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Single-Photon Emission Computed Tomography/Computed Tomography in Lung Cancer and Malignant Lymphoma

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In nuclear oncology, despite the fast-growing diffusion of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), single-photon emission computed tomography (SPECT) studies can still play an useful clinical role in several applications. The main limitation of SPECT imaging with tumor-seeking agents is the lack of the structural delineation of the pathologic processes they detect; this drawback sometimes renders SPECT interpretation difficult and can diminish its diagnostic accuracy. Fusion with morphological studies can overcome this limitation by giving an anatomical map to scintigraphic data. In the past, software-based fusion of independently performed SPECT and CT images proved to be time-consuming and impractical for routine use. The recent development of dual-modality integrated imaging systems that provide functional (SPECT) and anatomical (CT) images in the same scanning session, with the acquired images coregistered by means of the hardware, has opened a new era in this field. The first reports indicate that SPECT/CT is very useful in cancer imaging because it is able to provide further information of clinical value in several cases. In SPECT, studies of lung cancer and malignant lymphomas using different radiopharmaceutical, hybrid images are of value in providing the correct localization of tumor sites, with a precise detection of the involved organs, and the definition of their functional status, and in allowing the exclusion of disease in sites of physiologic tracer uptake. Therefore, in lung cancer and lymphomas, hybrid SPECT/CT can play a role in the diagnosis of the primary tumor, in the staging of the disease, in the follow-up, in the monitoring of therapy, in the detection of recurrence, and in dosimetric estimations for target radionuclide therapy.
Semin Nucl Med 36:275-285

Lung cancer remains the most common cause of death from malignant disease in the world both in women and in men, despite the fact its incidence rates are declining in men and have leveled off for the first time in women after increasing for many decades, with 163,510 deaths estimated in the United States in the year 2005.[1] It is worth noting that lung cancer surpassed breast cancer as the leading cause of cancer death in women from 1987 onward and it is expected in the United States to account for 31% and 27% of all male and female cancer deaths in 2005, respectively.[1]

Malignant lymphomas are a group of neoplasms originating in the lymphoid tissue that include Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). HD is comparatively uncommon, but at young adult ages it accounts for approximately 1 cancer in 6.[2] There have been decreases in its incidence in older patients, whereas in adolescents and young adults, modest decreases or increases have been observed; mortality from HD has significantly decreased since the 1960s as the result of the great improvements in treatment.[2] NHL represents 4% of all invasive tumors in the United States, and it accounts for 3% of cancer deaths. In 2005, the American Cancer Society estimated 56,390 new cases and 19,200 deaths from this disease.[1] Trends in incidence show that there have been large increases during the last 30 years; also, the mortality rate increased in older adults, whereas it has decreased in children and young adults.[2]

In nuclear oncology, despite the growing applications of positron emission tomography (PET) and PET/computed tomography (CT), single-photon emission computed tomography (SPECT) studies are still very useful in numerous conditions. In fact, SPECT is broadly available also in the most peripheral centers, and several single-photon radiopharmaceuticals have demonstrated of clinical value in a wide variety of neoplasms,[3] including lung cancer and malignant lymphoma. Their application in oncology comprises diagnosis and staging of the primary tumor, follow-up, monitoring of therapy, detection of recurrence, and prediction of therapy effect. Moreover, the continuous improvements in SPECT instrumentation and, in particular, the recent development of integrated hybrid SPECT/CT systems, which provide functional and anatomical images in the same scanning session, could significantly improve its diagnostic capability.[4]

This article deals with the applications of SPECT/CT with tumor seeking agents in lung cancer and malignant lymphomas.

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0001-2998/06/$-see front matter
doi:10.1053/j.semnuclmed.2006.05.003

Radiopharmaceuticals

This section analyzes the uptake mechanisms of the currently most used single photon radiopharmaceuticals for lung cancer and malignant lymphomas imaging. Tc-99m sestamibi (SM) and tetrofosmin (TF) are 2 small cationic complexes of technetium introduced for myocardial perfusion imaging, which then were proposed as tumor-avid agents.[5] SM uptake and retention in cancer cells depend on several factors, such as regional blood flow, plasma and mithocondrial membrane potentials, metabolic activity, increased blood flow, and angiogenesis, with approximately 90% of tracer activity accumulated in the mitochondria.[6,7] Similar mechanisms also have been suggested for TF: nonetheless, Arbab and coworkers[8,9] showed in tumor cell lines that its uptake mechanism is partially related also to Na^+/K^+ pump, and it predominantly concentrates in the cytosol with only a small fraction accumulating in the mitochondria. Moreover, both these radiopharmaceuticals are transport substrates for the P-glycoprotein (Pgp), a M_r 170,000 plasma membrane protein encoded by the multidrug resistance gene (MDR), and MDR-related protein (MRP), that function as energy-dependent efflux pumps for many drugs, including chemotherapy agents.[10] These proteins are involved in the process of cancer resistance to multiple chemotherapeutic agents, which remains a major obstacle in therapy and could lead to a complete ineffectiveness of any treatment. Several techniques are available for studying the expression of chemoresistance transporter proteins at the protein and mRNA levels. Nevertheless, the presence of Pgp and/or MRP in cancer cells does not answer questions about the functionality of these drug efflux pumps; both SM and TF SPECT demonstrated clinical usefulness in clarifying this functionality.[11]

Gallium-67 citrate (^{67}Ga) has been used for tumor imaging since the end of the 1960s.[12] Despite several reports describing the possible factors responsible for ^{67}Ga tumor uptake, there is still no general agreement on the exact mechanism of localization. However, it has been well established that ^{67}Ga circulates in the blood bound to transferrin, lactoferrin, or similar compounds; in addition, several factors affecting the accumulation of ^{67}Ga within the cancer cells have been postulated: increased capillary and plasma membrane permeability, and the presence of transferring and lactoferrin receptors in tumor cell surfaces, which are responsible for the internalization of the protein-^{67}Ga complexes.[13-15] ^{67}Ga became rapidly the functional method of choice for imaging malignant lymphomas, and it is still used in this application, whereas it has no more clinical relevance in today's nuclear medicine study of lung cancer.

Somatostatin receptor scintigraphy (SRS) with radiolabeled somatostatin analogs mostly is used to image tumors overexpressing somatostatin receptors (there are 5 subtypes) and, above all, neuroendocrine tumors. In vitro studies have demonstrated the presence of somatostatin receptors in small cell lung carcinoma (SCLC), bronchial carcinoids, neuroendocrine lung tumors and both HD and NHL.[16] ^{111}In pentetreotide has been the first labeled peptide approved by the Food and Drug Administration for imaging neuroendocrine tumors; this somatostatin analog binds with high affinity to somatostatin receptors 2 and 5 and, to a lesser extent, to somatostatin receptors 3.[17] Afterward, a cyclic somatostatin analog labeled with ^{99m}Tc was developed: ^{99m}Tc-depreotide is a synthetic peptide that binds with high affinity to somatostatin receptors 2, 3, and 5.[17]

The use of radiolabeled antibodies against tumor-associated antigens to detect carcinoma has attracted the interest of many researchers; therefore, during the past years, many reports have been published on the clinical applications of different monoclonal antibodies labeled with single-photon radiotracers both in lung cancer and lymphoma.[15,18–20]

Imaging Fusion of SPECT Studies

It is well known that SPECT imaging demonstrates function, rather than anatomy, and it is very useful for early diagnosing various disorders because of its ability to detect changes before there are identifiable anatomical correlates and clinical manifestations. Nevertheless, the anatomical landmarks provided by SPECT studies are usually limited, and, especially in cancer imaging, this drawback is not trivial because it could be important to precisely identify and differentiate the sites of abnormal uptake from the structures normally containing activity. On the contrary, radiological imaging is the main sources of information on anatomical details of normal and diseased organs: it detects structural abnormalities in an accurate way, but it lacks information on physiopathology, and it is less effective in patients in whom the normal anatomy is variable, such as in the postsurgery follow-up.[21]

