and management of patients with endocrine tumors.

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Endocrine tumors constitute a heterogeneous group of neoplasms that originate in the pituitary, thyroid, parathyroid and neuroendocrine adrenal cells, the endocrine islets within the pancreas, or in cells dispersed in organs such as the digestive (gastroenteropancreatic) and respiratory tract. Endocrine tumors, whether benign or malignant, usually are slow growing and difficult to localize despite their metabolically active peptide secretion into the circulatory system.

The surgical approach, the mainstay of treatment of endocrine tumors, is facilitated by accurate preoperative lesion localization, using optimal anatomical and functional imaging modalities. These techniques provide com-

plementary information for diagnosis, staging, and evaluation of treatment efficacy. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) may fail to disclose small tumor sites that have not yet caused morphologic alterations or are obscured by structural changes related to previous surgery. Functional imaging modalities using single-photon emission computed tomography (SPECT) with various tumor-characteristic radiopharmaceuticals may detect lesions before their anatomical visualization and express the functional significance of solitary or multiple suspicious foci, although with sparse anatomical delineation. The interpretation of functional images may therefore benefit from coregistration with anatomical views. The combination of sequential transmission-emission tomography, using a hybrid system of gamma camera and CT, provides a new level of diagnostic confidence in the field of nuclear medicine. The display of structural and functional images through accurate fusion of SPECT and CT data in a single study facilitates the anatomic localization of the tracer uptake, and the patient-specific attenuation correction of SPECT imaging.

The pioneer SPECT/CT system (Millennium VG & Hawkeye; General Electric Health care Technologies) combines a dual-detector, variable angle gamma camera with a low-dose radiograph tube, mounted on the same gantry. This system provides adequate localization of SPECT findings, and it may act as a bridge to diagnostic high-resolution, contrast-enhanced CT or

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MRI of an area of clinical interest. Recently, more advanced SPECT/CT systems in clinical practice incorporate state-of-the-art SPECT with improved CT devices. This review evaluates the contribution of SPECT/CT to image interpretation and to management of patients with the following endocrine disorders: neuroendocrine tumors, differentiated thyroid cancer and parathyroid adenoma.

## Imaging Protocols

Hybrid images of functional SPECT and anatomical CT data following sequential acquisition of the two techniques in a single scanning session have been provided by dual-modality integrated SPECT/CT imaging systems.<sup>1-4</sup> Depending on the clinical indication at hand, SPECT/CT images are acquired at various time intervals after tracer administration, following planar imaging. CT acquisition is performed using recommendations for the specific component of the hybrid imaging device. SPECT is acquired with protocols depending on the administered tracer. For <sup>99m</sup>Tc- and <sup>123</sup>I-labeled radiopharmaceuticals, high-resolution, low-energy collimators are used and 360° SPECT images are acquired in a matrix size of 128 × 128, with a 3° angle step, at 20 s per frame. For <sup>111</sup>In and <sup>131</sup>I, the latter on a 64 × 64 matrix, a 6° angle step at 30 s per frame is used, with medium-energy collimators. Reconstruction is performed by filtered backprojection or iteratively using the ordered subsets expectation maximization (ie, OSEM) technique. The resultant emission images, obtained in transaxial, sagittal, and coronal planes, are inherently registered to the transmission data, using the workstation software, to generate hybrid images of the superimposed anatomical maps (CT) and functional (SPECT) data. The sequence of SPECT and CT acquisition is interchangeable; however, in currently used routine protocols, CT acquisition is, in principle, the initial procedure followed by SPECT.

## Neuroendocrine (NE) Tumors

NE tumors are well-differentiated solid tumors characterized by membrane-bound secretory granules, marker proteins, and cell-type specific hormonal products. They include gastroenteropathic (GEP) tumors, neural crest tumors originating from chromaffin cells, and medullary thyroid cancer originating from C cells of the gland. Tumors may be associated with hyperfunctional syndromes (functioning tumors) or may only exhibit immunopositivity for endocrine markers and/or elevated serum markers, with no distinct clinical syndrome (nonfunctioning tumors).

Management of patients with NE tumors is based on surgical removal of the primary tumor and of solitary metastases, with radical tumor surgery being curative albeit rarely possible, and on treatment with labeled ligands for metastatic spread. At initial staging, early detection of tumor sites is mandatory; however, small size, multiplicity, and occasional location in hollow organs hamper the diagnosis and localization of the primary lesion and its metastases. Because patients with disseminated disease may experience prolonged survival, successful treatment of disseminated NE tumors requires a multimodal approach. Although some NE tumors occasionally exhibit aggressive behavior, most tend to grow slowly, with retention of their differentiation capacities, as reflected in production and secretion of a variety of metabolically active substances (amines and peptides), leading to distinct clinical syndromes. In addition, NE tumors possess neuroamine uptake mechanisms and/or specific cell membrane receptors, such as somatostatin receptors, which play a major role in identifying, localizing, and treating these tumors. Use of radiopharmaceuticals such as <sup>123</sup>I-metaiodobenzylguanidine (MIBG), which is taken up by a specific uptake mechanism, and <sup>111</sup>In-pentetreotide, which binds to somatostatin receptors, is based on these physiological characteristics rather than on anatomical alterations, and may identify lesions beyond the diagnostic sensitivity of conventional imaging modalities. Radiolabeled MIBG or somatostatin analogs also have been used for therapy of tumors exhibiting uptake on a diagnostic scan, to eradicate microscopic residual disease following surgery or later during the course of disease, if conventional treatment fails.

The main anatomical modalities used in diagnosis and staging of NE tumors include conventional, intraoperative, and endoscopic US, CT, MRI, and selective arteriography. The major functional SPECT techniques are based on receptor expression on the tumors, such as somatostatin receptor

scintigraphy (SRS) and on uptake of analogs such as MIBG. Recently, uptake of amines in the metabolic process of hormone production has been studied, such as C11-5-hydroxytryptophan, C11-F18-dihydroxyphenylalanine and 6-[F18]-fluorodopamine, using positron emission tomography (PET). In both SPECT and PET studies, the lack of structural delineation and the affected specificity may be resolved by hybrid imaging using SPECT/CT and PET/CT.

## Gastroenteropancreatic Tumors

According to recent World Health Organization classification, gastroenteropancreatic (GEP) tumors, comprised of carcinoid and islet cell tumors, are subdivided into well-differentiated endocrine tumor, well-differentiated endocrine carcinoma, and poorly differentiated endocrine carcinoma. According to previous classification, carcinoid tumors are classified according to site of origin such as the foregut (including respiratory tract, thymus, stomach, duodenum, and pancreas), the midgut (including small intestine, appendix, right colon), and the hindgut (including transverse colon, sigmoid, and rectum) tumors, with different metastatic spread and different symptoms.

