SPECT/CT in Tumor Imaging: Technical Aspects and Clinical Applications

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Diagnostic imaging has gained a major role in the management of patients with cancer and has made a further step forward with the introduction of fusion techniques into the field. This technology provides hybrid images of two independent modalities, a functional scintigraphic technique and an anatomical procedure, yielding a superior imaging study. Scintigraphy is based on the use of single photon or positron emitting tracers providing a description of function or processes, whereas computed tomography (CT), ultrasound, or magnetic resonance imaging (MRI) depict the precise localization and type of morphological changes that have occurred in the lesions. Initial attempts to coregister the functional and anatomical information following acquisition of the two imaging modalities on separate machines, in different sessions, failed to disclose the proper alignment with precise coregistration, in particular for non-head studies, and were associated with patient preparation and mathematical modeling that were too cumbersome to be used on a routine basis. The recent introduction of a hybrid imaging device containing a low dose CT system and a gamma camera on a single gantry enabled the sequential acquisition of the two imaging modalities, with subsequent merging of data into a composite image display. These hybrid studies have led to a revolution in the field of imaging, with highly accurate localization of tumor sites, assessment of invasion into surrounding tissues, and characterization of their functional status.

OUTCOME OF PATIENTS with various tumors is affected by early detection of the primary tumor, correct staging of the disease, and adequate follow-up of treatment. Localization of the primary tumor and evaluation of disease extent requires precise localization of the tumor sites. These goals may be achieved by anatomical and functional imaging modalities, which play a complementary role in the clinical management. Anatomical imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI), provide accurate morphological information necessary for tumor localization and detection of structural abnormalities, but do not reflect the functional or metabolic activity of the tumor. During follow-up, these studies are also affected by prior surgical procedures or the presence of necrosis and fibrosis following chemo- or radiotherapy. Highly sensitive scintigraphic procedures lack the structural delineation of the pathological processes and function that they detect. Therefore, these techniques have complementary roles, which, through coregistration, may provide answers to complex medical issues.

The registration process is based on correct alignment of point sets and data provided by the different imaging modalities.[1,2] Side-by-side comparison of unregistered or poorly registered, separately performed studies depends on the interpreter's memory and his or her ability to reorient the images. This method has proven sufficient for a general comparison of two images, but is inaccurate for small lesions. In contrast, coregistration of sequential studies of the two imaging modalities on a hybrid gamma camera/CT scanner may lead to improved interpretation accuracy of both tests. The technique helps in localization of tumor sites, definition of their confinement to certain organs or invasion into adjacent tissues, and characterization of the functional significance of CT-detected lesions.

TECHNICAL ASPECTS FOR SPECT/CT IN ONCOLOGY

Fusion methods of separately performed functional and structural imaging data are usually based on extrinsic or intrinsic body markers. External fiducial markers are attached to the body surface and may provide the required transformation when in the same location, if the patient is positioned identically for both studies. External markers, however, have been found impractical and cumbersome for routine use because of the need for complex patient preparation and prospective planning because most studies are performed on different days, in different geographic locations, and by using different stretchers. Furthermore, measurements based on surface points do not, as a rule, extrapolate well for application to points in the interior of the body.[3] Internal anatomical landmarks eliminate the need for external fiducial markers and patient preparation. Reliable identification and accurate localization of these landmarks is, however, not always possible and requires considerable operator skill, with automatic detection being difficult. These drawbacks are more prominent in nuclear medicine studies, which, as a rule, suffer from relatively low resolution.[3] Inaccurate registration of separately acquired data may be due to differences in patient positioning between studies, as well as to differences in internal organ

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location, position, filling status, and volume at the time of imaging.

Sequential acquisition of nuclear medicine and CT data during a single imaging session can potentially eliminate many of the errors described with coregistration of independently performed studies and excludes the need for internal or external fiducial markers and complicated mathematical registration algorithms.[4-6] One of the earliest developed dual-modality devices consisted of a scanner with combined anatomical (CT) and functional (single photon emission computed tomography [SPECT]) capabilities,[7,8] that used high-purity germanium as the detector for both modalities. The data obtained from the x-ray CT images were also used to generate attenuation maps for correction of the SPECT data. The device allowed the performance of simultaneous emission-transmission acquisitions.

This concept of a single device capable of performing both functional and anatomical imaging further led to the development of novel hybrid imaging systems with a significant improvement in the accuracy of attenuation correction and coregistration. These systems allow for sequential acquisition of anatomic and functional data by combined transmission (using CT) and emission (using either positron emission tomography (PET), camera based coincidence, or SPECT) acquisition during a single session.

One of these new hybrid-imaging systems, a SPECT/CT device, combines a dual head sodium iodide crystal gamma camera and a low energy CT, mounted on a common gantry (Millennium VG™ & HAWKEYE™, GE Medical Systems, Milwaukee, Wisconsin).[5,6] The combination of these two modalities facilitates the precise anatomical localization of radiopharmaceutical uptake and the subsequent characterization of its clinical significance. In addition, attenuation correction results in improved image quality for both coincidence positron and SPECT imaging.

The emission part of the study is acquired according to the radiopharmaceutical in use. SPECT is performed with a 360° rotation, consisting of 60 projections 6° apart in a matrix of 128 × 128. Reconstruction is performed by a back projection method that uses a Metz filter or iteratively by using the ordered subsets expectation maximization (OSEM) technique. Images are obtained in the transaxial, sagittal, and coronal planes.