Thus, in a vision of optimal assessment of most cancer patients, SPECT is a molecular imaging modality that naturally complements CT and magnetic resonance imaging (MRI) data.[22] In fact, the fusion with structural images is not only a helpful adjunct to the interpretation of functional images, but this process also offers the possibility to overcome some intrinsic limitations of SPECT studies, such as poor spatial resolution, low signal-to-noise ratio, and sometimes low tracer uptake in the tumor cells.[23] Therefore, the combination of SPECT images with anatomical ones is certainly of value for accurately localizing radiopharmaceutical accumulations, for detecting occult pathological sites, for characterizing the metabolically active area of a known lesion, and for precisely drawing regions of interest (ROIs) to perform quantization.[24] Moreover, fusion can lead to additional clinical information not apparent in the separate images.[25,26]

The main goal of fusion in cancer imaging with single-photon radiopharmaceuticals is to impose a structural anatomical framework on SPECT images because often they have not enough anatomical detail to precisely determine, for example, the position and the extension of a tumor lesion. This purpose can be achieved using several methods.[27,28] However, although often successful for the head and brain, software approaches usually encounter various difficulties in the chest and abdomen–pelvis,[29-31] and so they have not reached routine clinical use. In fact, fusion software requires access to images from different modalities whose alignment is labor intensive and uncertain of success, especially when the content of the 2 imaging sets is very dissimilar. Moreover, even when external fiducial markers are used, identical positioning of the patient when the scans are performed with 2 different devices may be inaccurate, and also problems because of involuntary movement of internal organs have to be taken into account.[27,32-36]

Most of the aforementioned problems in fusing data can be overcome combining SPECT and CT into one scanner able to acquire functional and anatomical images in a single session, using the same gantry.[4,37,38] This approach is the basis for the development of hybrid systems capable of performing both functional and structural imaging without patient movement and change in patient positioning, so allowing correct registration of SPECT and CT images.

Until recently, only one commercial SPECT/CT device has been available: this hybrid system combines a dual-detector, variable-angle gamma camera with a low-dose x-ray tube; it enables, in a sequential interchangeable sequence, the acquisition of SPECT data and cross-sectional x-ray transmission images, which accurately localize the anatomical sites of radiotracer uptake; the CT data also can be used for attenuation and scatter correction of the emission images.[39] After acquisition, matching emission and transmission slices are quickly fused in the nuclear medicine workstation, generating images of SPECT data superimposed on the corresponding anatomic planes.

More potent imaging systems have been now introduced that combine state-of-the-art SPECT with multislice CT up to 16 slices, which allows the acquisition of diagnostic CT imaging. In fact, the main drawback of the previously described hybrid device is its low-dose CT scan, which provides images useful for spatial localization and fusion with SPECT data but which cannot substitute diagnostic CT.[40] However, this system is able to provide adequate information for the precise assessment of SPECT findings in most studies; moreover, in the possible rare cases with insufficient information to precisely localize a site of radiopharmaceutical uptake, the low-resolution CT images are useful to accurately define the appropriate slice to review from a diagnostic quality CT scan or MRI that match up with the area of interest. Then, it's worth noting that the radiation burden caused by CT in this device is only approximately 0.5 mSv, because the x-ray tube operates at 2.5 mA[41]; this dosimetry value is significantly smaller than the dose delivered to the patient by a typical diagnostic CT. It is very important that the radiation burden added to SPECT with this SPECT/CT device is negligible and it should be taken into account, especially when a patients has been submitted to a diagnostic CT scan within a short period before the SPECT/CT study.

Lung Cancer

The first data on SPECT/CT fusion in lung cancer imaging were reported in clinical trials using radiolabeled antibodies, both in nonsmall cell lung cancer (NSCLC) and SCLC patients.

A group of 14 patients with NSCLC (from stage IIa to stage IV) were studied after the intravenous administration of ^{99m}Tc-labeled IMMU-4 anti-CEA Fab' antibody fragment to evaluate the potential role of immunoscintigraphy SPECT fusion with CT in NSCLC staging.[42] Chest SPECT acquisitions were performed either at 5 to 8 and 22 to 24 hours or at 16 to 18 hours after the radiopharmaceutical injection, with Co-57 markers placed at the coracoid process, sternal notch, and xyphoid process. A dual-energy window was used: one for immunoscintigraphy and the other one for the markers. CT scans of the thorax were always performed after the administration of both oral and intravenous contrast medium. Image fusion of the transaxial slices was obtained by means of a landmark-based algorithm. Only SPECT slices showing suspected abnormalities and CT slices of interest were chosen for fusion. A total of 40 SPECT and CT pairs were registered; for each registration, a 15- to 20-min time was used. To verify the precision of the fusion algorithm, a ROI drawn on the descending aorta on CT scan was warped onto the SPECT and compared with a ROI independently drawn on SPECT imaging. The average distance between the centers of the warped and SPECT ROIs was 1.3 ± 0.8 pixels. Nevertheless, only a poor overlap between the pixels in the SPECT and in the warped ROIs was obtained, with an average of 54 ± 8%.

Image fusion was able to distinguish physiologic blood pool activity from tumor sites (both primary and lymph-nodal) in 50% of patients. Moreover, in 3 cases, SPECT/CT differentiated the viable portion of the tumor from areas of necrosis in large inhomogeneous masses on CT, and, in 3 patients previously submitted to lung cancer surgery, it was of value in the differential diagnosis of recurrent tumor from fibrosis and/or scar. In mediastinal lymph-node staging, fused images confirmed the presence of metastases in 7 of 8 patients with enlarged nodes on CT and excluded tumor involvement in the remaining one with benign sinus histiocytosis. These findings indicated that fusing SPECT and CT data improves the information obtained by each single modality; in particular, fusion demonstrated useful in reducing the number of the possible SPECT false-positive results, especially in areas close to normal blood pool containing structures, which often show on immunoscintigraphy an activity similar to that of pathologic tumor uptake. The author's conclusion was that the fusion of immunoscintigraphy with CT appeared promising for NSCLC staging, for assessing treatment response and residual tumor volumes, and for radioimmunotherapy (RIT) planning.[42]

The possible role of SPECT/CT fusion in mediastinal staging in NSCLC also has been evaluated using ^{99m}Tc NR-LU10, a radiolabeled Fab fragment of a murine monoclonal antibody specific for a 40-kDa glycoprotein that is expressed on several adenocarcinomas.[24] CT scan of the thorax and upper abdomen was performed after the intravenous injection of contrast medium. Chest SPECT was acquired 17 to 20 h after the radiolabeled antibody administration, with 2 Co-57 markers on the skin of the patient (one at the tip of the xiphoid and one at the sternal notch) used to recognize the SPECT slices that represented the 2 sternal levels, which were then matched with the corresponding CT slices. SPECT and CT fusion was performed in 5 patients, choosing SPECT slices with suspected abnormalities or CT slices showing lymphoadenopathy by means of a warping algorithm. Fusion was useful for the interpretation of SPECT images; in fact, because of the high uptake in the thyroid, the lower neck and superior mediastinum regions were difficult to evaluate using scintigraphic images alone. Moreover, SPECT/CT helped differentiating blood pool containing structures from hilar and mediastinal lymph nodes. Three of five patients had enlarged nodes on CT scan: in 2 cases, fusion imaging precisely localized the specific sites of lymph-nodal antibody uptake.

Grant and coworkers[43] performed SPECT and CT fusion in 10 patients with SCLC receiving the monoclonal antibody SF8 labeled with I-131, and directed against the antigen disialogangloside GD2, expressed on tumor cells in the majority of human SCLCs. Scintigraphy detected all known tumor sites, except multiple small brain metastases in one patient, and fused images confirmed the precise localization of the radiolabeled antibody.