The primary carcinoid of the gastrointestinal (GI) tract is difficult to diagnose at an early stage because of small size, multiplicity, and localization in walls of hollow organs. CT and MRI allow for the detection of larger primary tumors (1–3 cm), liver and lymph node metastases, mesenteric invasion, and vascular encasement. Endoscopic ultrasonography (EUS) is suggested for diagnosing and staging of gastric and duodenal carcinoids, proctoscopy and colonoscopy for rectal carcinoid, and colonoscopy for midgut tumors.

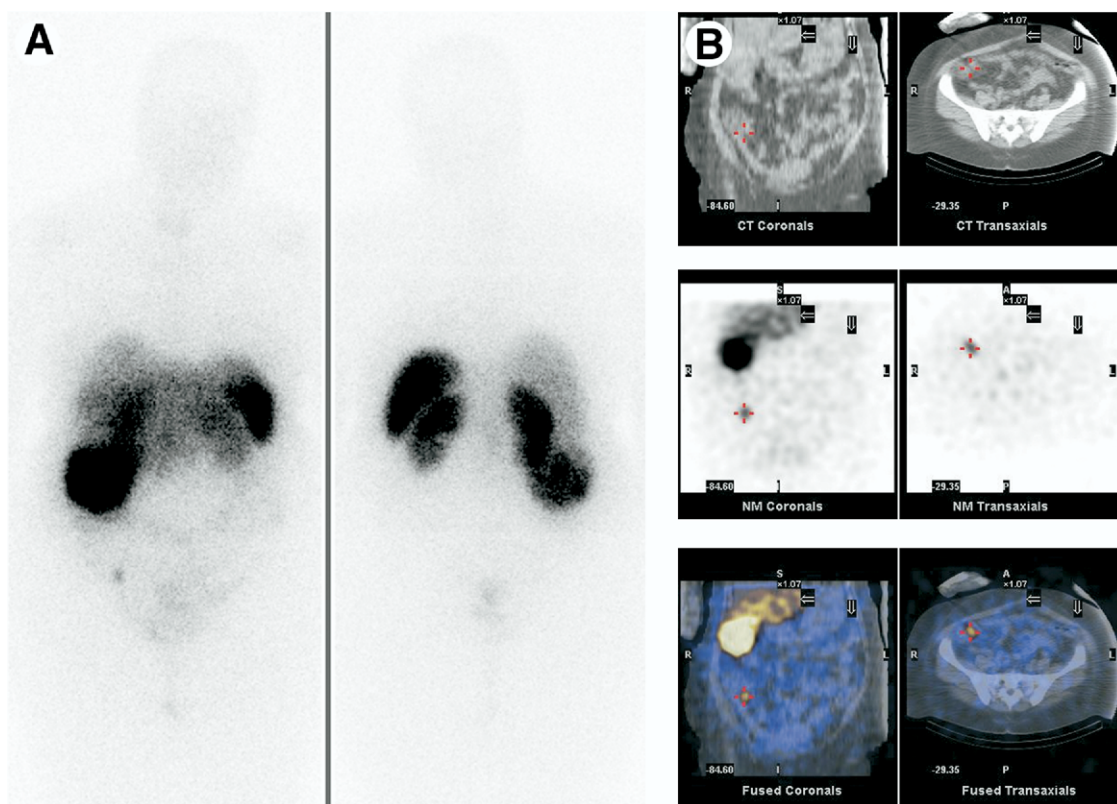
Endocrine pancreatic tumors are classified according to their hormonal secretion. Approximately 20% of these are nonsecreting tumors that may remain undetected until progression to an unresectable stage, with mass effect of the tumor or metastatic disease. Tumors can be localized in approximately 50% of cases using US, CT, MRI, and/or angiography.<sup>5</sup> EUS, combined with biopsy, which is the most sensitive method for detection of pancreatoduodenal tumors, is the initial study suggested for patients with biochemically proven insulinoma (sensitivity 94%). CT, however, remains the imaging of choice for detection of islet cell tumors, with MRI usually reserved for identification of small functional tumors.<sup>6</sup>

The expression of high density of somatostatin receptors in tumor cells has led to a major breakthrough in assessment of NE tumors via somatostatin receptor scintigraphy (SRS), with a reported sensitivity of 82% to 95%. The major clinical indications for SRS include detection and localization of the primary tumor, staging before surgery, early detection of tumor recurrence, and determination of receptor status as a predictor of response to octreotide therapy<sup>7-10</sup> or to targeted peptide receptor radionuclide therapy.<sup>11-13</sup>

SRS has been found superior to CT, MRI, angiography, and EUS for identifying and assessing the staging of carcinoid and of islet cell tumors, except for insulinoma. SRS induced a change in classification in 24% and in surgical strategy in 25% of 160 patients with GEP tumors,<sup>14</sup> and in patient management in 47% of patients with gastrinomas.<sup>15</sup> A high density of somatostatin receptor subtype2 expression forms the basis for peptide receptor radionuclide therapy in patients with multiple inoperable metastases, using <sup>90</sup>Y-DOTA-Tyr3-octreotide, <sup>177</sup>Lu-DOTA-Tyr3-octreotate, and Y90-DOTA-lanreotide, with suggested combination of <sup>90</sup>Y- and <sup>177</sup>Lu- analogs.<sup>16</sup>

Despite the high sensitivity of SRS in most tumors, this technique is limited by small tumor size and by lack of precise anatomic localization. Furthermore, specificity is affected by the physiologic biodistribution of the radiolabeled octreotide related to receptor status of target tissues, and/or to the elimination route of the ligand via the kidneys and GI tract. Biodistribution and tracer accumulation in benign processes such as recent surgery, accessory spleen, renal cyst, breast disease, and granulomatous lung disease may lead to a decrease in diagnostic accuracy and subsequent impaired patient management.<sup>17</sup> These limitations of SRS may be alleviated by integration of nuclear medicine and CT or MRI studies. Improved image interpretation has been obtained by fusion of SPECT and helical CT data, using external<sup>18</sup> or internal markers<sup>19</sup> or by SPECT/CT imaging<sup>20-23</sup> (Fig. 1).

