Fusion of Immunoscintigraphy Single Photon Emission Computed Tomography (SPECT) with CT of the Chest in Patients with Non-Small Cell Lung Cancer*

Sanjeev Katyal, Elissa Lipcon Kramer, Marilyn E. Noz, Dorothy McCauley, Abraham Chachoua, and Alan Steinfeld

Introduction

The diagnostic and staging evaluation of a patient with NSCLC depends on a variety of imaging modalities. SPECT imaging techniques combined with immunoscintigraphy are a new technique that can provide unique functional information, i.e., the detection of abnormal concentrations of tumor antigen. Immunoscintigraphy has been shown to be a preliminary use in NSCLC to date (1–5). Immunoscintigraphy offers improved sensitivity in detection of tumors such as colorectal carcinoma when used in conjunction with conventional imaging modalities (6). SPECT contributes to the sensitivity of this technique by enhancing contrast and by providing more exact localization of scan abnormalities in colorectal cancer (7, 8) and in NSCLC (5). However, the SPECT scan can often be limited by poor spatial resolution with inadequate anatomic detail, i.e., although an abnormal area of increased uptake is noted, the precise location and adjacent structures frequently are not well visualized.

One area of difficulty in the interpretation of SPECT images is in the differentiation of abnormal antibody uptake from normal blood-containing structures (5). This is particularly true in the mediastinum, where the prominent normal vascular activity may compromise the utility of immunoscintigraphy SPECT in patients with NSCLC. On occasion, other non-specific localizations can be difficult to distinguish from abnormal areas of uptake.

In contrast to SPECT images, structural imaging modalities such as CT or MRI provide excellent anatomic detail. These modalities frequently are used to detect and localize abnormal masses or enlarged lymph nodes. However, they cannot differentiate reliably tumors from benign masses or malignant lymphadenopathy from hyperplastic adenopathy seen in NSCLC. Also, when the normal anatomy of the patient is altered, i.e., in a postsurgical patient, detection of recurrent cancers may be difficult using only CT or MRI imaging.

In NSCLC, accurate, noninvasive staging is important in deciding between potentially curative surgical resection and palliative treatment. This may also be important to the surgeon in planning surgical treatment or exploration. The combination of tissue-specific information with anatomic information becomes useful in the staging of NSCLC to better characterize the information provided on each separate modality. Image registration, or fusion, precisely matches the data from different imaging modalities and enhances the information provided by both types of modalities. In the past, we have used this image registration algorithm to analyze radiolabeled anti-carcinoembryonic antigen antibody scans in patients with colorectal cancer (9). Using fusion, it is now possible to simultaneously examine functional and structural details of cross-sectional images in the chest (10–12).

In this study, we have fused CT with 99mTc-labeled IMMU-4 Fab’ antibody fragment SPECT images for 14 patients with NSCLC to explore the potential role of image registration in the diagnosis and noninvasive staging of NSCLC.

Materials and Methods

Subjects

Fourteen patients (7 men and 7 women) with biopsy-proven NSCLC were studied. The mean age of the patients was 69 years, with a range of 38–92. The histological types included poorly to well-differentiated bronchogenic adenocarcinoma, bronchoalveolar carcinoma, mixed adenocarcinoma and squamous carcinoma, and mixed adenocarcinoma and carcinoid. The clinical stage ranged from stage IIB to stage IV. All patients were further evaluated by medical history, physical examination, bone scan, and chest, brain, and abdominal CT. Written informed consent was obtained according to the guidelines of the Institutional Review Board.

Imaging Techniques

Patients received 20–30 mCi of 99mTc-labeled IMMU-4 anti-CEA Fab’ antibody fragment (Immunomedics, Morris Plains, NJ). The fragment was prepared by reduction of the F(ab’)2 fragment of the IMMU-4 antibody, an IgGκ isotype specific for the Mr 200,000 epitope of CEA. The lyophilized fragment was provided in kit form for radiolabeling. Radiolabeling was performed by mixing 99mTc-labeled pertechnetate in saline with 1.25 mg lyophilized fragments for 5 min. Instant TLC in saline was performed to determine the radiolabeling efficiency. This averaged 96.8 ± 3.7%. Immunoreactivity was determined using a CEA affinity column and was found to average 61 ± 8.1%. The antibody was administered i.v. over 20–30 min.