Despite these interesting initial results describing immunoscintigraphy SPECT fusion with CT by means of externally placed landmarks and the use of a warping algorithm, to our knowledge, no other study in lung cancer imaging using this method has been reported. As a matter of fact, this fusion technique is time-consuming and not very accurate[42] and therefore is not feasible enough for routine clinical use. The new technology combining SPECT and CT in the same device, allowing the automatic precise alignment and fusion of functional and anatomical slices in a few minutes by using the same workstation and software, now offers a solution to this problem.[39]

In the recent years, both SM and TF imaging has been used predominantly for SPECT imaging of lung cancer.[44] These radiopharmaceuticals have several attractive advantages over traditional single-photon radionuclides used in lung cancer, like ^{67}Ga and ^{201}T1: patients can be imaged earlier (10-20 min after injection), they are available in a commercial kit form, and they are ideally suitable for SPECT studies because of the favorable gamma emission characteristics of ^{99m}Tc.

In the largest series using SM to detect lung malignancies, a group of 116 patients with a potentially resectable pulmonary lesion, SPECT visualized 81 of 99 tumors, whereas no benign lesions had a positive finding.[45] Therefore, SM imaging yielded a 100% specificity and positive predictive value. Sensitivity, accuracy, and negative predictive value were 90%, 91%, and 63%, respectively. In 81 patients with an abnormal chest radiograph and/or CT demonstrating a single lung lesion (range: 0.6–12 cm), TF SPECT[46] was positive in 51 of 54 lung malignancies (sensitivity 94%) and detected only 4 of 27 benign lesions (specificity 85%). Using TF, Buccheri and coworkers[47] studied 61 patients who were strongly suspected of having lung cancer: all the 57 patients whose lung carcinoma was pathologically confirmed showed TF uptake but, in addition, 3 of the 4 nonmalignant lesions were positive. The SPECT study including the most numerous patient population with thoracic lesions was performed in 304 patients by means of TF[48]: 239 were at initial diagnosis, 11 were in follow-up for a previously operated NSCL, and 54 were in follow-up for other kinds of tumor. SPECT showed higher sensitivity, specificity, and accuracy values than CT (98%, 91%, and 97% vs 96%, 81%, and 94%, respectively). The findings in this large series indicate that TF SPECT could play a complementary role to CT in selected patients with suspected lung cancer. Nevertheless, discouraging results in differentiating malignant from benign lung lesions have been reported by Kao and coworkers, using both SM and TF in patients with single solid lung masses.[49,50]

The first cases of SPECT/CT fusion in lung cancer imaging with SM or TF were reported recently in a clinical trial aimed to assess the usefulness of a hybrid SPECT/CT system for functional anatomical mapping using various radiopharmaceuticals and the additional value of fused SPECT/CT images compared with SPECT alone.[51] In 33 of 81 (41%) consecutive patients studied for various clinical situations, SPECT/CT added significant information to SPECT alone by providing a correct anatomical localizations of scintigraphic findings and the definition of the functional significance of CT lesions and by excluding disease in sites of physiologic tracer uptake. The transmission anatomical maps allowed for precise anatomical localization of SPECT images in 79 of 81 cases; the only 2 mislocalized studies were performed in the chest and were likely the result of respiratory movements. This series included 7 patients with an indeterminate solitary pulmonary node (SPN), 5 submitted to TF and 2 to SM imaging for the functional characterization of the nodule, and 5 patients with NSCLC studied with TF for mediastinal lymph node staging. Hybrid images facilitated SPECT interpretation in all the cases; moreover, they allowed the correct functional definition of 2 SPNs previously detected by anatomical imaging (Fig. 1) and located near sites of physiologic radiopharmaceutical uptake (ie, the liver and vascular structures), and the precise anatomical localization of TF accumulation in 2 patients with mediastinal node involvement from NSCLC.

The characterization of SPN represents an important clinical problem; in fact, approximately 150,000 of such nodules are identified each year in the United States and, although the causes may include many benign conditions, the incidence of lung cancer in patients with SPN has been increasing, especially in the elderly.[52] The first clinical data suggest that both SM and TF SPECT could be of value in differentiating malignant from benign SPNs. Minai and coworkers[53] used SM scintigraphy in 25 patients with a SPN who were classified as indeterminate by clinical and radiographic criteria; 18 of the 21 patients with malignant lesions had increased SM uptake, and all 4 patients with benign lesions had negative findings. In a group of 86 pa-

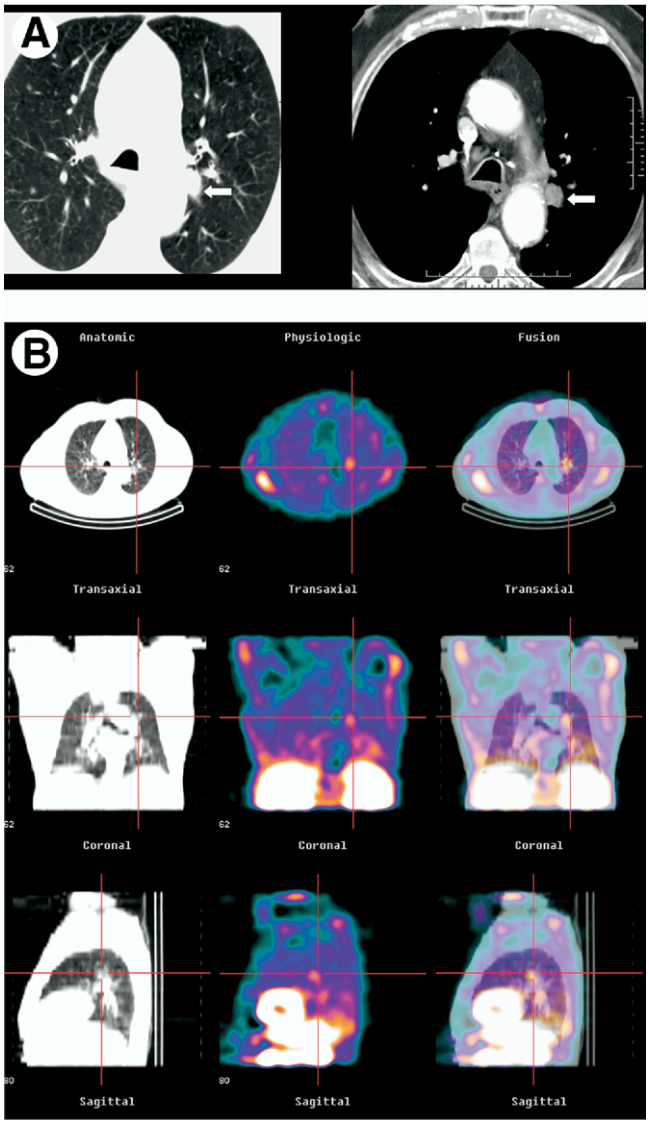

Figure 1 Shown is a 65-year-old man with a SPN in the upper lobe of the left lung, near the descending aorta, and clearly visible in a previous diagnostic CT scan (A, arrows), both in the image with the parenchymal (left) and the mediastinal window. (B) SPECT/CT demonstrates that the focal TF uptake corresponds to the SPN. The final diagnosis was NSCLC.

tients,[54] with SPN indeterminate at CT, TF SPECT was true positive in 61 of 67 malignant nodules (sensitivity 93% in primary carcinomas and 87% in metastatic lesions), and true negative in 17 of 19 patients with benign lesions (specificity 89%).