External fiducial markers fixed on a cushion and internal markers such as boundaries of abdominal organs have been used by Forster and coworkers<sup>18</sup> in 14 studies of 10 patients with NE tumors. A helical CT was followed by SPECT of the abdomen with no change in the patient's position, and a second SPECT study was acquired 24 hours post-injection after reposition-



**Figure 1**  $^{111}\text{In}$ -pentetreotide-SPECT/CT for localization of a primary carcinoid tumor. A 51-year-old female patient, diagnosed with metastatic carcinoid of the liver, was referred for somatostatin receptor scintigraphy, to detect the primary tumor and evaluate the extent of disease. (A) Planar whole-body (WB) scintigraphy (left: anterior, right: posterior) shows an extensive focus of increased density of somatostatin receptors in the liver and a faint focus in the right lower abdomen that persisted throughout the study. (B) SPECT/CT images of the abdomen (lower row) and coronal (left column) and transaxial (right column) planes provide precise localization of focal uptake seen on SPECT (middle row) to a primary tumor in the distal ileum (upper row). At surgery, the tumor mass, 13 cm in diameter, was removed from the liver and a carcinoid tumor, 2.1 cm in diameter, was identified 4 cm proximal to the ileocecal valve, and resected.

ing the patient in the molded vacuum cushion. Image fusion using a total of nine external markers fixed on the cushion was faster and easier to handle compared with internal landmarks. Internal markers of skeletal structures visualized on  $^{99\text{m}}\text{Tc}$ -methylene diphosphonate bone scintigraphy were used for coregistration with separately performed CT during dual-isotope acquisition with  $^{111}\text{In}$ -pentetreotide in 2 patients with carcinoid tumor, in an attempt to localize the primary tumor in one patient and to detect metastasis in the second. This technique enabled localization of a tumor site in the small intestine, not visualized on CT, and guided biopsy of a suspicious liver lesion, confirmed histologically.<sup>19</sup> This protocol, however, requires injection of an additional radionuclide, is cumbersome to perform on a routine basis, and is affected by displacement of the thoracoabdominal organs between the SPECT and CT studies.

Several reports have shown the contribution of hybrid SPECT/CT, as an adjunct to SRS, to image interpretation and patient management. In an initial study, SPECT/CT delineated a soft tissue tumor, confinement to the liver or invasion into an adjacent bone, with impact on management in 4 of 8 patients with GEP tumors, with subsequent impact on management.<sup>20</sup> In a cohort study of 68 patients with GEP tumors, SPECT/CT improved the image interpretation in 23 patients (33%): in detection of the primary tumor (3 patients), at staging (11 patients), and during follow-up (9 patients). In 17 of these 23 patients, SPECT/CT precisely confined the tracer uptake to the organ involved, identified unsuspected extension into the bone, and differentiated tumor uptake from physiological tracer activity. Patient management was affected in 10 patients (14%). SRS-SPECT/CT changed the surgical approach in 6 patients, spared unnecessary surgery with invasion of soft-

tissue tumor in the bone in 2 patients, and defined confinement of metastases to the liver in 2 patients, who were subsequently referred for liver transplantation and chemoembolization.<sup>21</sup> In a prospective study, Pfannenber and coworkers<sup>22</sup> evaluated the contribution of SPECT/CT in 54 patients with NE tumors, using  $^{111}\text{In}$ -pentetreotide ( $n = 43$ ) and  $^{123}\text{I}$ -MIBG ( $n = 11$ ). When compared with contrast-enhanced spiral CT, fused images re-classified lesions on 39 CT and on 19 SPECT studies in 58 of 114 lesions (51%), and modified therapy in 14 of 50 patients (28%). In an additional study, SPECT/CT improved the image interpretation in 47% of 19 patients with GEP tumors.<sup>23</sup> Anatomical-functional images revealed unsuspected bone metastases in 2 patients, provided an accurate localization of SPECT findings in 6 cases, and provided the exclusion of disease in sites of physiologic tracer uptake in 1 patient.<sup>23</sup>

When SRS is negative, SPECT/CT is of no additional value, except for verification of absence of receptor density in a tumor visualized on CT. In summary, SRS combined with SPECT/CT acquisition, is a valuable tool for assessment of most GEP tumors, with subsequent impact on patient management. The hybrid imaging defines the localization and functional status of the tumor, optimizes the surgical approach in patients with resectable tumors and helps tailor the optimal treatment strategy for advanced disease.

## Neural Crest Tumors

Pheochromocytoma and neuroblastoma are tumors originating in the adrenergic nervous system. Pheochromocytoma resides mainly in the adrenal gland. However, 10% of adult cases and 30% of pediatric cases have extra-

adrenal lesions, and 10% of tumors are bilateral. The prevalence of malignancy ranges from 13% to 26%, with a high incidence of metastatic disease.

Adrenal pheochromocytomas are best visualized on CT or MRI, which serve as its primary imaging modalities, with an overall sensitivity of 93 to 100%.<sup>24</sup> Radiolabeled MIBG scintigraphy contributes to functional characterization of equivocal noncontrast enhanced CT findings and to detection of extra-adrenal and metastatic spread, with an overall sensitivity of 86% to 88% and specificity of 96% to 99%.<sup>25</sup> Tumors are visualized as intense focal areas of MIBG uptake at 24 to 72 h after tracer injection. Scintigraphically detected MIBG-avid foci may require a detailed anatomical localization, mainly with unilateral, asymmetric, low-intensity uptake, which occurs in 10% to 33% of cases,<sup>26</sup> with verification obtained with an anatomic lesion detected on separately performed CT, following fusion of MIBG with MRI,<sup>27</sup> or with SPECT/CT.<sup>28</sup>

Hybrid images may characterize areas of normal MIBG biodistribution or excretion and facilitate the detection of recurrent or metastatic disease in the vicinity of normal structures showing high MIBG uptake, such as the myocardium and the liver.<sup>28,29</sup> Furthermore, hybrid images can differentiate MIBG uptake in a retroperitoneal recurrence from hyperplastic adrenal gland after contralateral adrenalectomy, especially when tumors tend to be bilateral.

Preliminary data showed MIBG-SPECT/CT to guide the diagnostic CT to the right adrenal gland, initially misinterpreted as the inferior vena cava in one patient,<sup>30</sup> and localized focal MIBG uptake to the ureter in another patient suspected of pheochromocytoma.<sup>20</sup> In 2 pheochromocytoma patients studied with <sup>123</sup>I-MIBG, among 81 consecutive patients evaluated for various clinical indications, using different radiopharmaceuticals, hybrid SPECT/CT allowed for the precise localization of an extra-adrenal tumor in one patient and excluded an adrenal tumor by localizing the suspected focus to the liver.<sup>31</sup>

The value of hybrid imaging in characterization of focal uptake on planar <sup>123</sup>I-MIBG scan recently has been studied in 31 patients with suspected pheochromocytoma.<sup>28</sup> In 25 cases (81%), fused images showed the site of abnormal activity to be confined to the GI tract, the kidneys, or the liver, thus reducing the number of false-positive results. Furthermore, SPECT/CT correctly localized focal accumulation in the adrenal glands of four patients, and differentiated bone metastasis from a local recurrence of pheochromocytoma in two patients.<sup>28</sup>

Neuroblastoma (NB), occurring in 10% of pediatric tumors, may arise anywhere along the sympathetic chain, but most commonly occurs in the adrenal gland, with metastases present in 50% to 60% of patients at diagnosis. Staging is crucial before attempt to remove the primary tumor or residual disease at the time of a second-look procedure. In contrast, advanced stage disease is treated by multiple-agent chemotherapy, and by administration of high therapeutic doses of <sup>131</sup>I-MIBG.