The attenuation is measured by using an x-ray imaging system, which rotates around the patient to acquire cross-sectional data. Because the gantry of the gamma camera is used to support the x-ray tube and detector, the rotation speed is limited to below 2.8 rpm. The x-ray tube is a fixed anode, oil cooled tube, operated at 140 kVp, 2.5 mA. X-rays are generated on a tungsten target and a beam filter of 0.5 mm copper is added to reduce the patient dose from soft x-rays. The fan beam formed by the x-ray tube on the detectors allows the measurement of patient attenuation along discrete paths. At the center of rotation, the beam paths from adjacent x-ray detectors spaced at approximately 1.2 mm, allowing the reconstruction of high-resolution transaxial slices. During an x-ray scan, data are gathered continuously by the x-ray detector as the gantry rotates through an angle of 220° to acquire the data necessary to reconstruct one transaxial slice. A "half scan" acquisition acquired over 220° takes a minimum of 13 s acquisition time for one slice. Multiple slices are obtained by moving the table by one step before acquiring the next slice. The slice step is defined in the transmission acquisition protocol and is, as a rule, equal to the slice width of 10 mm.

Factors that influence the dose delivered to the patient from the CT component of the device include the x-ray voltage, which determines the energy of the radiation; the x-ray current, which determines the rate of x-ray production, the x-ray scan time, which determines the duration of exposure; and the slice collimation, which restricts the exposure to a certain region of the patient. By using appropriate filtration, collimation, and x-ray detectors, radiation doses to the patient are minimized to the lowest possible level. Based on phantom measurements, when the x-ray tube operates at its working power of 140 kV and 2.5 mA, a patient dose for a typical scan ranges from 1.3 mGy at the center to 5 mGy at the surface of the body. These dosimetry values are significantly smaller than the dose of 20 mGy delivered to the patient by a typical diagnostic body CT.

The transmission measurements taken through the patient are corrected and logged to produce attenuation measurements, which are reconstructed by using filtered back-projection to give cross-sectional attenuation images in which each pixel represents the attenuation of the imaged tissue. The attenuation is represented on the expanded scale used in CT imaging where the CT number of a particular material, CT [material], is computed with reference to the linear attenuation coefficients of water and air:

$$\text{CT [material]} = \frac{1000 \times (\mu[\text{material}] - \mu[\text{water}])}{\mu[\text{water}] - \mu[\text{air}]}$$

The linear attenuation value μ [material] is dependent on the density and atomic number of the material, as well as on the effective energy of the x-ray beam. On the CT scale, water is defined to have a CT number of 0, and air has a CT number of −1000. Muscle, fat, lung and bone have CT numbers around 40, −100, −700, and 1000 to 2000, respectively. To correct nuclear medicine data for attenuation, attenuation coefficients are derived from CT data as follows: for CT values less than 0, materials are assumed to have an energy dependency similar to water and for CT values above 0 they are treated as having an energy dependency of a mixture of bone and water.

The x-ray and nuclear medicine data are acquired, stored and processed on the acquisition station. X-ray images are reconstructed, and transmission data are integrated into the nuclear medicine database. At the end of the acquisition and reconstruction process, the nuclear medicine and CT data sets can be reviewed both separately and as fused images in three tomographic plane slices.

The structural information obtained from the CT data was also found to improve the quantification of SPECT measured activity concentration by using a phantom model study.[9] Further assessment of the contribution of this modality to SPECT quantification accuracy is needed.

CLINICAL APPLICATIONS OF SPECT/CT IN ONCOLOGY

SPECT/CT in Differentiated Thyroid Carcinoma

Differentiated thyroid cancer (DTC) is associated with an excellent prognosis, but the risk of local recurrence and distant metastases decades after initial therapy demands continuous life-long monitoring of these patients.[10] Staging and follow-up are performed by using radioiodine whole body (WB) scintigraphy and serum thyroglobulin measurements. The scan is based on uptake of radioiodine occurring via the sodium iodide symporter and on organification in the thyroid remnant and in cancer cells.[11,12] The high contrast between the lesion and surrounding tissues enables the identification of recurrent disease before visualization by other techniques, with an overall sensitivity of 70 to 80% and an overall specificity of 90 to 100%. The scintigraphic data have an impact on patient management, with surgical removal of localized disease when feasible, and treatment with high dose of I131, when multiple I131-avid foci are visualized.

Occasionally, planar WB scans and even SPECT images fail to precisely characterize the nature and location of I131-avid foci because of the ill-defined body contour. Localization of the focal lesions may, therefore, benefit from registration of SPECT and CT data by using either an external fiduciary band and three-dimensional surface fitting[13] or fused anatomical and functional images, as obtained by SPECT/CT.[5] The hybrid SPECT/CT images may provide precise delineation of the pathological focus (Fig 1) when confined to one organ or when invading adjacent structures.[14-16] Such attempts to define the precise extent of disease are of critical significance because diagnosis of limited disease indicates the need for curative surgery. Complete resection of metastases confined to the bone in young patients, when feasible, may lead to improved survival.[17] In contrast, soft tissue masses invading bony structures are non-resectable and require the administration of therapeutic radioiodine doses or external irradiation, with additional embolization being suggested in the presence of vertebral involvement.[18]

SPECT/CT also improves the specificity of the WB scan that may be affected by artifacts, anatomical variants and tracer uptake in non-thyroidal diseases.[19] Hybrid images are capable of differentiating pathological radioiodine uptake from physiological tracer uptake in normal tissues or excretion into the bowel lumen.[15,16] Furthermore, they can define non-thyroidal I131-avid conditions, such as ectopic gastric mucosa, lead to CT-guided biopsy of an I131-avid ovarian mass, or may spare further diagnostic procedures or I131 treatment when identifying an anterior mediastinal mass as hyperplasic thymus.[20,21]

SPECT/CT fusion of functional and morphological data, therefore, helps to localize the increased focal uptake of I131 and to analyze its significance in light of avidity, site, and invasion into surrounding tissues, with impact on patient management.

SPECT/CT in Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) accounts for 3 to 10% of thyroid tumors and is frequently associated with cervical and mediastinal lymph node involvement at the time of diagnosis. Surgery is the first line of treatment and may be curative even in the presence of lymph node metastases.[22] Multiple imaging techniques have been developed for early detection of minimal residual and metastatic disease in patients with MTC. MRI facilitates the planning of surgery for macroscopic metastases.[23] Occult MTC is best localized by selective venous catheterization,[24] although several radiopharmaceuticals, with limited sensitivity, have been suggested over the years, such as Tc99m-MIBI and radiolabeled antiCEA and anticalcitonin antibodies.