Recently we have evaluated the efficacy of SM SPECT/CT and multislice CT in the assessment of SPN of uncertain significance.[55] For this study, we selected 23 patients with a SPN <2 cm in size (mean size 1.3 cm) that was discovered at CT initially performed to investigate a chest radiography finding or as a diagnostic examination for another condition. CT examinations were conducted with a 16-slice CT scanner before and after administration of nonionic iodinated contrast material; the volume of the lesion was calculated by means of an automatic segmentation software. Thereafter, within 5 days, SM hybrid SPECT/CT was obtained. Immediately after chest SPECT acquisition, a low-resolution CT was done, with a field of view of 40 cm, exactly equal to that of the SPECT: multiple slices (slice thickness 1 cm) were obtained by moving the table by a slice step before acquiring the next slice. CT data were reconstructed using the nuclear medicine workstation to produce cross-sectional attenuation images (256 × 256 matrix), that were fused with the corresponding SPECT slices.[39] Patients with positive nodules at scintigraphy underwent invasive procedures for histological characterization; patients with negative nodules at SPECT/CT repeated multislice CT after 3 to 4 months, with reassessment of volume and subsequent histological characterization. Of the 23 SPNs, 11 were positive at SPECT/CT imaging and 12 were negative; among the positive nodules, 10 were found to be malignant by subsequent histological examination and there was one false positive result. Of the 12 negative nodules, there was only one false-negative scintigraphic finding, from an adenocarcinoma of 0.8 cm. In SPECT interpretation, fused images were always decisive in identifying the lesions with no SM uptake, and they were very helpful for the correct characterization of perihepatic lesions, which are affected by the normal uptake of the radiopharmaceutical by the liver. These preliminary results suggest a more-extensive use of SM SPECT/CT that is noninvasive and simple and that could be helpful to anticipate histological assessment and surgical treatment of SPNs identified at diagnostic CT.

In NSCLC, an accurate preoperative staging of mediastinal lymph node is crucial in assessing operability and prognosis[56]; CT is still the most commonly used noninvasive method for evaluating mediastinum, but its limitations are well known.[57] These shortcomings have led to consider functional images for the assessment of mediastinal lymph nodes: ^{18}F-fluorodeoxyglucose (FDG)-PET is widely used in this setting, nevertheless also SM and TF can play a role.

Chiti and coworkers[58] evaluated 36 patients with NSCLC who underwent staging procedures including CT; lymph node involvement was demonstrated by histology. SM SPECT and CT had a diagnostic sensitivity and specificity of 91% versus 84% and 84% versus 60%, respectively; also, the scintigraphic results of positive and negative predictive value and accuracy were better than those of CT. Thereafter, SM was used in 87 patients with a resectable NSCLC submitted to cervical mediastinoscopy and/or mediastinal lymph node dissection during lung resection.[45] Twelve of the 22 patients with mediastinal lymph nodes metastases had positive SPECT results; none of the patients with negative mediastinal lymph nodes had a positive scintigraphic finding. SM images demonstrated a 100% specificity and positive predictive value in detecting mediastinal lymph node metastases; sensitivity, accuracy, and negative predictive value were 55%, 89%, and 87%, respectively. No statistical differences between CT and SPECT in terms of sensitivity and accuracy were found, whereas SM imaging resulted more specific.

In a prospective study on 83 patients, according to histopathological results, we have reported, in detecting mediastinal lymph node involvement on a per-patient basis, that TF SPECT yielded a sensitivity of 86%, a specificity of 90%, and an accuracy of 88%; for CT a sensitivity of 69%, a specificity of 75%, and an accuracy of 72% were observed.[59] In our series, SPECT accuracy was significantly greater than that of CT; in particular, in the 36 patients with positive findings at CT (ie, those with enlarged mediastinal nodes), TF imaging correctly detected the presence or absence of lymph node metastases in 33 of them, with a global accuracy of 92%. Similar results were obtained by Shiun and coworkers[60] in 34 patients with large primary NSCLC (T2 or greater): sensitivity, specificity and accuracy were 85%, 86%, and 85% for TF SPECT and 84%, 60%, and 74% for CT, respectively. Despite the better performances of TF, the authors recommend the combined use of SPECT and CT to improve the diagnostic accuracy in mediastinal lymph nodes assessment. In a small series of 16 patients with pathologically staged mediastina, Buccheri and coworkers[47] found a sensitivity, specificity, and accuracy of 73%, 100%, and 81% for TF SPECT and of 91%, 100%, and 94% for CT, respectively; therefore, the investigators concluded that surgical staging remains essential for a correct classification of patients.

Despite the fundamental role of FDG-PET in NSCLC staging, SM and TF imaging could offer a reasonable low-cost and easily available presurgical noninvasive method to assess mediastinal lymph node involvement. In particular, SPECT could play a clinical role in reducing the number of invasive staging surgical procedures in selected patients, especially in those with enlarged lymph nodes at CT. However, there are some drawbacks in the diagnostic ability of SM and TF in mediastinal lymph node assessment, mainly as the result of the limited spatial resolution of SPECT. In fact, when abnormal radiopharmaceutical uptake is found in the mediastinum, the location of the lymph node is only roughly estimated and could not be precisely evaluated; moreover, it is difficult to define the exact number of involved nodes. SPECT imaging is simple to perform, but it yields images

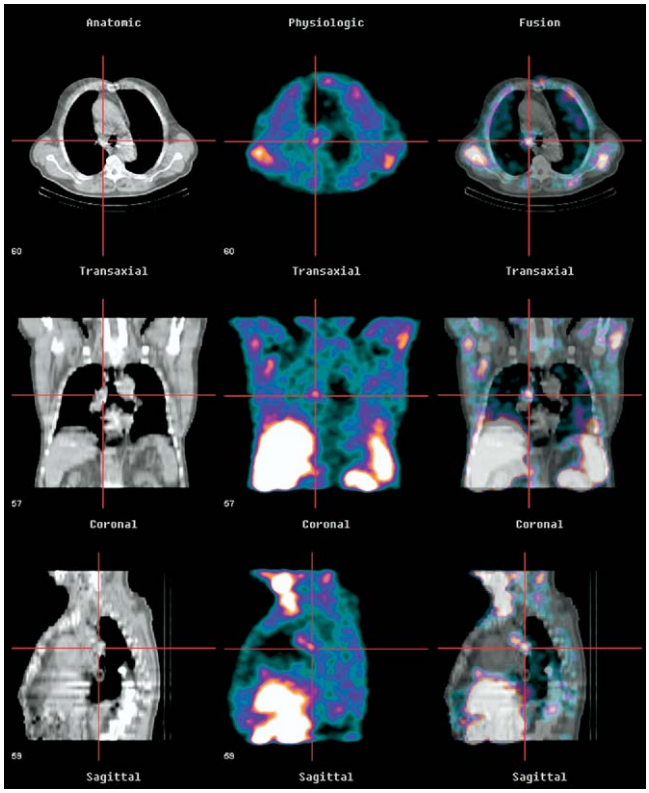

Figure 2 Shown is a 59-year-old man with right lung NSCLC. SPECT/CT precisely localizes a focal SM mediastinal accumulation as due to metastatic lymph-node involvement in the right paratracheal region. This diagnosis was confirmed after thoracotomy.

that could not be easy to analyze, because of the lack of anatomic landmarks; furthermore, the heart and many vascular structures can interfere with a correct interpretation of the images, even when only the mediastinum is evaluated.[59] Combining the anatomic localizing capability of CT with SPECT findings through image fusion, with the precise matching of the structural and the functional data, a more accurate identification of disease sites can be made (Fig. 2). In particular, fusion with hybrid systems is easy to perform and it allows a better anatomic localization of abnormal SM and TF activity, together with the exclusion of disease in sites of physiologic radiopharmaceutical uptake.[51]