CT and MRI provide detailed anatomic information essential for definition of resectability of the tumor. MIBG scintigraphy is used for diagnosis of the primary lesion when inaccessible to biopsy, staging of disease, radio-guided surgery, evaluation of prognosis and response to therapy, and for targeted radiotherapy, with an overall sensitivity of 92% and specificity of 96%.<sup>32,33</sup> SPECT improves the lesion detectability and location, although whether significantly more lesions can be detected with SPECT than with planar images has been a subject of controversy.<sup>34,35</sup>

SPECT/CT improves the delineation of physiologic diffuse intraluminal bowel activity, and may alleviate the need for delayed imaging at 48 h with its associated decrease in sensitivity. SPECT/CT improves the localization of tumor sites, and the detection of bone and bone marrow involvement (Fig. 2). It can optimize characterization of tumor recurrence adjacent to organs taking up MIBG physiologically and of increased uptake in an adrenal gland after contralateral adrenalectomy. In pediatric patients, SPECT/CT may clarify the diffuse heterogeneous physiologic uptake in the right heart, sometimes misinterpreted as malignant paramedian mediastinal, sternal, or vertebral sites of tumor involvement. SPECT/CT can differentiate bilateral symmetric upper thoracic activity, probably related to physiologic pleural, neck muscle, or brown fat uptake, from scapular or costal bone metastases or from involved supraclavicular lymphadenopathy.<sup>36</sup> SPECT/CT has been advocated as a tool for the quantification of radiation doses delivered during <sup>131</sup>I-MIBG therapy, using CT-based tumor volume-of-interest.<sup>37</sup> When the MIBG scan is negative, SPECT/CT is of no additional consequence, although

visualization of a mass on CT with absence of MIBG-avidity may exclude residual active disease. SPECT/CT is therefore a clinically important tool for localization of sites of abnormal MIBG uptake and for characterization of their benign or malignant significance, with subsequent impact on treatment with labeled MIBG.

## Medullary Thyroid Carcinoma (MTC)

MTC accounts for 3% to 10% of thyroid tumors, with cervical and mediastinal lymph node metastases found in 35% to 50% of patients at presentation. Surgical excision, the sole curative therapeutic approach, requires optimal localization of tumor sites. Diagnostic procedures, such as CT and MRI, and scintigraphy using various radiopharmaceuticals, often fail to disclose tumor involvement. A multicenter study on 85 MTC patients compared FDG-PET, <sup>111</sup>In-pentetreotide, <sup>99m</sup>Tc-sestamibi, CT, and MRI. On the basis of 55 cases with histological confirmation, sensitivity and specificity were 78% and 79% for FDG-PET, 25% and 92% for SRS, 25% and 100% for sestamibi, 50% and 20% for CT and 82% and 67% for MRI, respectively.<sup>38</sup>

Coregistration of anatomical and functional imaging data has been used in a small number of patients with MTC, as part of a larger series of NE tumors. Perault and coworkers<sup>19</sup> used skeletal structures observed on a bone scan in 3 patients with MTC as internal markers for fusion of <sup>111</sup>In-pentetreotide SPECT with CT data. The fusion technique enabled localization of five tumor sites, 3 not visualized on CT, and led to refinement of surgical procedure.<sup>19</sup> This protocol, however, required injection of an additional radionuclide and is impractical on a routine basis.

SRS-SPECT/CT, with no additional tracer injection, detected tumor invasion into the clavicle of an MTC patient with uptake in the lower neck and superior mediastinum on planar images, thus sparing unnecessary surgery.<sup>20</sup> Four MTC patients were included among 54 patients in the study of Pfannenbergl and coworkers, using SPECT/CT in NE tumors.<sup>22</sup> In one patient, SPECT/CT excluded the presence of a NE metastasis in an adrenal mass initially visualized on CT.<sup>22</sup>

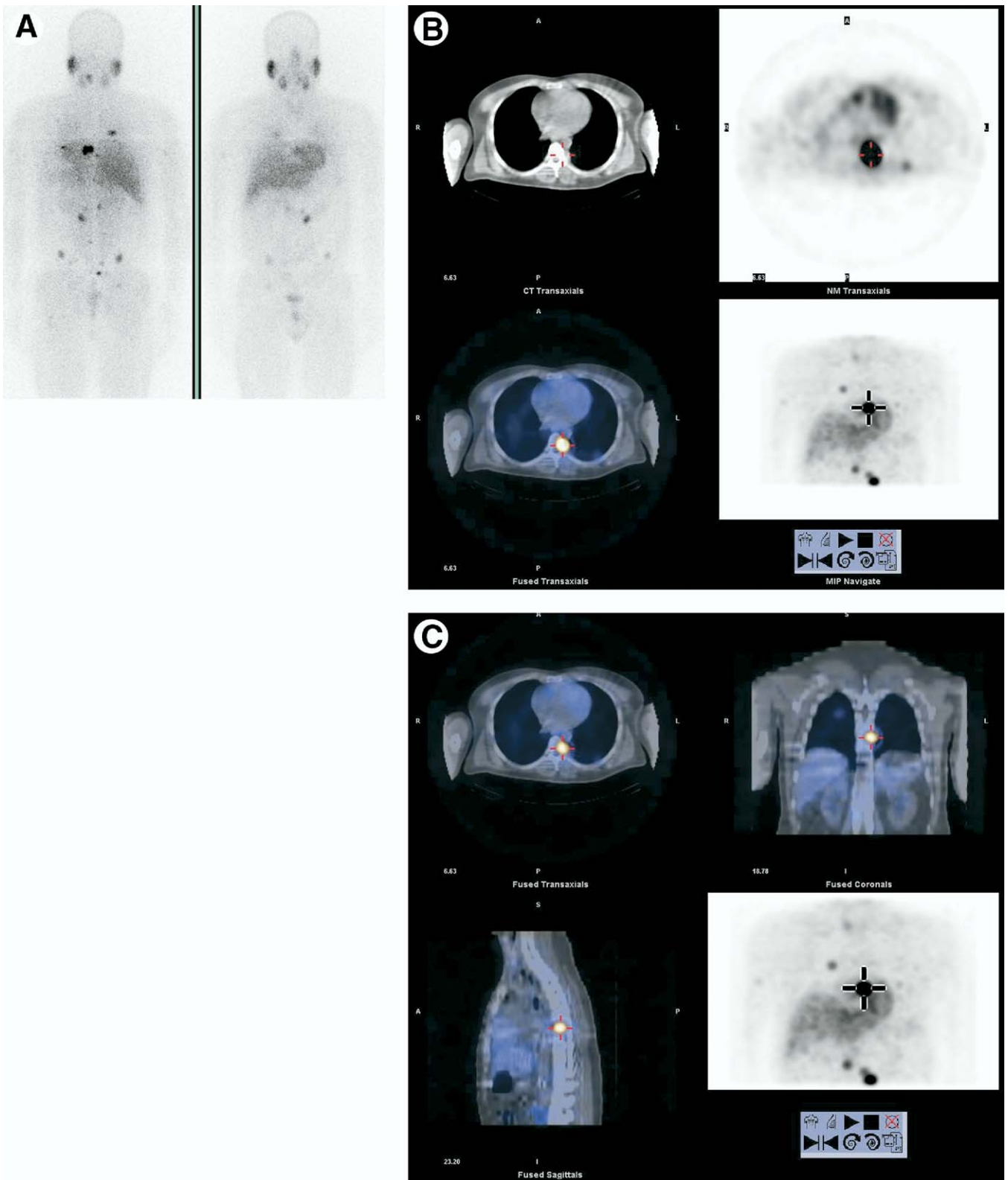
## Differentiated Thyroid Cancer (DTC)