The role of somatostatin receptor scintigraphy (SRS) in MTC, while using In111- pentetreotide, is controversial because of considerable heterogeneity in receptor expression, both in different foci and within different areas of the same tumor site, and also because of tumor dedifferentiation.[25,26] Precise localization of tumor sites before surgery may improve with the use of coregistration of SPECT with CT. Coregistration may also detect the invasion of the tumor mass into an adjacent bone, sparing unnecessary surgery. Perault et al described coregistration of separately performed SRS and CT in three patients with MTC by using skeletal structures observed on an additionally performed Tc99m-methylene-diphosphonate (MDP) bone scan as internal markers during dual phase acquisition with In111-pentetreotide.[27] The described fusion technique enabled the localization of tumor sites that were not visualized on CT, defined the pathological significance of suspicious findings, and contributed to patient management by biopsy guidance

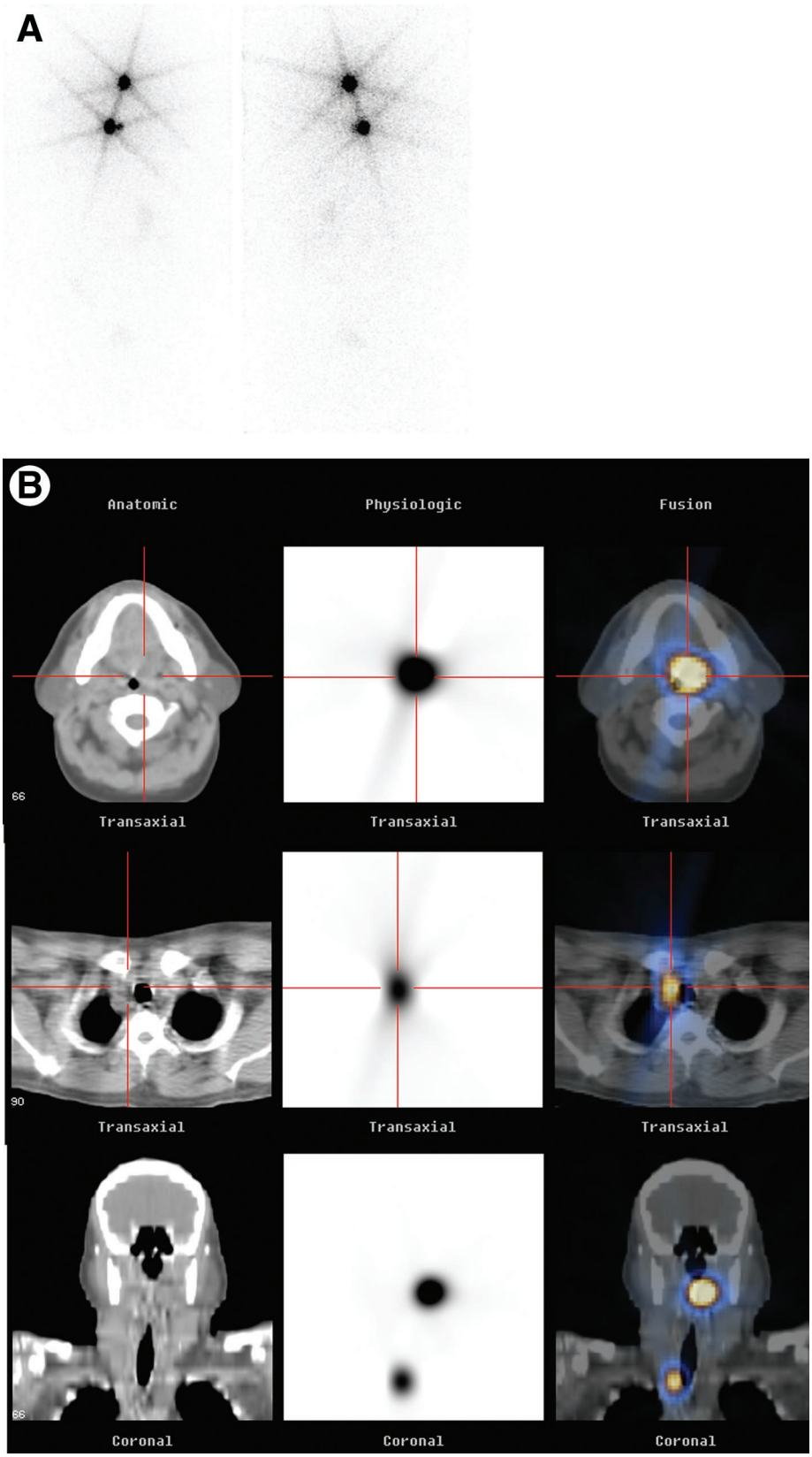

Fig 1. SPECT/CT for precise characterization of abnormal Iodine-131 uptake in a patient with papillary thyroid cancer after subtotal thyroidectomy. (A) Planar WB Iodine-131 scintigraphy (anterior view–left, posterior–right) shows two foci of increased tracer uptake in the neck, with significant scatter masking the body contours. (B) Iodine-131 SPECT/CT (CT–left column; SPECT–center; Fusion–right; upper transaxial–top row, lower transaxial–mid row, and coronal–bottom row), shows the precise localization of the proximal lesion in an enlarged lymph node at the left aspect of the base of the tongue and the lower site of uptake in remnant tissue of the right lobe of the thyroid. Surgical re-exploration confirmed metastatic lymphadenopathy at the base of the tongue.

or refinement of surgical procedure.[27] This protocol, however, requires injection of an additional radionuclide and is impractical on a routine basis.