SRS using ^{111}In pentetreotide is a well-established method to evaluate patients with neuroendocrine tumors, but it also has been demonstrated to detect other kinds of lung cancers.[18] In patients with bronchial carcinoids, ^{111}In pentetreotide is of value in visualizing the primary tumor, and it helps in staging by detecting lymph node involvement and by confirming or ruling out distant metastases, including bone ones; in the follow-up, SRS could be considered the principal procedure for an early diagnosis of recurrence.[61-63]

Despite the fact that somatostatin receptors are not expressed in patients with NSCLC, ^{111}In pentetreotide is not useful in distinguishing this tumor from SCLC: in fact, scintigraphy was highly sensitive for detecting all primary bronchogenic carcinomas.[64] For staging purposes, ^{111}In pentetreotide is of limited value,[65] which is also the case if the visualization of unexpected SCLC metastases, especially in the brain, have been reported.[66]

The main drawback of ^{111}In pentetreotide imaging is certainly the poor anatomic delineation of SPECT. The impact of hybrid SPECT/CT on SRS interpretation has been recently indicated in a study involving 72 patients with proven or high clinical suspicion for neuroendocrine tumors.[67] SPECT/CT improved localization of the ^{111}In pentatreotide-detected lesions in 23 of the 44 positive studies: by defining the extent of disease in 17, by showing unsuspected bone involvement in 3, and by differentiating physiological from tumor uptake in 3. Moreover, hybrid images SPECT/CT affected the clinical management in 10 patients. The study population included 45 patients with carcinoids, but no data were provided about the primary origin of these tumors. Nonetheless, we think that similar useful results could be obtained when applying ^{111}In pentetreotide SPECT/CT specifically to patients with bronchial carcinoids. In this group, hybrid imaging may distinguish physiological from tumor sites, may help in detect when tracer uptake occurs in benign processes, such as recent surgery or lung granulomas, may define the precise organ involved, and may determine the presence or absence of invasion into surrounding tissues (Fig. 3). Furthermore, SPECT/CT also could play an important role in patients with ectopic adrenocorticotropin Cushing's syndrome, for an accurate localization of bronchial carcinoids, that are the most common neoplasms causing this disease.[68] Moreover, the advantages of having an anatomical map for better interpretation of the functional data also could be useful in ^{111}In pentatreotide studies of patients with both NSCLC and SCLC (Fig. 4).

^{99m}Tc-depreotide was approved by the Food and Drug Administration for noninvasive differentiation of SPNs, and it represents a cost-effective alternative to FDG-PET in this application.[69] In a multicenter trial evaluating 114 patients,[70] using ^{99m}Tc-depreotide, researchers were able to correctly identify 85 of 88 malignant SPNs (sensitivity 97%) and to exclude malignancy in 19 of 26 benign histologic findings (specificity 73%). Recently, ^{99m}Tc-depreotide SPECT and FDG-PET demonstrated the same specificity (86%) for small (up to 1.5 cm) and equal sensitivity (92%) for large (more than 1.5 cm) SPNs.[71] The role of ^{99m}Tc-depreotide in staging patients with NSCLC is still under investigation; nonetheless, a high rate of false-positive results in the hilar/mediastinal regions have been reported as a result of nonspecific tracer uptake.[72,73] Hybrid SPECT/CT may be of value in facilitating image interpretation both for diagnosis and staging and differentiating physiologic activity (parahilar mediastinal region, bone marrow of the spine, ribs and sternum) from uptake in the primary tumor or into metastatic lymph nodes[74]; moreover, x-ray-based attenuation-correction, by improving the image contrast, could increase the detection rate of smaller nodules (Fig. 5).

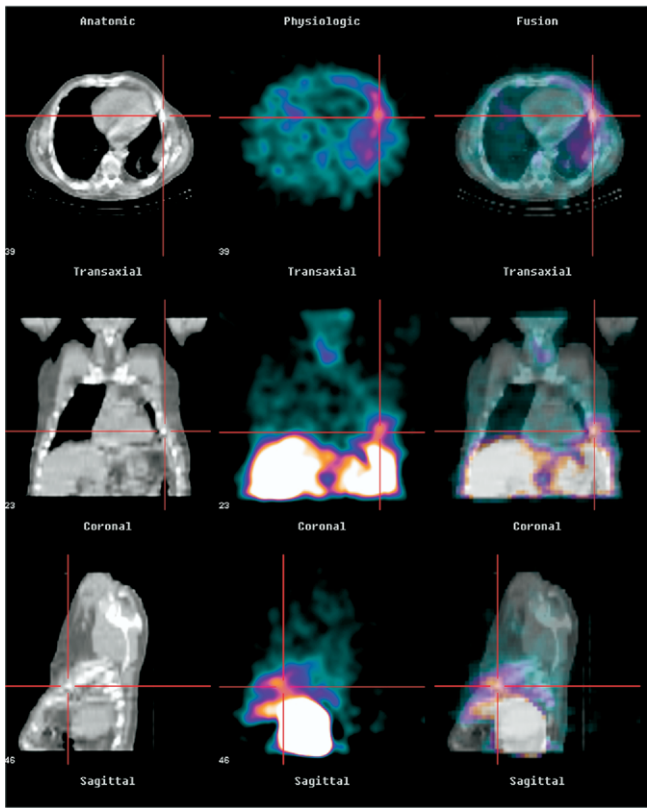

Figure 3 Shown is a 52-year-old man with a previously resected bronchial carcinoid of the left lung. There is a focal ^{111}In pentetreotide accumulation in the chest, that SPECT/CT precisely localizes in the sixth left rib.