Whole-body (WB) <sup>131</sup>I scanning plays an integral part in management of patients with DTC. Scintigraphy can detect residual, recurrent, or metastatic tumor before visualization on anatomical imaging modalities. These malignant foci will then be removed surgically, if resectable, or be treated with high doses of <sup>131</sup>I. Occasionally, abnormalities detected on planar WB and <sup>131</sup>I-SPECT are difficult to interpret because of a lack of anatomical landmarks and limited specificity. This decreased specificity is caused by normal active radioiodine transport in salivary glands, nasopharynx, gastric mucosa, and breast tissue by excretory activity and by uptake in nonthyroidal pathological conditions, such as ectopic gastric mucosa and ovarian tumor.<sup>39</sup> Diagnostic pitfalls leading to additional images or diagnostic procedures were found in 59% among a total of 500 WB scans from 300 consecutive patients, mainly as the result of contamination, intestinal retention, hot nose, unexpected breast activity, as well as kidney and isolated peripheral metastasis.<sup>40</sup>

CT often lags behind WB scintigraphy in identification of DTC sites, but coregistration of <sup>131</sup>I-avid sites with correlative anatomical imaging may lead to proper image interpretation and further therapy, whether surgery or irradiation, or may spare the patient unnecessary treatment.

Image coregistration has been previously achieved in DTC using external markers,<sup>41</sup> or internal landmarks using dual-isotope acquisition.<sup>19</sup> Datasets of CT and SPECT were fused using external landmarks, placed in 3 locations on the patient's skin to adjust the sections of CT and SPECT in the same geometric plane.<sup>41</sup> The fusion images of <sup>131</sup>I-SPECT and CT were contributory in 15 of the 17 patients (88%) studied. They showed abnormal findings in normal-sized lymph nodes on CT of 4 patients, and disclosed 5 bone metastases and 1 muscle metastasis, not visualized on CT. These images also provided precise localization of <sup>131</sup>I-avidity in 3 patients with bone metastases, and defined the physiological <sup>131</sup>I uptake in 2 patients. Realignment was facilitated by the use of external markers.

Internal landmarks relating to sites of physiologic uptake have not been used with <sup>131</sup>I SPECT but has been provided by dual-isotope acquisition of



**Figure 2**  $^{123}\text{I}$ -MIBG-SPECT/CT for detection of metastatic pheochromocytoma. A 45-year-old man, 20 years after left adrenalectomy for a very large pheochromocytoma (22 cm), was referred for  $^{123}\text{I}$ -MIBG scan to establish MIBG avidity of paraaortic lymph node metastases visualized on diagnostic high-resolution, contrast-enhanced CT, and for targeted high-dose  $^{131}\text{I}$ -MIBG therapy. (A) Planar WB  $^{123}\text{I}$ -MIBG scan (left: posterior, right: anterior) shows multiple foci, including a right lung field lesion, a centrally located mass in the lower chest, paraaortic lymph nodes, and tumor sites at the level of the entrance to the pelvis. (B) SPECT/CT images of the chest in a transaxial slice (lower left) show the centrally located MIBG-avid prevertebral soft tissue mass, as detected on SPECT (upper right) and on the maximal intensity projection image (lower right), with invasion of the 8th dorsal vertebra. (C) SPECT/CT images of the chest show the same tumor mass in a coronal slice (upper right) and in a sagittal slice (lower left), reflecting the involvement of the dorsal vertebra.

$^{131}\text{I}$  and  $^{99\text{m}}\text{Tc}$ -methylene diphosphonate, to obtain information on skeletal structures for subsequent correlation with anatomic data provided by CT. Perauld and coworkers, assessed the feasibility of dual-isotope registration with CT in 5 patients with DTC evaluated with  $^{131}\text{I}$ , with validation of metastases in two patients and physiologic thymus uptake in one patient.<sup>19</sup>

These modalities are limited by potential inaccurate realignment when SPECT images lack a well-defined contour. In addition, manual definition of external markers is confounded by inter- and intraobserver variability,<sup>41</sup> whereas internal landmarks require administration of a second radiopharmaceutical to the patient,<sup>19</sup> limitations not observed with SPECT/CT.

Hybrid SPECT/CT was found to contribute to localization of an  $^{131}\text{I}$ -avid site to the anterior chest wall at the level of the carina, to the left coracoid and to the sternum, with referral of the latter patient to surgery.<sup>1,20</sup> The incremental value of SPECT/CT also was documented in a preliminary report of 54 patients who underwent 67 SPECT/CT studies among 565  $^{131}\text{I}$  WB scans of 298 patients with DTC over the course of 40 months.<sup>42</sup> SPECT/CT was performed in these patients when an extra-thyroidal  $^{131}\text{I}$ -avid site could not be attributed to physiological uptake or to a well-defined metastasis. SPECT/CT contributed to image interpretation of 54 among the 80 ill-defined  $^{131}\text{I}$ -avid foci (68%) in 38 patients (70%), mainly in cervical nodes, pelvic soft tissue and bone. SPECT/CT affected the management of 22 patients (41%). Diagnosis of bone involvement led to radiation therapy in 3 patients. Resectable tumor mass removed at surgery was identified in 3 patients, and unnecessary  $^{131}\text{I}$  treatment was spared after the characterization of physiologic activity in the bowel and in the thymus, in 3 and 13 patients, respectively.<sup>42</sup> In a study of 25 patients with inconclusive WB findings after ablative radioiodine therapy, SPECT/CT improved the anatomical assignment in 17 of evaluable 39 sites (44%), with impact on management in 6/24 (25%) patients.<sup>43</sup> Tharp and coworkers<sup>44</sup> compared  $^{131}\text{I}$ -SPECT/CT to planar imaging data in 71 patients from 2 medical centers. Incremental value of SPECT/CT was documented in 41 of the 71 patients (57%). Major impact on management was observed in 41% of patients, when SPECT/CT optimized localization of  $^{131}\text{I}$  uptake to lymph node metastases versus remnant thyroid tissue, to lung versus mediastinal metastases, and to the skeleton.