Other radiopharmaceuticals have been suggested for the evaluation of patients with MTC, showing a superior sensitivity to SRS. Tc99m-Pentavalent-dimercapto-succinic acid (DMSA) may be used in radio-guided surgery, [^{18}F]-fluorodeoxyglucose (FDG)-PET appears to be taken up by this type of tumor, as do radiolabeled cholecystokinin-B/Gastrin receptor-targeting peptides, with potential future therapeutic implications.[28-33] The role of hybrid imaging while using these tracers remains to be further explored.

SPECT/CT in Neural Crest Tumors

Pheochromocytoma and neuroblastoma are the most common tumors originating in the adrenergic nervous system. Pheochromocytoma mostly resides in the adrenal gland. However, 10% of all adult cases and 30% of all pediatric cases have extra-adrenal lesions, 10% of tumors are bilateral, and 10% are malignant, with high prevalence of metastatic disease.[34]

At diagnosis, adrenal pheochromocytomas are best visualized on CT or MRI, which serve as its primary imaging modalities, with an overall sensitivity of 100%.[35] Radiolabeled meta-iodobenzylguanidine (MIBG) scintigraphy contributes to the functional characterization of equivocal 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%.[36] When scintigraphy is used as the initial imaging modality, a detailed anatomical evaluation of MIBG-avid foci is required[37] and may be performed by using fusion of labeled MIBG SPECT images with MRI[38] or hybrid SPECT/CT[14,39]

MIBG scintigraphy plays its major role in the early detection of recurrent disease and in the triage of relapsed disease that may be amenable to surgical resection or that should be treated with therapeutic doses of I131-MIBG when multiple MIBG-avid tumor sites are observed. Hybrid imaging may help to characterize a residual viable mass detected on anatomical imaging, similar to findings reported when using FDG with the same camera-based PET/CT device.[6,40]

Positive MIBG scintigraphy shows intraadrenal, extra-adrenal, and malignant pheochromocytoma as intense focal areas of MIBG uptake at 24 through 72 hr and occasionally as unilateral asymmetric uptake, less than or equal to the liver, in 10% and 33% of all cases, respectively.[37,41] Findings can then be verified with an anatomic lesion on CT or on the fused SPECT/CT images. These hybrid images can also differentiate MIBG uptake in a hyperplasic adrenal gland following contralateral adrenalectomy from retroperitoneal recurrence, especially when tumors tend to be bilateral in the clinical settings of multiple endocrine neoplasia (MEN) type 2 and Von Hipple-Lindau disease. Correlative imaging of focal tracer uptake with high resolution CT or hybrid images may also 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.[39] In the absence of corresponding physiological or pathological patterns, other functional imaging modalities, such as C-11 hydroxyephedrine, F18-fluorodopa, and F18-fluorodopamine, or follow-up MIBG scans have been indicated as a possible solution to complex diagnostic problems.[42-44]

Neuroblastoma (NB) comprises 10% of all pediatric tumors and accounts for 15% of all cancer deaths in children.[45] The disease 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 the time of diagnosis. Prognosis is affected by age, site of primary tumor, and surgical resectability.[46] Low-stage NB is treated by surgery, with an attempt to remove the entire primary tumor, as well as any residual disease at the time of a second-look procedure. Advanced stage disease is treated by multiple-agent chemotherapy and by administration of high therapeutic doses of I131-MIBG.

The wide spectrum of presentation and the potential involvement of many body systems require the contribution of multi-modality imaging to improve overall diagnosis of NB. CT and MRI are used for initial imaging and to provide detailed information on the anatomical relationship of the tumor to the surrounding structures, which is essential for determination of tumor resectability and the extent of surgical resection. MIBG has an overall sensitivity of 87% and specificity of 94 to 96% for NB.[47] At diagnosis, a positive scan may establish the diagnosis of NB in a child presenting with a tumor of unknown origin, mainly when inaccessible to biopsy. MIBG may also improve the staging of disease, detecting lesions in the bone (with a sensitivity of 91 to 97%), in the soft tissues, and in the bone marrow. MIBG scan also reflects the prognosis of the patient and its response to therapy; a poor outcome has been associated with MIBG-positive scans in stage IV patients older than 1 yr at presentation and also when the scan remains positive after induction chemotherapy.[48,49] MIBG scintigraphy is particularly sensitive for detection of recurrence after treatment, and may be used as the tracer for radio-guided surgery when re-excision of the tumor is indicated, but identification of the exact tumor location may be difficult because of altered anatomy.[50] Delayed 48-hr planar scanning may occasionally depict more lesions than 24-hr imaging, but it may also miss lesions with rapid washout. SPECT imaging may improve lesion detectability and location, although it is controversial whether significantly more lesions can be detected with SPECT than with planar images.[51,52]

Combined functional and anatomic imaging that uses the hybrid SPECT/CT system may provide a better localization of tumor deposits. Fused imaging at 24 hr after tracer injection may also clarify the significance of increased focal uptake, improve the delineation of physiologic diffuse or linear intraluminal bowel activity, and therefore alleviate the need for further delayed imaging with its associated decrease in sensitivity. SPECT/CT may also improve the detection of bone and bone marrow involvement, both at diagnosis and at follow-up. It may also help characterize a tumor recurrence close to the heart or liver, organs taking up MIBG physiologically, or the increased uptake in an adrenal gland after prior contralateral adrenalectomy. In pediatric patients, SPECT/CT may also help clarify the diffuse heterogeneous physiologic uptake in the right heart that may be misinterpreted as a malignant uptake in paramedian mediastinal tumor or sternal and vertebral metastases. SPECT/CT may also 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.[53] False-negative MIBG studies are caused by limitations in spatial resolution, tumor heterogeneity, and rapid washout of MIBG from the storage pool or poor uptake following chemo- or radiotherapy. When the MIBG scan is negative, SPECT/CT is of no additional consequence, but the visualization of a mass on CT with absence of MIBG-avidity may exclude residual active disease.

SPECT/CT may also be of potential clinical significance as a diagnostic scan preceding treatment of patients with residual, recurrent, or progressive NB with high therapeutic doses of I131-MIBG.[54] It can improve quantification of the radiation dosimetry to the tumor, with calculation of the mean activity concentration in each tumor site, while estimating the coregistered CT tumor volume of interest.[55]

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.