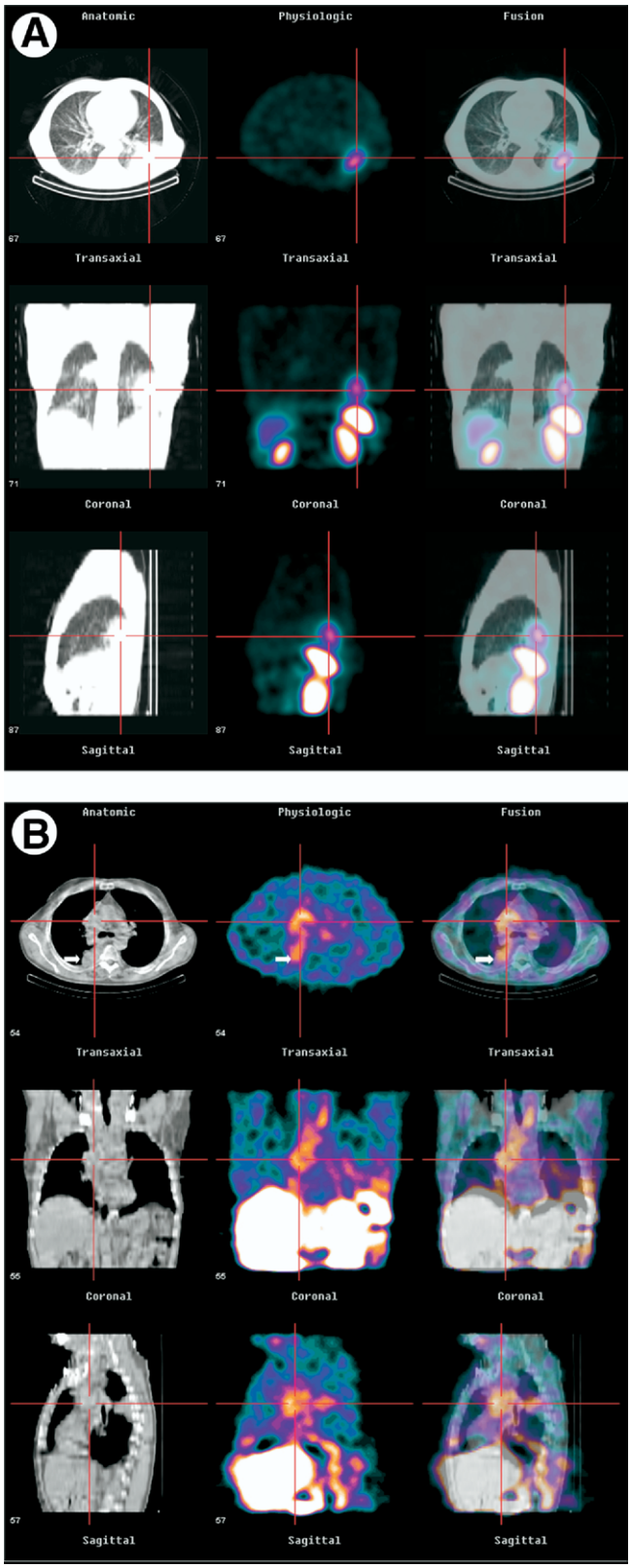

Figure 4 Shown is a 62-year-old man with SCLC. ^{111}In pentetreotide SPECT/CT correctly located the pathological uptakes in the lower lobe of the left lung (A), in the mediastinal right lower paratracheal lymph nodes (B), and in the upper lobe of the right lung (B, arrows).

Malignant Lymphoma

^{67}Ga demonstrated useful in evaluating lymphoma patients: however, its accuracy depends on several factors, including the proper technical protocol of imaging.[15] It is well known that SPECT should be always performed to improve the sensitivity of planar scans and to better localize the abnormal sites of tracer uptake.[75] Nonetheless, the precise anatomical localization of malignant lesions can remain difficult despite optimal technical conditions and careful visual correlation with morphological images. These difficulties are related to the lacking of anatomical landmarks and to the physiological

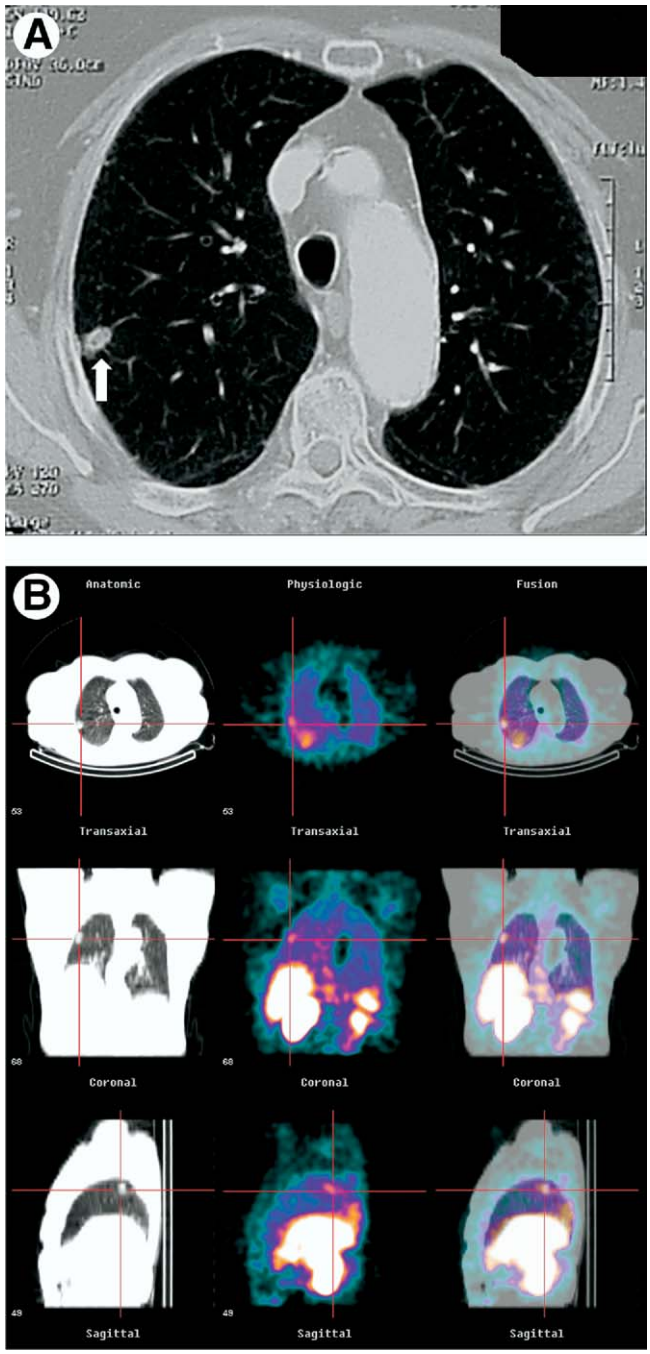

Figure 5 Shown is a 72-year-old woman with a SPN in the upper lobe of the right lung, adjacent to the chest wall, on diagnostic CT scan (A, arrow). ^{99m}Tc depreotide SPECT/CT (B) demonstrates a focal tracer uptake corresponding to the SPN. The final diagnosis was NSCLC.

^{67}Ga distribution: the liver, spleen, bone, and bone marrow show uptake of the tracer, which is excreted through the kidneys and the colon.[15]

The value of fusion with CT in helping the interpretation of ^{67}Ga SPECT was first reported in a group of 10 patients with suspected recurrence of lymphoma; SPECT/CT allowed the correct localization of relapse inside residual masses, thereby optimizing radiotherapy planning.[76]

The benefit of fused images in lymphoma has been then confirmed by Chajari and coworkers,[77] who coregistered ^{67}Ga SPECT and CT using external markers. A group of 38 patients (22 with HD and 16 with NHD) underwent 52 fusion studies, which permitted precise identification of the areas of ^{67}Ga accumulation and also the detection of lesions nonvisible on CT scans. In assessing the osseous involvement, imaging fusion proved very useful for distinguishing bone lesions from lesions adjacent to bone. In fact, the presence of several nodal or extranodal sites adjacent to bone can lead to misdiagnosis, because of the variable physiological ^{67}Ga accumulation in the skeleton. In the thorax, SPECT/CT was able to clarify tracer uptake at the edges of the chest, projecting over either the hepatic dome or the ribs, sternum or thoracic spine; in the abdomen and pelvis, it was of value in discriminating pathological foci from physiological bowel elimination, that is a clear limitation of ^{67}Ga imaging. In particular, fusion was of benefit in confirming pathological uptake in the left hypochondrium, accurately locating lesions in neighboring viscera, including the spleen, left liver lobe, celiac area, stomach wall, and the splenic flexure.

On the basis of SPECT alone, the discrimination between physiological and abnormal ^{67}Ga accumulation in abdomen/pelvis usually is committed to the comparison of 48-h and 6-day acquisitions. Therefore, SPECT/CT capability of characterizing areas of normal ^{67}Ga biodistribution or excretion is of the utmost importance for alleviating the need for delayed images, which are time consuming and unwelcome for patients. In this series, SPECT/CT fusion improved the diagnosis in 12 studies (23%) when compared with SPECT and CT interpretation alone, allowing the confirmation and/or localization of sites of pathological ^{67}Ga uptake (n = 10) or the identification of lesions not visible at CT (n = 2). The benefit of fusion was obtained in different clinical conditions, either at initial staging (n = 4) or after treatment, including the evaluation of a residual mass (n = 4) or the assessment of a possible recurrence (n = 4). These findings led to a change in management of 4 patients. However, despite the authors' conclusion is that SPECT/CT fusion is of value for facilitating the interpretation of ^{67}Ga scan and therefore its use in patients with lymphoma is recommended, they clearly state that their method of fusing images is time-consuming and limited by some factors.[77] In fact, it requires an accurate planning of SPECT and CT that must be performed on the same day, with the patient imaged in the same position, and the external markers carefully matched. These prominent disadvantages for a systematic adoption of this process have been overcome by the introduction in the clinical practice of dual-modality integrated devices.