Image registration also has been suggested for 3-dimensional absorbed dose calculation before  $^{131}\text{I}$  therapy.<sup>45</sup> In summary, SPECT/CT may help localize increased focal uptake of  $^{131}\text{I}$  and highlight its significance in light of avidity, site and invasion into surrounding tissues, with subsequent impact on patient management.

## Parathyroid Adenoma

The debate regarding the necessity for preoperative localization of a parathyroid adenoma has been ongoing since the Consensus Statement formulated at the National Institute of Health Conference in 1991 on the Diagnosis and Management of Hyperparathyroidism. Bilateral neck exploration, the "orthodox" approach of treatment, is associated with a cure rate of 95% to 98% in the hands of an experienced endocrine surgeon.<sup>46</sup> This approach has gradually been replaced by various minimally invasive surgical procedures in patients with primary hyperparathyroidism caused by a solitary adenoma (accounting for 85% of cases), because these procedures are associated with decreased risk of hypoparathyroidism and of recurrent laryngeal nerve injury, as well as shortening of surgery time and hospitalization.

The limited surgical procedures include unilateral neck exploration with assessment of the ipsilateral parathyroid gland,<sup>47</sup> minimally invasive parathyroidectomy,<sup>48</sup> endoscopic surgery,<sup>49</sup> and video-assisted thoracic surgery for resection of ectopic mediastinal parathyroid glands.<sup>50</sup> Radio-guided surgery can be considered as a completion of preoperative scintigraphic imaging,<sup>51</sup> with contribution of rapid PTH assay to circumvent the need for visualization of all glands.

The new era in surgical approach to hyperparathyroidism has become feasible with the introduction of improved preoperative localization modalities that direct treatment algorithms for the surgical removal of a parathyroid adenoma.

Among the various imaging modalities,  $^{99\text{m}}\text{Tc}$ -MIBI (MIBI) scintigraphy was found to play a major role in the preoperative localization of a parathyroid adenoma, although the documented sensitivity ranges from 39% to 95%.<sup>52,53</sup> Scintigraphy has a high diagnostic accuracy when intense tracer

uptake and retention in a single lesion on delayed images indicate a high probability of a solitary parathyroid adenoma; however, its accuracy decreases in the presence of concomitant MIBI-avid thyroid nodules, previous neck surgery or irradiation, and/or history of familial hyperparathyroidism and multiple endocrine neoplasia.

The combined approach of MIBI and US is considered the diagnostic strategy of choice for noninvasive detection of a parathyroid adenoma localized in the neck, with a sensitivity of 83% for US and 85% for subtraction MIBI and increasing to 94% when using the combined imaging approach.<sup>54</sup> When MIBI and US are concordant, focused parathyroidectomy can be used with a predicted success rate of approximately 95%.<sup>55</sup> In the presence of a mediastinal parathyroid adenoma, CT and MRI have a complementary role, with MIBI and MRI reaching a sensitivity and positive predictive values of 94% and 98%, respectively.<sup>56</sup>

In addition to early and delayed planar MIBI scintigraphy, most authors now favor a wider application of MIBI-SPECT, with a 96% sensitivity, superior to that of planar imaging (79%).<sup>57</sup>

Even MIBI-SPECT, however, may not provide detailed anatomical information and, therefore, coregistration of MIBI and CT has been suggested. Coregistration of separately acquired techniques, using radio-opaque and radioactive markers placed on the patient's skin, improved the localization of an upper mediastinal parathyroid adenoma, with removal by limited median sternotomy,<sup>58</sup> and of a 9-mm ectopic parathyroid adenoma located anterior to the aorta at the level of the carina, with removal via the thoracoscopic approach.<sup>59</sup> In a prospective study of 24 patients, fusion of CT and MIBI images, following the use of a head holder, a vacuum cushion, and radiographic and scintigraphic markers, predicted the localization of solitary adenomas in five of six patients,<sup>60</sup> and was found superior to MIBI-SPECT alone in a prospective study of 24 patients, with a sensitivity of 93% versus 31%, respectively.<sup>61</sup> Coregistration using external markers, however, may be associated with misalignment and cumbersome mathematical processing.

The impact of SPECT/CT initially was described in several case reports and in a few series of patients. SPECT/CT precisely localized 2 and 4 mediastinal parathyroid adenomas, respectively, with facilitation of surgery.<sup>20,62</sup> In a study of 48 patients with primary hyperparathyroidism, SPECT/CT data were compared with those of SPECT-only. SPECT-only imaging identified 89% of the surgically confirmed diseased parathyroid glands, and SPECT/CT changed the diagnosis in one patient (2%) from positive to negative and improved localization in 4 patients (8%). SPECT/CT was particularly helpful in locating 2 ectopic parathyroid adenomas diagnosed in this cohort of patients.<sup>63</sup>

A major impact of SPECT/CT in ectopic parathyroid adenomas was reported in a study of 36 patients with primary hyperparathyroidism who subsequently underwent neck or mediastinal exploration.<sup>64</sup> Of 33 patients with a positive MIBI study, SPECT/CT facilitated the surgical exploration in all 10 ectopic parathyroid adenomas, but only in 4 of 23 cervical adenomas. In the 4 patients with cervical parathyroid adenoma, hybrid images indicated the proximity of the adenoma to the thyroid, trachea, and esophagus, including 3 patients after failed initial surgery and 1 patient with an adenoma localized to the retroesophageal space and nonvisualization of the thyroid gland after thyroidectomy. In all 10 patients with lower neck/mediastinal parathyroid adenomas, SPECT/CT identified its proximity to the trachea, esophagus, thymus, spine, or sternum and optimized the surgical procedure in all of these patients. Among a subgroup of 6 patients scheduled for re-exploration after failed initial surgery, SPECT/CT facilitated the surgical resection of 4 adenomas, including one located in the retro-esophageal space, an adenoma in the left retrotracheal space, one anterior-located adenoma in the neck, and one ectopic "lower" parathyroid adenoma.<sup>64</sup>

In summary, in the majority of patients with primary hyperparathyroidism, planar MIBI scintigraphy facilitates the localization of a PTA in the neck, mainly when the thyroid gland serves as anatomical landmark in the early phase of the study. SPECT improves the sensitivity of MIBI scintigraphy and provides the in-depth information. Coregistered anatomical mapping, however, may help in the localization of deep-seated or ectopic adenomas and may therefore facilitate the surgical intervention in patients with distorted anatomy after neck surgery.