For the SPECT of the chest, 57Co markers were placed at the cardiac processes, sternal notch, and xiphoid process. SPECT images were acquired using a triple-headed rotating SPECT camera (Triad; Trionix Corp), fitted with low-energy high resolution collimators, and interfaced to a SUN SPARC 390 (SUN Microsystems). Planar and SPECT imaging were performed either at 5–8 and 22–24 h or at 16–18 h after i.v. administration of the radiolabeled antibody. Acquisitions were performed with dual energy windows: a 20%...
energy window centered at 140 KeV for the antibody images ($^{99m}$Tc) and a 4% window centered at 122 KeV for the markers ($^{57}$Co). One hundred twenty projections were acquired at 25–30 s/view, over a 360° interval, into either a $64 \times 64$ or $128 \times 128$ matrix. This yielded two simultaneously acquired sets of images: one showing the radioimmunoconjugate distribution and the other, the radioactive markers. The projections were reconstructed into 3.5-mm thick transaxial sections by using filtered back projection with a Hamming filter, 0.7 cyc/cm Nyquist and 0.4—0.55 cyc/cm high cut frequency, and Chang's method of attenuation correction.

All CT studies of the chest were performed after the administration of oral and i.v. contrast. The iodinated i.v. contrast material was administered as two bolus infusions for dynamic incremental CT scanning. A total of 200 ml of 43% contrast material was delivered by a power injector (Angiomat CT injector: Liebel-Flarsheim, Cincinnati, OH) in a 50-mI bolus (2.5 ml/s), followed by a 150-ml infusion (1 ml/s). Scanning, using either a GE 9800, High-Light Advantage or a High Speed (Helical) CT, commenced approximately 15 s after initiation of the infusion phase. Contiguous axial 5–10-mm thick CT sections of the chest were obtained in a $512 \times 512$-pixel matrix.

**SPECT-CT Image Registration**

The transaxial CT, SPECT antibody, and the SPECT markers slices were transferred offline, via Ethernet, to a Sun SPARC 670MP and converted to a standard AAPM/interfile format. Qsh, a hardware independent image display and handling toolkit composed of several software modules, was used to handle the standardization of image data from the contrasting modalities (SPECT and CT). To match pixel dimensions within the plane of reconstruction, the images were interpolated to a corresponding matrix size. Using standard bilinear interpolation, the $64 \times 64$ SPECT images were enlarged to a $128 \times 128$ format, and the $512 \times 512$ CT images were reduced to a $128 \times 128$ matrix format. The SPECT and CT slices were simultaneously displayed side-by-side on the same monitor with individualized color scales chosen for each image. Saturation, background, window widths, and levels were adjusted for optimal visualization of each modality. The marker slices were selected and used to determine the level of the cardioaortic processes, sternal notch, and the xiphoid process. Since the marker and antibody views were acquired simultaneously, the marker slice level was used to identify the corresponding slice in the antibody image. These SPECT levels were matched with appropriate CT slices containing the corresponding anatomy marked on the SPECT. The images were reviewed by two of the authors (S. K. and E. L. K.), and SPECT slices with suspected abnormalities and CT slices of interest, e.g., tumor or possible adenopathy, were selected for fusing. In addition, a reference slice through the descending aorta was chosen. These levels, identified on the CT or SPECT images, were then matched with appropriate corresponding slice in the other modality. The correspondence for other CT/SPECT slices of interest was calculated by measuring the number of pixels from already-matched CT/ SPECT slice pairs and then using the known thickness of the SPECT slices (~3.5 mm) and the CT images (5–10 mm) to find the corresponding slice.

On the SPECT, landmarks were identified along the body edge, defined by the pattern of scatter. By matching the features of the body edge on SPECT to features of the clearly delineated body edge on the CT, corresponding point pairs were selected (Fig. 1). To define the outline of the lungs, body wall, and an intermediate “surface” using the color, SPECT images were displayed normalized to a consistent color scale. Using this intermediate “surface,” as well as the points placed along the body wall, 12–15 point pairs were generated for each slice pair. An in-plane, polynomial-based warping algorithm generated a polynomial transformation from these landmarks, and the correspondence between the point pairs in terms of scale, rotation, translation, and skew was determined.

To preliminarily assess the correctness of the match, ROIs were initially drawn around lung fields on CT, for one slice pair per patient, and then warped onto the SPECT. If this initial analysis of the image fusion was unsatisfactory, one or more landmarks were adjusted on either the CT or SPECT image, and the ROIs were automatically regenerated.