The first data on the use of hybrid imaging systems with ^{67}Ga in lymphoma patients was very encouraging. SPECT/CT was able to furnish additional diagnostic information in 40% of cases, distinguishing pathological from physiological uptakes and guiding to the diagnosis of previously undetected sites of disease.[78] When used in monitoring response to treatment and follow-up of lymphoma patients, SPECT/CT provided better localization of lesions visible on SPECT alone, adding clinically useful information in 50% of cases, by showing the relationship between residual mass and residual tumor, guiding biopsy, or indicating the correct radiotherapy planning.[79] In another preliminary series, SPECT/CT proved able to give more information with respect to SPECT alone in a good number of lesions (27%). In particular, the fused images allowed the additional diagnosis of lymphoma lesions located in the abdomen, the precise anatomical identification of malignant sites, and the definition of the areas of tracer physiologic uptake or the presence of pathologic non neoplastic lesions.[80]

More recently, Palumbo and coworkers[81] have published the first peer-reviewed study aimed to investigate the clinical usefulness of ^{67}Ga hybrid SPECT/CT in lymphoma imaging. A group of 24 patients (21 HD and 3 NHL), who had supra- and subdiaphragmatic lesions, were studied to evaluate the possible additional value of SPECT/CT in comparison to SPECT alone for their clinical management. They were included in the study if scheduled to undergo initial staging (n = 9) or if they presented a residual mass on CT or MRI during or after therapy (n = 15). Patients imaged for initial staging underwent CT and/or MRI before the beginning of treatment, the other ones did so at midtreatment or at the end of therapy. Each patient underwent SPECT/CT 48 hours after the administration of ^{67}Ga in the region in which CT-MRI evidenced suspected disease (thorax in 18 subjects, abdomen in 6). SPECT and SPECT/CT outcomes were confirmed by CT scan data and/or MRI and clinical follow-up (at least 6 months). A total of 49 lesions were detected by SPECT/CT, and 45 lesions were visualized by SPECT alone; 40 of the 45 lesions identified by scintigraphic images alone were confirmed to be malignant. SPECT/CT allowed the identification of an additional 9 neoplastic lesions: 4 in para-aortic lymph-nodes, 3 in the spleen, 1 in the liver, and 1 in para-iliac lymph nodes. It is worth noting that all 9 lesions detected by SPECT/CT but not by SPECT alone were subdiaphragmatic, thereby confirming the ability of fusion in reducing the possible interpretation errors caused by bowel activity.

Moreover, SPECT/CT correctly classified as benign the 5 false-positive lesions revealed by SPECT that were the result of various causes: blood pool activity in the thoracic aorta, sialoadenitis in the submandibular gland, bowel activity, recent rib fracture, and bone marrow activation caused by radiotherapy. SPECT/CT provided additional information that was useful for a more accurate anatomical localization of 5 lesions already detected by SPECT alone. Therefore, globally SPECT/CT was able to improve interpretation of 19 of 59 sites (32%) of increased ^{67}Ga accumulation. Hybrid imaging findings added important clinical data in 13 of 24 of the patients evaluated (54.2%), and changed the treatment in 8 cases (33.2%). This strategy variation was the result of a modification of previous CT-MRI staging: the therapeutic options were modified in 4 patients studied for initial staging (44%) and in another 4 evaluated during treatment (17%). In particular, potentially toxic further therapy was spared in 4 cases of downstaging, and more aggressive treatment was chosen in 4 patients who were upstaged.

The clinical value of ^{67}Ga hybrid SPECT/CT in lymphoma has been confirmed by Carrera and coworkers.[82] They performed 59 studies in 44 patients (22 with HD and 22 with NHL): 2 in the skull-cervical area, 33 in the cervical-chest area, and 24 in the abdomen. When compared with SPECT alone, SPECT/CT improved the anatomical localization or changed the extension of the disease in 23 studies (12 in cervical-thorax area, 9 in the abdomen, and 2 in the skull-cervical area), and modified the staging in 4 cases. Therefore, fusion augmented the diagnostic accuracy in 46% of studies, mainly in assessing bone involvement and in evaluating the lesions in the diaphragmatic area and in the abdomen.

The data reported in these 2 studies are very interesting and show the potential advantages of SPECT/CT in lymphoma imaging with ^{67}Ga. They include the precise anatomical localization of abnormal ^{67}Ga accumulations, the identification of tumor lesions near sites of physiological uptake, and the accurate detection of viable lymphoma tissue inside residual masses (Fig. 6). However, it is crucial establishing with further investigations in larger series the clinical impact of hybrid SPECT/CT on patient management, especially when considering the growing role of FDG-PET/CT, which has become the preferred functional imaging modality in lymphoma.[83]

Hybrid SPECT/CT also can allow a more efficient use of radiopharmaceuticals by performing nonuniform attenuation correction of self-absorption of photons that results in improved image quality of emission studies. The effect of x-ray attenuation correction using a dual-modality device on lesion detection in ^{67}Ga SPECT imaging was specifically evaluated in a small group of 11 patients, including 7 cases of lymphoma.[84]A total of 27 lesions were considered: their detection was quantified by volumes of interest drawn over the lesion, adjacent to it, and over the region with least amount activity (background). The results obtained indicate that the x-ray attenuation- and scatter-corrected SPECT data reconstructed with an iterative algorithm significantly improve lesion detection, showing better both signal-to-background and lesion-to-nonlesion ratio in comparison with the uncorrected SPECT images.

SM and TF have been used in the study of patients with lymphomas, also if the biliary-intestinal route of elimination makes investigation of the subdiaphragmatic region difficult. In the workup of lymphoma patients with these radiopharmaceuticals, hybrid imaging devices might be useful in various clinical situations, eg, for precise functional characterization and staging of the disease at diagnosis; for detecting tumor tissue after treatment and its exact localization within a residual mass (Fig. 7); and for early diagnosis of

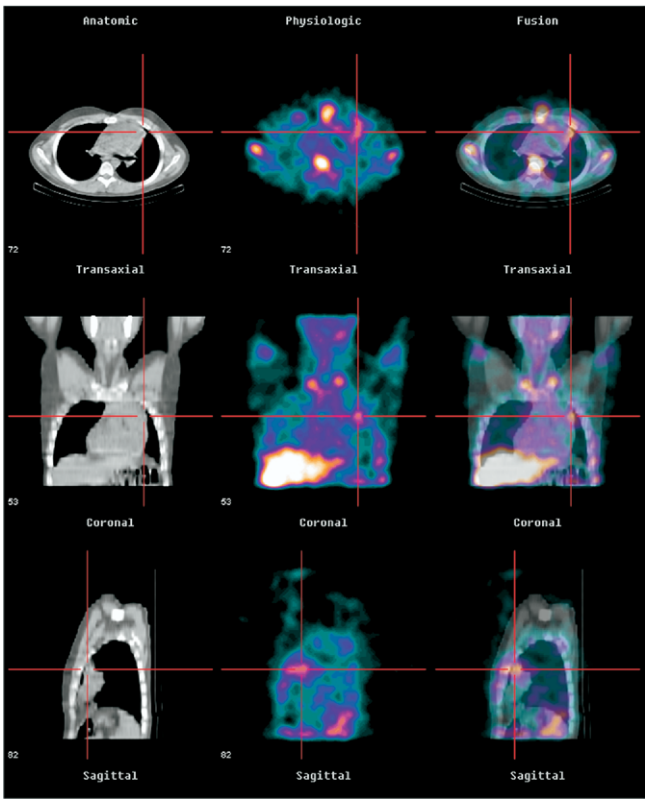

Figure 6 Shown is a 36-year-old man with HD. ^{67}Ga SPECT/CT accurately detected the presence of viable tumor tissue within the mediastinal residual mass after treatment.

relapse, especially if the findings of anatomical studies are not conclusive.[44] These applications are possible because SPECT/CT provides a better definition of organs involved in radiotracer uptake and their precise relationship with adjacent structures, it defines the functional significance of CT lesions and improves the specificity of SPECT excluding disease in sites of uptake unrelated to lymphoma lesions.