## Summary

Hybrid SPECT/CT devices play an increasing role in imaging of endocrine tumors, for precise functional characterization and staging of disease during

initial workup, for early detection of tumor recurrence after treatment, especially in the presence of inconclusive anatomical studies, and for accurate dosimetric estimation for targeted radionuclide therapy. SPECT/CT provides better definition of organs and tumors that take up the radiotracers and of their precise relationship with adjacent structures, defines the functional significance of CT lesions and improves the specificity of SPECT by excluding disease at sites of physiological uptake or excretion.

## References

- Bocher M, Balan A, Krausz Y, et al: Gamma camera-mounted anatomical X-ray tomography: technology, system characteristics and first images. *Eur J Nucl Med* 27:619-627, 2000
- von Schulthess GK, Pelc NJ: Integrated-modality imaging: the best of both worlds. *Acad Radiol* 9:1241-1244, 2002
- Keidar Z, Israel O, Krausz Y: SPECT/CT in tumor imaging: technical aspects and clinical applications. *Semin Nucl Med* 33:205-218, 2003
- Schillaci O: Hybrid SPECT/CT: a new era for SPECT imaging? *Eur J Nucl Med Mol Imaging* 32:521-524, 2005
- van der Lely AJ, de Herder WW, Krenning EP, et al: Octreoscan radio-receptor imaging. *Endocrine* 20:307-311, 2003
- Noone TC, Hosey J, Firat Z, et al: Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. *Best Pract Res Clin Endocrinol Metab* 19:195-211, 2005
- Krenning EP, Kwekkeboom DJ, Bakker WH, et al: Somatostatin receptor scintigraphy with [<sup>111</sup>In-DTPA-D-Phe1]- and [<sup>123</sup>I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 20:716-731, 1993
- Krausz Y, Bar-Ziv J, de Jong RB, et al: Somatostatin receptor scintigraphy in the management of gastroenteropancreatic tumors. *Amer J Gastroenterol* 93:66-70, 1998
- Bombardieri E, Maccauro M, De Deckere E, et al: 2001 Nuclear medicine imaging of neuroendocrine tumours. *Ann Oncol* 12:S51-S61, 2001 (suppl 2)
- Kwekkeboom DJ, Krenning EP: Somatostatin receptor imaging. *Semin Nucl Med* 32:84-91, 2002
- Otte A, Mueller-Brand J, Dellas S, et al: Yttrium-90-labelled somatostatin-analog for cancer treatment. *Lancet* 351:417-418, 1998
- De Jong M, Breeman WA, Bernard HF, et al: Therapy of neuroendocrine tumors with radiolabeled somatostatin-analogs. *Q J Nucl Med* 43:356-366, 1999
- De Jong M, Valkema R, Jamar F, et al: Somatostatin receptor-targeted radionuclide therapy of tumors: preclinical and clinical findings. *Semin Nucl Med* 32:133-140, 2002
- Lebtahi R, Cadiot G, Sarda L, et al: Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. *J Nucl Med* 38:853-858, 1997
- Teramani B, Gibril F, Reynolds JC, et al: Value of somatostatin receptor scintigraphy: a prospective study in gastrinoma of its effect on clinical management. *Gastroenterology* 112:335-347, 1997
- de Jong M, Breeman WA, Valkema R, et al: Combination radionuclide therapy using <sup>177</sup>Lu- and <sup>90</sup>Y-labeled somatostatin analogs. *J Nucl Med* 46:135-175, 2005 (suppl 1)
- Gibril F, Reynolds JC, Chen CC, et al: Specificity of somatostatin receptor scintigraphy: a prospective study and effects of false-positive localizations on management in patients with gastrinomas. *J Nucl Med* 40:539-553, 1999
- Forster GJ, Laumann C, Nickel O, et al: SPET/CT image co-registration in the abdomen with a simple and cost-effective tool. *Eur J Nucl Med Mol Imaging* 30:32-39, 2003
- Perault C, Schwartz C, Wampach H, et al: Thoracic and abdominal SPECT-CT image fusion without external markers in endocrine carcinomas. *J Nucl Med* 38:1234-1242, 1997
- Even-Sapir E, Keidar Z, Sachs J, et al: The new technology of combined transmission and emission tomography in evaluation of endocrine neoplasms. *J Nucl Med* 42:998-1004, 2001
- Krausz Y, Keidar Z, Kogan I, et al: SPECT/CT hybrid imaging with <sup>111</sup>In-Pentetreotide in assessment of Neuroendocrine Tumors. *Clin Endocrinol* 59:565-573, 2003
- Pfannenber AC, Eschmann SM, Horger M, et al: Benefit of anatomical-functional image fusion in the diagnostic work-up of neuroendocrine neoplasms. *Eur J Nucl Med Mol Imaging* 30:835-843, 2003
- Schillaci O: Functional-anatomical image fusion in neuroendocrine tumors. *Cancer Biother Radiopharm* 19:129-134, 2004
- Pacak K, Linehan WM, Eisenhofer G, et al: Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med* 134:315-329, 2001
- Freitas JE: Adrenal cortical and medullary imaging. *Semin Nucl Med* 25:235-250, 1995
- Mozley PD, Kim CK, Mohsin J, et al: The efficacy of iodine-123-MIBG as a screening test for pheochromocytoma. *J Nucl Med* 35:1138-1144, 1994
- Fujita A, Hyodoh H, Kawamura Y, et al: Use of fusion images of <sup>131</sup>I metaiodobenzylguanidine, SPECT, and magnetic resonance studies to identify a malignant pheochromocytoma. *Clin Nucl Med* 25:440-442, 2000
- Ozer S, Dobrozemsky G, Kienast O, et al: Value of combined XCT/SPECT technology for avoiding false positive planar <sup>123</sup>I-MIBG scintigraphy. *Nuklearmedizin* 43:164-170, 2004
- Bar-Shalom R, Keidar Z, Krausz Y: Prospective image fusion: the role of SPECT/CT and PET/CT, in Henkin RE, Bova D, Dillehay GL et al (eds): *Nuclear Medicine* (ed 2). St. Louis, CV Mosby, 2006, pp 1527-1544
- Klein M, Kopelewitz B, Krausz Y, et al: Contribution of SPECT/CT to bridging between MIBG scan and diagnostic CT. *J Nucl Med* 45:361, 2004 (abstr)
- Schillaci O, Danieli R, Manni C, et al: Is SPECT/CT with a hybrid camera useful to improve scintigraphic imaging interpretation? *Nucl Med Commun* 25:705-710, 2004
- Biasotti S, Garaventa A, Villavecchia GP, et al: False-negative metaiodobenzylguanidine scintigraphy at diagnosis of neuroblastoma. *Med Pediatr Oncol* 2000; 35:153-155, 2000
- Leung A, Shapiro B, Hattner R, et al: Specificity of radioiodinated MIBG for neural crest tumors in childhood. *J Nucl Med* 38:1352-1357, 1997
- Rufini V, Fisher GA, Shulkin BL, et al: Iodine-123-MIBG imaging of neuroblastoma: utility of SPECT and delayed imaging. *J Nucl Med* 37:1464-1468, 1996
- Gelfand MJ, Elgazzar AH, Kriss VM, et al: Iodine-123-MIBG SPECT versus planar imaging in children with neural crest tumors. *J Nucl Med* 35:1753-1757, 1994
- Bonnin F, Lumbroso J, Tenenbaum F, et al: Refining interpretation of MIBG scans in children. *J Nucl Med* 35:803-810, 1994
- Tang HR, Da Silva AJ, Matthey KK, et al: Neuroblastoma imaging using a combined CT scanner-scintillation camera and <sup>131</sup>I-MIBG. *J Nucl Med* 42:237-247, 2001
- Diehl M, Risse JH, Brandt-Mainz K, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography in medullary thyroid cancer: results of a multicentre study. *Eur J Nucl Med* 28:1671-1676, 2001
- Shapiro B, Rufini V, Jarwan A, et al: Artifacts, anatomical and physiological variants, and unrelated diseases that might cause false-positive whole-body <sup>131</sup>I scans in patients with thyroid cancer. *Semin Nucl Med* 30:115-132, 2000
- Leitha T, Staudenherz A: Frequency of diagnostic dilemmas in <sup>131</sup>I whole body scanning. *Nuklearmedizin* 42:55-62, 2003
- Yamamoto Y, Nishiyama Y, Monden T, et al: Clinical Usefulness of Fusion of <sup>131</sup>I SPECT and CT images in patients with differentiated thyroid carcinoma. *J Nucl Med* 44:1905-1910, 2003
- Krausz Y, Klein M, Uzieli B, et al: Impact of SPECT/CT on assessment of <sup>131</sup>I-avid sites in differentiated thyroid cancer. *J Nucl Med* 45:349, 2004 (abstr)
- Ruf J, Lehmkühl L, Bertram H, et al: Impact of SPECT and integrated low-dose CT after radioiodine therapy on the management of patients with thyroid carcinoma. *Nucl Med Commun* 25:1177-1182, 2004
- Tharp K, Israel O, Hausmann J, et al: Impact of <sup>131</sup>I-SPECT/CT images obtained with an integrated system in the follow-up of patients with thyroid carcinoma. *Eur J Nucl Med Mol Imaging* 31:1435-1442, 2004
- Ljungberg M, Sjogreen K, Liu X, et al: A 3-dimensional absorbed dose calculation method based on quantitative SPECT for radionuclide therapy: evaluation for (<sup>131</sup>I) using Monte Carlo simulation. *J Nucl Med* 43:1101-1109, 2002