SPECT/CT in Neuroendocrine Tumors of the Gastrointestinal Tract

Neuroendocrine (NE) tumors of the gastrointestinal tract include carcinoid and islet cell tumors, for which surgery is the treatment of choice. Detection of tumor sites is critical for optimal surgical treatment planning, but localization of lesions may be difficult because of their small diameter and their lack of anatomical delineation.[56] Detection rates of radiological procedures range from 13% to 85%, depending on the type, site and size of the tumor and on the imaging protocol used.[57] Diagnosis, staging, and follow-up have advanced considerably with the advent of SRS when using In111-labeled pentetreotide. This modality, with a reported sensitivity of 82%-95%, can successfully detect in 30 to 50% of various NE tumors additional metastases not visualized on conventional imaging.[58,59] It improves the localization of primary occult tumors, staging, and early detection of recurrence.[60] SRS facilitates the detection of receptor-dense microscopic foci during radio-guided surgery and determines the completeness of the surgical procedure, both at initial diagnosis and at follow-up. It identifies the receptor-status of metastases for octreotide treatment[61-63] or for targeted radiotherapy.[64-66] As previously reported, SRS induced a change in classification of 24% and in surgical strategy in 25% of patients with gastroenteropancreatic (GEP) tumors[67] and changed the patient management in 47% of patients with gastrinomas.[68]

Despite the high sensitivity and adequate specificity of SRS in the detection of various tumors, the technique is limited by the lack of precise anatomic localization and often requires correlation with high-resolution anatomic imaging modalities.[67,69] When SRS is negative, SPECT/CT is of no additional value, except for verification of receptor density in a tumor visualized on CT. Improved sensitivity and resolution may be obtained with a positron emitting agent bound to octreotide, both for detection of smaller tumors and quantification of tumor uptake.[70]

The overall specificity of SRS, around 50%, may be affected by tracer uptake in physiological sites or benign conditions. False-positive interpretations may be caused by the receptor status of normal organs, such as the pituitary gland, thyroid, liver, and spleen, or by physiological excretion of the tracer via the kidneys or the bowel. Hepatobiliary excretion, accounting for 2% clearance of the administered dose, may lead to occasional visualization of the gallbladder, with false interpretation as a hepatic metastasis.[71] SPECT/CT may differentiate physiological sites from tumor uptake, sparing patient re-scheduling. SPECT/CT may also improve image interpretation when tracer uptake occurs in benign processes, such as recent surgery or colostomy, increased thyroid uptake in Graves' disease, accessory spleen, renal parapelvic cyst, breast disease, and granulomatous lung disease.[61,72] SRS fusion with CT results in a specificity of 86%, positive predictive value of 85%, and a change in management in 3 to 14% of patients.[72,73] Hybrid imaging using SPECT/CT can define the precise organ involved, determine the presence or absence of invasion into surrounding tissues, and has been previously reported to have an impact on patient management in 5 of 10 patients with NE tumors.[14] SRS SPECT/CT may also help in the choice of the appropriate treatment modality, such as chemotherapy, surgery, embolization, or liver transplant.[74-76] When disease is confined to a single organ, such as the liver, a localized mode of organ-specific therapy is suggested.[14] When soft tissue tumor has invaded an adjacent bone, surgery is inadvis-

able. In extensive, unresectable disease, systemic therapy is required (Fig 2).

SPECT/CT in Lymphoma

Lymphoma is a treatable malignancy, with high rates of cure and prolonged disease-free survival. Successful, optimized therapy tailored to the individual patient is based on accurate prognostic data and on correct staging. Gallium67-scintigraphy (GS) provides information of clinical significance to management of the individual lymphoma patient and has, therefore, been considered until recently the modality of choice for functional assessment of this tumor. Although inferior to CT in the initial staging, GS is unique for early detection and discrimination of viable lymphoma from a residual fibrotic or necrotic nonmalignant mass.[77,78] GS is of clinical value after initiating therapy in defining complete response and in early detection of relapse.[77–80] GS has also proven to be a good predictor of long-term prognosis and of patient stratification in both HD and NHL.[81-86]

GS offers, however, a "loaded" image. Interpretation of GS is difficult and is often impaired by numerous areas of tracer uptake related to its physiologic biodistribution and to various benign processes unrelated to lymphoma. Healthy, normal tissues, such as the liver, bone, bone marrow, and spleen, take up Ga-67, even though the kidneys and colon are its main excretory pathways. Benign processes, such as inflammation, infection, lactating breast, recent surgical scar, hyperplasic thymus, and benign parahilar lymph nodes, also show Ga67-avidity.[87,88] Coregistration and hybrid SPECT/CT imaging, by precisely localizing Ga67-uptake, has the potential to improve lymphoma lesion detectability and to characterize physiologic, benign, or equivocal lesions. Coregistration of Ga67-SPECT with CT or MRI has been used for exact definition of nonspecific Ga67-uptake in the hilar region and for identification of a residual retrosternal tumor in the anterior mediastinum masked by normal bone uptake.[89] Lymphomatous lesions located in the bone could be discriminated from soft tissue involvement adjacent to skeletal structures and have enabled the differentiation of physiological bowel uptake from lymphoma. Information provided by coregistration of GS and CT, performed separately on the same day, without the patient moving between both tests and by using external fiducial markers, improved the diagnosis in 23% of the patients compared with the interpretation of stand-alone SPECT and CT.[90] In addition, fused data enables retrospective detection of peritoneal lesions initially missed on CT.[90]

SPECT/CT overcomes the technical difficulties of coregistration of separately performed Ga-SPECT and CT. Hybrid imaging using Ga67 provided additional information in 40% of the patients.[91,92] SPECT/CT enables the correct localization of lymphoma lesions, defines areas of Ga-67 activity as physiologic uptake (Fig 3) or pathology other than lymphoma, and led to the diagnosis of additional, previously unidentified sites of disease.