The possible role of SRS in lymphoma imaging has been reviewed recently in the October 2005 issue of *Seminars in Nuclear Medicine*.[85] Despite its generally limited impact in patients with lymphoma for diagnostic purposes, SRS is of value in staging and restaging of extragastric mucosa-associated lymphoid tissue-type NHL.[85] In this application, the use of hybrid imaging could improve the accuracy of SRS, that lacks of anatomic localization capacity, in defining the precise organ involved and in determining the presence or absence of invasion into surrounding tissues.

Dosimetry Estimations for Radionuclide Therapy

Another possible application of hybrid imaging is to use the structural information obtained from the CT data for an accurate activity quantification in SPECT studies. In a phantom model (ie, a cylinder containing 6 hot spherical inserts in a warm background), Erlandsson and coworkers[86] have reported that a SPECT/CT acquisition shows an improvement in image contrast and in the measurement of SPECT activity concentration. This aspect is particularly important in RIT applications, where the exact determination of dose to normal and tumor tissues is of the utmost significance, but difficult with the conventional dosimetry techniques.

There have been a large number of studies in recent years demonstrating the usefulness of RIT in patients with NHL.[87,88] In fact, the efficacy of immunotherapy with monoclonal antibodies is augmented when they are combined with a radioisotope like ^{131}I or ^{90}Y.[89] In particular, RIT using ^{131}I- and ^{90}Y-labeled anti-CD20 monoclonal antibodies is now indicated for the treatment of patients with CD20 antigen-expressing relapsed or refractory, low-grade or transformed NHL, including patients who are refractory to anti-CD20 monoclonal antibody (rituximab) therapy.[90] The CD20 antigen is a pan B-cell antigen, which is homogenously expressed on more than 90% of B-cell lymphomas at a very high density.[91] Myelosuppression is the main side effect associated with RIT, and it is dose-limiting; therefore, bone marrow dosimetry calculation is of the utmost importance to minimize the risk of myelotoxicity, especially in patients whose marrow reserve is compromised by previous treatments and tumor infiltration. Moreover, bone marrow dosimetry calculation in RIT of lymphoma is difficult, and conventional methods of dosimetry may not accurately account for doses actually received by the critical organ.[92]

The validation of prospective whole-body bone marrow dosimetry by hybrid SPECT/CT in ^{131}I rituximab anti-CD20 RIT of NHD has been recently proposed.[93] Twenty-seven patients with relapsed NHL after 1 to 5 previous course of chemotherapy plus often immunotherapy, undergoing a clinical study of ^{131}I rituximab anti-CD20 RIT, had SPECT/CT images acquired 5 to 7 days after the therapeutic dose administration to quantify bone marrow uptake. This approach using hybrid imaging was developed to validate a patient-specific prospective dosimetry method that uses the whole-body effective half-life of antibody and the patient's ideal weight to calculate the administered activity to deliver a fixed total body dose of 0.75 Gy in each patient. SPECT/CT was performed over the pelvis, because this area contains a relatively high volume of bone marrow, and the 3 marrow compartments in which uptakes were measured (spine, pelvis and femur). ROIs identifying the marrow tissue in each of the compartments were drawn on CT scan, and then moved onto corresponding SPECT slices of SPECT/CT display to measure the antibody uptake, that was corrected for inactive marrow and bone tissue volume. SPECT/CT demonstrated very useful to precisely identify bone marrow and differentiate it from the activity in the involved para-aortic lymph-nodes and in the aorta. Measurements of activity concentration in spine, pelvis, and femoral compartments correlated very closely; moreover, bone marrow activity concentration resulted proportional to administered

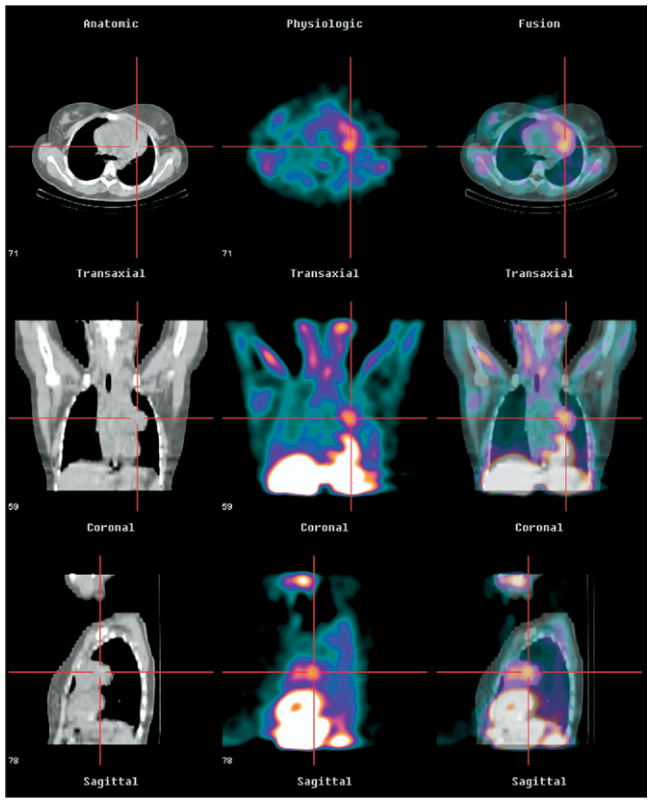

Figure 7 Shown is a 29-year-old woman with NHL. SM SPECT/CT after chemotherapy precisely demonstrates residual viable tumor tissue inside a mediastinal mass.

activity per unit weight, height, or body surface area. Furthermore, in a subgroup of 6 patients, 3 SPECT/CT studies were acquired on day 5, day 7, and days 10 to 12 after therapy administration to measure bone marrow clearance. A strong, significant correlation between whole-body effective half-life of antibody and effective marrow half-life was found. The findings of this study clearly demonstrate the important role of quantitative hybrid SPECT/CT imaging in optimizing RIT dosimetry, in particular to minimize marrow toxicity and to preserve tumor treatment efficacy.

Before this study, Koral and coworkers,[94-97] from the University of Michigan, had published several manuscripts on tumor dosimetry of ^{131}I-labeled anti-B_1 antibody RIT in untreated patients with follicular NHL, by means of SPECT/CT fusion. The CT scans acquired before RIT were fused with the intratherapy–SPECTs using a mutual-information–based algorithm. Through this fusion, the attenuation maps could be computed from CT and the tumor boundaries chosen on the CT slices and then applied to the SPECT images. Thus, an individual SPECT activity estimate was obtained for each tumor, defined by a combination of CT regions of interest.

Conclusions

In the era of FDG-PET, SPECT imaging with several different radiopharmaceuticals still can play an important clinical role in the workup of patients with lung cancer and malignant lymphomas. The combination of scintigraphic data with anatomical images, such as CT, adds structure to function and helps in overcoming some intrinsic limitations of SPECT studies. The introduction of hybrid systems in the clinical practice has rendered the fusion of SPECT and CT images of routine availability. The increasing use of hybrid SPECT/CT devices will facilitate image interpretation and will significantly improve the diagnostic accuracy of SPECT examinations in various oncology applications, also affecting the clinical strategies. In the future, ongoing technologic improvements, including the optimization of integrated SPECT/CT cameras, will keep SPECT studies useful in imaging lung cancer and malignant lymphomas for diagnosis, staging, monitoring and treatment planning, comprising dosimetric estimations for RIT, with a positive impact on patient management.

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