46. Clark OH: How should patients with primary hyperparathyroidism be treated? *J Clin Endocrinol Metab* 88:3011-3014, 2003
47. Bergenfelz A, Lindblom P, Tibblin S, et al: Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. *Ann Surg* 236:543-551, 2002
48. van Vroonhoven TJ, van Dalen A: Successful minimally invasive surgery in primary hyperparathyroidism after combined preoperative ultrasound and computed tomography imaging. *J Intern Med* 243:581-587, 1998
49. Ohshima A, Simizu S, Okido M, et al: Endoscopic neck surgery: current status for thyroid and parathyroid diseases. *Biomed Pharmacother* 56: 48s-52s, 2002 (suppl 1)
50. Medrano C, Hazelrigg SR, Landreneau RJ, et al: Thoracoscopic resection of ectopic parathyroid glands. *Ann Thorac Surg* 69:221-223, 2000
51. Mariani G, Gulec SA, Rubello D, et al: Preoperative localization and radioguided parathyroid surgery. *J Nucl Med* 44:1443-1458, 2003
52. Denham DW, Norman J: Cost-effectiveness of preoperative sestamibi scan for primary hyperparathyroidism is dependent solely upon the surgeon's choice of operative procedure. *J Am Coll Surg* 186:293-305, 1998
53. Gotthardt M, Lohmann B, Behr TM, et al: Clinical value of parathyroid scintigraphy with technetium-99m methoxyisobutylisonitrile: discrepancies in clinical data and a systematic metaanalysis of the literature. *World J Surg* 28:100-107, 2004
54. Lumachi F, Ermani M, Basso S, et al: Localization of parathyroid tumours in the minimally invasive era: which technique should be chosen? Population-based analysis of 253 patients undergoing parathyroidectomy and factors affecting parathyroid gland detection. *Endocr Relat Cancer* 8:63-69, 2001
55. Arici C, Cheah WK, Ituarte PH, et al: Can localization studies be used to direct focused parathyroid operations? *Surgery* 129:720-729, 2001
56. Gotway MB, Reddy GP, Webb WR, et al: Comparison between MR imaging and 99mTc-MIBI scintigraphy in the evaluation of recurrent or persistent hyperparathyroidism. *Radiology* 218:783-790, 2001
57. 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* 44:904-908, 2003
58. Rubello D, Casara D, Fiore D, et al: An ectopic mediastinal parathyroid adenoma accurately located by a single-day imaging protocol of Tc-99m pertechnetate-MIBI subtraction scintigraphy and MIBI-SPECT-computed tomographic image fusion. *Clin Nucl Med* 27:186-190, 2002
59. Ng P, Lenzo NP, McCarthy MC, et al: Ectopic parathyroid adenoma localised with sestamibi SPECT and image-fused computed tomography. *Med J Aust* 179:485-487, 2003
60. Profanter C, Prommegger R, Gabriel M, et al: Computed axial tomography-MIBI image fusion for preoperative localization in primary hyperparathyroidism. *Am J Surg* 187:383-387, 2004
61. Profanter C, Wetscher GJ, Gabriel M, et al: CT-MIBI image fusion: a new preoperative localization technique for primary, recurrent, and persistent hyperparathyroidism. *Surgery* 135:157-162, 2004
62. Kaczirek K, Prager G, Kienast O, et al: Combined transmission and 99mTc-sestamibi emission tomography for localization of mediastinal parathyroid glands. *Nuklearmedizin* 42:220-223, 2003
63. Gayed IW, Kim EE, Broussard WF, et al: The value of 99mTc-sestamibi SPECT/CT over conventional SPECT in the evaluation of parathyroid adenomas or hyperplasia. *J Nucl Med* 46:248-252, 2005
64. Krausz Y, Bettman L, Guralnik L, et al: Tc99m-MIBI SPECT/CT in Primary Hyperparathyroidism. *World J Surg* 30:76-83, 2006