Encouraging results achieved with radioimmunotherapy for various malignancies, such as non-Hodgkin's lymphoma, have revived the use of labeled monoclonal antibodies for imaging.[93] The overall lesion sensitivity of radioimmunoscintigraphy in lymphoma ranges from 80 to 89% and the positive predictive value is high, leading to upstaging and change in patient management in 17 to 27% of patients.[94-96] Interpretation of radioimmunoscintigraphy may, at times, be difficult because of the physical characteristics of the radioisotope used for labeling and the physiological biodistribution of the compound. Increased uptake is often seen in the blood pool, especially during the early phase of the study and, therefore, high activity in the heart and great vessels may obscure pathological uptake in adjacent areas. Pitfalls may also be related to the physiologic renal and splenic accumulation of the tracer, making the evaluation of involvement of these organs or of lymph nodes in their vicinity difficult.[95] These limitations may be resolved by SPECT/CT differentiating between physiological activity, mostly in the blood pool of normal organs, and abnormal uptake in lymphoma lesions.

Increased uptake of a tracer dose of the labeled antibody suggests a benefit from radioimmunotherapy. Precise dosimetry data, however, are needed and can be provided by quantitative nuclear medicine techniques[97] by using fusion of SPECT data following administration of tracer doses with anatomic volume data provided by CT. SPECT and CT coregistration have been shown to improve radiation dosimetry in lymphoma patients referred for I131-Anti-B1 antibody therapy.[98-100] Technical problems in fusing separately performed studies have, however, limited the routine use of coregistration for dosimetry to pilot studies in small numbers of patients.[89]

SPECT/CT in Additional Tumor-Related Clinical Settings

SPECT/CT for Colorectal Cancer

Using radiolabeled antibodies for scintigraphy has been shown to improve the detectability of occult tumors in patients with colorectal cancer and in differentiating postsurgical changes from viable tumor tissue. The difficult interpretation of findings in radioimmunoscintigraphy due to the physiological biodistribution of the labeled antibody may be overcome by fusion of functional (immunoscintigraphic) and anatomical (CT) data.[101,102] By coregistration of transaxial CT slices and radiolabeled monoclonal antibody SPECT in eight patients with colorectal cancer, Kramer and coworkers showed an incremental value of this technique for both scintigraphic and CT data.[103] Coregistration, based on an