To quantitatively assess the match, a ROI was generated over the descending aorta on CT and warped onto the SPECT. A reference ROI was drawn over the descending aorta directly on the SPECT image for comparison with the warped ROI from the CT image. To avoid the introduction of bias in image registration, the reference ROIs were drawn on the SPECT image without reference to the warped ROIs. Additional ROIs were drawn over features of interest, e.g., areas of suspected tumor, lymphadenopathy, and abnormal areas of increased density on CT, and then warped onto the SPECT image. The fusion algorithm was also used in the reverse manner with ROIs drawn over areas of abnormal activity (hot spots) on SPECT and then warped onto the corresponding fused CT slice. For each SPECT-CT slice pair, registration required 15–20 min.

**Methodology Validation**

Quantitative analysis of the SPECT-CT image fusion was performed to ascertain the precision of the warping algorithm. Two methods, which compared the descending aorta ROI generated on the CT and warped onto the SPECT with the ROI generated independently on the SPECT, were used.

**ROI Center-to-Center Distance.** The centers of the ROIs were calculated by averaging the x and y coordinates of the pixels comprising each ROI. Using vector analysis, the distance in pixels between the centers of the warped ROI and the SPECT ROI were then calculated.

**ROI Overlap.** Ideally, one would expect complete overlap of the pixels in the warped ROI and the SPECT ROI. To determine the degree of overlap, the number of pixels which were within both the warped and reference ROIs were determined. The number of pixels common to both ROIs was then determined and expressed as a percentage of the number of pixels in the independently drawn SPECT ROI.

**Results**

Image registration was successfully performed for the fourteen patients studied and resulted in a total of 40 registered structural-functional image slice pairs. The calculated difference between the centers of the warped and reference SPECT ROIs ranged from 0.2 to 3.4 pixels. The average ROI center-to-center distance was 1.3 ± 0.8 pixels. The number of pixels common to both the warped and reference ROIs averaged 54 ± 8% of the pixels in the reference SPECT ROI.

CT-SPECT fusion helped differentiate areas of tumor and mediastinal lymphadenopathy from normal cardiac blood pool in 7 of 14
patients studied. In one patient with evidence of right hilar lymphadenopathy on CT, it was possible to differentiate the ascending aorta and superior vena cava activity from enlarged right hilar node activity. In two other cases studied, the left and right main pulmonary artery activity was differentiated from adjacent tumors, and in another two patients, areas of increased uptake adjacent to the descending aorta activity could be identified conclusively as abnormal on SPECT (Fig. 2). In the last two patients, fusion helped differentiate the medial aspect of left apical tumors from the left brachiophecal vein and the left carotid and subclavian arteries and helped to clearly define the size and intensity of the tumor activity.

Lung tumors are often ill-defined and heterogeneous with varying degrees of viable tissue. On CT alone, it can be difficult to distinguish the viable portion of a tumor from areas of necrosis. This differentiation may be important in assessing treatment response. In three patients, image registration clearly differentiated the viable areas from areas of necrosis within large inhomogeneous tumors. In one, a well-defined central area of decreased density on CT correlated well with an area of photopenia on SPECT (Fig. 3). In two other cases, low density areas in an inhomogeneous mass on CT correlated well, in size and shape, with photopenic areas on the heterogeneous SPECT image.

Three patients who had undergone surgical resection of their primary tumors were studied. In each, CT could not differentiate between recurrent tumor and scar. In one patient who had undergone a wedge resection for a right upper lobe mixed amine precursor uptake and decarboxylase cell and adenocarcinoma tumor, CT showed increased soft tissue density in the pulmonary parenchyma at the surgical site. Fusion demonstrated that this density did not correspond to increased activity on the SPECT image, supporting the diagnosis of scar. Clinical follow-up of this patient confirmed the absence of tumor. The remaining two postsurgical patients presented with hilar soft tissue density at the site of surgical resection. With fusion, the presence of increased uptake on SPECT corresponding to the soft tissue supported the diagnosis of recurrence (Fig. 4).

Accurate mediastinal staging is critical for the management of NSCLC. Fusion of antibody SPECT and CT images was used to evaluate mediastinal lymphadenopathy or activity. Eight of our 14 patients demonstrated lymphadenopathy on CT. In seven, fusion clearly localized abnormal areas of increased activity to the enlarged nodes noted on CT. In six surgical patients, confirmation or clinical follow-up confirmed the presence of mediastinal disease. In the seventh patient, no confirmation was available. This patient had extensive distant metastases and lung recurrence. In the eighth patient, fusion demonstrated the absence of activity in the pretracheal space and aorticopulmonary window, where CT showed adenopathy. At surgery, biopsies of the enlarged nodes revealed benign sinus histiocytosis (Fig. 5).