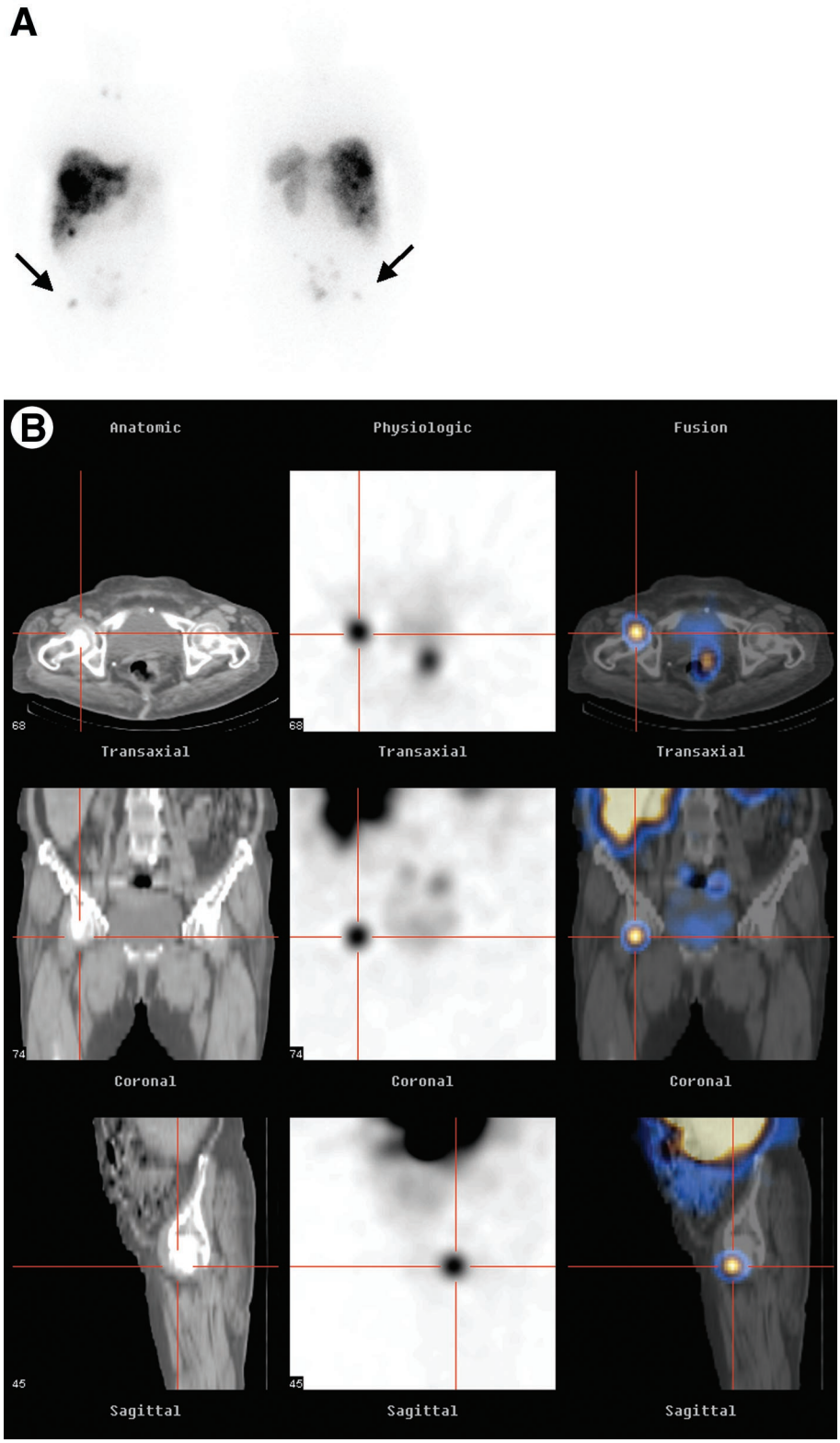

Fig 2. SPECT/CT for precise anatomic localization of abnormal In-111 Pentetreotide uptake in a patient referred for staging of carcinoid with multiple liver metastases at presentation. (A) Planar WB somatostatin receptor scintigraphy (anterior view–left, posterior–right) shows multiple foci of increased uptake in the liver. An additional focus of abnormal uptake is demonstrated in right pelvis (arrow). (B) In-111 pentetreotide SPECT/CT (CT–left ; SPECT–center; Fusion–right; transaxial–top row, coronal–mid row, and sagittal–bottom row) localizes the pelvic lesion to the right femoral head (red markers). The diagnosis of bone involvement led to a change in patient management.

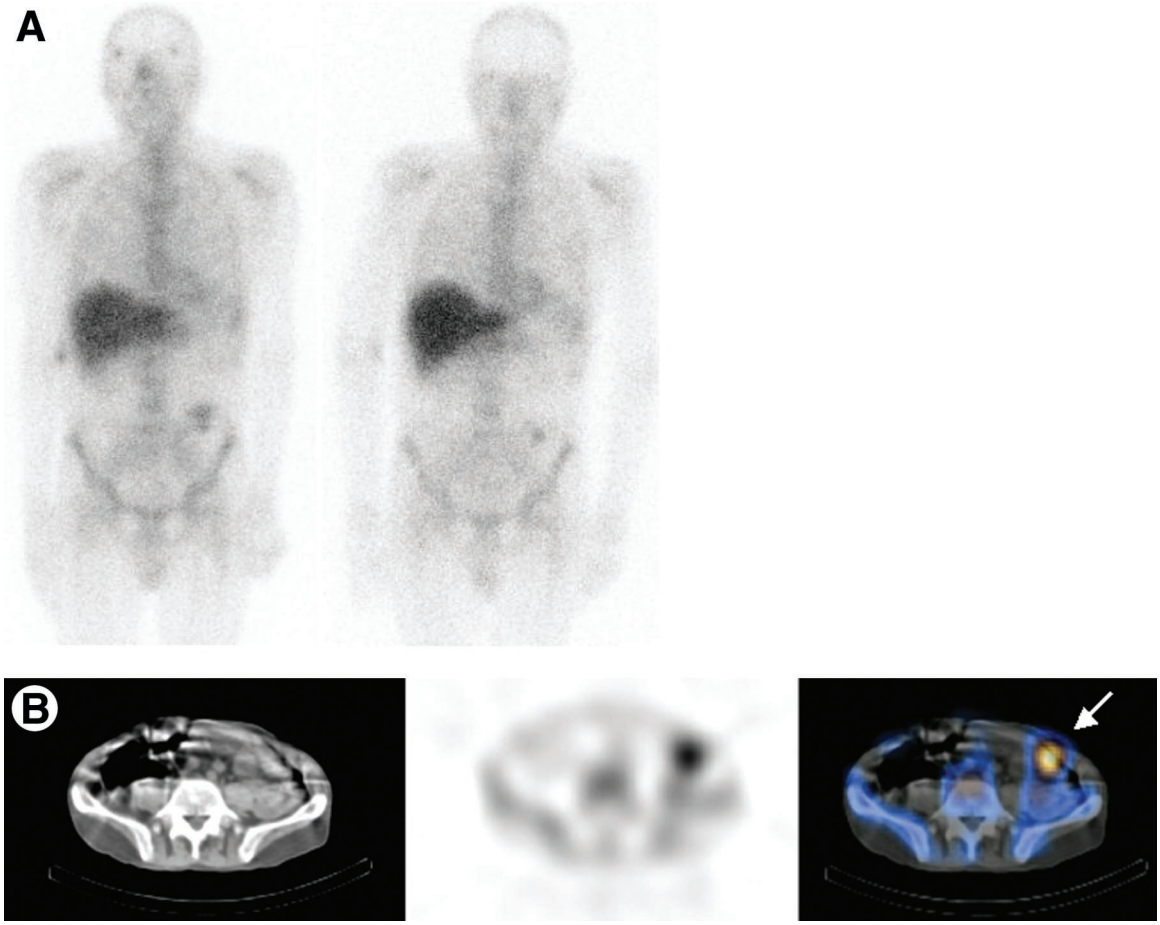

Fig 3. SPECT/CT for exclusion of malignancy in a patient with newly diagnosed abdominal T-cell non-Hodgkin's lymphoma and increased uptake of Ga-67 in the left pelvis. (A) Planar BW Ga-67 scintigraphy (2 d postinjection study–left, 7 d postinjection study–right) shows a single focus of increased uptake in the left pelvis. (B) Ga-67 SPECT/CT transaxial slices (CT– left, SPECT– center, Fusion– right), localize the suspicious scintigraphic finding to physiological uptake in the bowel, thus excluding a site of disease (arrow). The patient was considered to have a non-Gallium avid lymphoma and was referred for other imaging modalities for staging and follow-up.

external marker technique, enabled the correct anatomic localization of disease sites in four patients and localized the tracer to nonspecific uptake in two patients. The fused data also led to retrospective detection of lesions on CT when localized to a positive site on scintigraphy.[103] Another study of 24 patients with metastatic colorectal carcinoma, using an I131-labeled monoclonal antibody and separately performed CT or MRI studies, showed that coregistration of SPECT with CT or MRI provided significant additional information in 11 of the 24 patients as compared with reading SPECT studies alone.[104]

SPECT/CT in Prostate Cancer

Prostate cancer is the second leading cause of cancer death in men. Over one third of patients with apparently clinically localized tumor at presentation have already extraprostatic disease.[105] Preoperative staging and postoperative evaluation of suspected recurrence can be performed by using radiolabeled monoclonal antibodies, such as Capromab Pendetide (Prostascint).[106] In the primary disease setting, Capromab Pendetide imaging should be reserved for patients at high risk for extracapsular extension or metastatic disease. In this subgroup of high-risk patients, radioimmunoscintigraphy represents a noninvasive, relatively sensitive tool for detecting occult lymphatic spread and may spare the patient unnecessary surgery.[106,107] Following primary therapy, Capromab Pendetide imaging is helpful in identifying those patients with PSA elevation after radical prostatectomy that are most likely to benefit from salvage radiotherapy.[105-108]

Capromab Pendetide scintigraphy interpretation is difficult because of the physical characteristics and the

physiological biodistribution of the compound.[106] Soon after injection, activity in the blood pool may obscure pathologic uptake in the adjacent lymph nodes or other soft tissues. Image degradation may be found on delayed studies because of poor count statistics. Excretion of the tracer through the bowel and bladder are responsible for large amounts of radioactivity in the rectum and bladder, in close vicinity to the prostate area, mimicking disease.[106-109] The combination of functional and anatomical imaging may play an important role in the identification of a lesion, in differentiating pathological from physiological uptake, and in revealing the functional status of structural changes seen on anatomic imaging modalities. A method of coregistration that relies on the identification of major blood vessels in the CT and Tc99m-labeled red blood cell SPECT images has been reported. Registration was performed by matching the surfaces of the segmented volumes. Dual isotope acquisition of In111 and Tc99m-labeled agents provided precise SPECT/SPECT registration and facilitated three-dimensional registration of the In111-monoclonal antibody and CT images by applying the same transformation obtained from the Tc99m-SPECT/CT registration.[110] This method provided accurate registration and improved significantly the interpretation of In111-monoclonal antibody studies. Sites suggested by the In111-monoclonal antibody imaging as prostate cancer could be localized to the anatomical data seen on CT.[110] Hybrid SPECT/CT imaging may further facilitate tumor detection and staging of prostate cancer.[111]

SPECT/CT for Sentinel Node Identification

Lymphoscintigraphy is used for mapping of the sentinel node (SN) of various primary neoplasms before biopsy. Lymphoscintigraphic SN mapping assists in tailoring the surgical field and in determining the site of surgical incision.[112-114] This assessment is important mainly for tumors located in regions with ambiguous lymph node drainage, such as the trunk, shoulder, and the head and neck.[115,116] Various radiopharmaceuticals, acquisition protocols, markers, and transmission images with a Co57 flood source have been used for optimizing nodal localization.[117-122] SPECT/CT images provide the topographic landmarks that may further facilitate surgical exploration. SPECT/CT identified SNs previously missed on planar imaging and allowed for their precise localization in 43% of patients with a primary tumor located in the region of the head and neck or trunk. These SNs were located close to the injection site and were hidden by its scattered radiation or in-transit nodes.[123] SPECT/CT also allowed for a correct estimate of the depth of SN, in regions of complex anatomy in 40% of patients with melanoma, leading to better surgery planning.[124]

SPECT/CT in Bone Metastases

Bone scintigraphy using Tc99m-MDP is a sensitive, simple, and efficient tool for the evaluation of cancer patients, but lacks specificity. When a bone scan demonstrates pathological tracer uptake, no definite diagnosis can be made, and there is often a wide range of differential diagnoses. In a study designed to evaluate the clinical value of hybrid imaging in oncological patients investigated for suspected bone metastases, 78 patients with equivocal findings on routine bone scan underwent SPECT/CT studies. Fusion of Tc99m-MDP SPECT and the corresponding CT slices was found to improve the specificity of scintigraphy and the diagnosis of the suspicious sites in about 80% of equivocal lesions found on bone scans.[125]

SPECT/CT in Parathyroid Adenoma

Parathyroid scintigraphy has gained an increasing role in the evaluation of patients with hyperparathyroidism for localization of a parathyroid adenoma. A planar Tc99m-MIBI scan alone or combined with cervical ultrasound (US) is considered the preferred localizing imaging procedure in most patients with hyperparathyroidism. The routine use of MIBI-SPECT before initial surgery is controversial, but MIBI-SPECT and CT image coregistration has been shown to improve the localization of an ectopic mediastinal parathyroid adenoma to be removed by limited median sternotomy.[126] In two of eight patients with ectopic thoracic adenoma studied with MIBI SPECT/CT, the fused data were the only imaging procedure to provide precise anatomic localization of the lesion for planning of the surgical approach.[14] The additional information provided by combined anatomical and functional data may be of value when planning minimally invasive parathyroidectomy. An incremental value of hybrid SPECT/CT images was also documented in all nine patients with hyperparathyroidism who were studied by Kienast et al, with a major benefit in four patients with an ectopic gland.[127] SPECT/CT facilitated successful surgery, even in a minimal invasive setting, and excluded the need for further radiological examinations in the majority of patients.[127]

CONCLUSION

Imaging has become increasingly important in the assessment of tumors at diagnosis, staging, treatment planning and monitoring, as well as for follow-up and early detection of recurrence. Functional imaging of cancer by using single photon-emitting radiopharmaceuticals and SPECT plays a major role in each and every one of the above-mentioned processes. Improvements in hardware, radiochemistry and clinical expertise have succeeded to overcome only in part the intrinsic limitations of nuclear medicine techniques. Anatomic imaging

modalities, considered until recently the gold standard in diagnostic evaluation of neoplasms, have also proven to be of limited value for more sophisticated questions and dilemmas arising during cancer patient management.

At times of significant changes and developments in the diagnosis and treatment of cancer, the novel technology of hybrid imaging by using SPECT/CT, as well as PET/CT, offers an optimal tool for the new goals ahead. While continuing to improve the diagnosis of cancer, hybrid imaging will play an increasing role in replacing or improving guidance of invasive diagnostic and therapeutic procedures. Hybrid imaging will also be extensively used in the future in solving increasingly complex clinical questions related to monitoring therapeutic outcomes.

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