Discussion

The aim of image registration or fusion of “functional” studies like immunoscintigraphy with structural studies like CT or MRI is to synthesize the different types of information available in each modality to enhance our understanding of the studies and the status of disease in a particular patient. Although structural cross-sectional studies may offer exquisite anatomic detail, they are hampered by a relative lack of tissue specificity. In contrast, immunoscintigraphy SPECT provides information about tissue specificity but without very much anatomic context.

We have used the method of image registration we reported previously for these studies (9, 10, 13, 14). The SPECT studies were acquired with dual energy windows to provide anatomic and landmark information in one window and antibody distribution in the other.
The most time-consuming task of image registration was landmark determination, and the ability to identify two truly coplanar slice pairs demonstrates a high degree of precision in the fusion technique. The difference between the centers of the warped and the reference ROIs corresponded to body wall muscle on CT, to increase the number of terms entered into the polynomial transformation algorithm has been shown to be the most important factors (14). We used a consistent pattern of scatter on the SPECT to define the features of the body edge and the lung outline on SPECT, which corresponded to body wall muscle on CT, to increase the number of point pairs for each slice of interest. Also, this permitted the wider dispersal of landmarks throughout a slice, which improves the tightness of the fit of the registered images. This was qualitatively appreciated upon fusion, with errors resulting from asymmetrical distribution of landmarks.

Quantitative evaluation of the fusion algorithm revealed that we may use fusion to localize a focus of increased uptake to the site of a soft tissue density or vice versa with excellent accuracy. The average difference between the centers of the warped and the reference ROIs in this study is similar to that achieved with phantom studies (15) and demonstrates a high degree of precision in the fusion technique.

The ROI overlap method addresses issues of edge detection, size determination, and the ability to identify two truly coplanar slice pairs. There was considerable lack of overlap between the reference and warped ROIs. Several factors may contribute to the poor results: (a) one is the difficulty in identifying the true edge of an object on SPECT. Possibly, a thresholding technique such as described by Front et al. (16) and used by Siegel (17) might improve the edge detection on the manually generated SPECT ROI; (b) a second contributing factor might be slight differences in the angle of reconstruction. This may lead to differences in the shape of the object in the SPECT image compared to the CT. Thus, a region drawn on the CT would represent a slightly different orientation than the region drawn directly on the SPECT. Although we have the capability of reorienting the tilt of the slices with the algorithm, we chose not to in this study because relatively fewer degrees of motion are possible in the chest; and (c) there may have been small differences between the transaxial levels depicted on the SPECT and CT slices. The inaccuracy in matching transaxial levels might be lessened by choosing slice thickness on the CT to better match the slice thickness of the SPECT. Also, using a three-dimensional display to identify landmarks in multiple planes at once might facilitate better matching.

In our study, CT-SPECT fusion helped differentiate areas of tumor and mediastinal lymphadenopathy from normal cardiac blood pool. The normal vascular activity seen on immunoscintigraphy often shows equal or greater intensity than areas of abnormal uptake (i.e., tumor or lymphadenopathy). Fusion will be useful in the interpretation of SPECT to eliminate false positives from blood pool and increase confidence in identifying abnormal foci of uptake adjacent to blood-pool containing structures.

Fusion also helped differentiate tumor from scar or fibrosis and tumor from necrosis within a mass on CT. This suggests a role for fusion of immunoscintigraphy with CT in assessing treatment response, residual tumor volumes, and possibly in radioimmunotherapy planning.

Perhaps the most exciting and clinically important potential appli-

---

Fig. 4. A 74-year-old man with previously resected NSCLC in whom scar was expected clinically but in whom CT detected an unanticipated soft tissue density at the surgical site. An ROI generated over the soft tissue density on CT was warped onto the 5762s

Fig. 5. A 67-year-old man with newly diagnosed NSCLC. A staging CT of the chest demonstrates precarinal soft tissue density. Fusion of this CT with 99mTc-labeled IMMU-4 Fab' SPECT shows that the warped ROI overlies an area of increased activity just posterior to the ascending aorta activity, consistent with neoplastic lymphadenopathy rather than lymph node hyperplasia.
FUSION OF CHEST SPECT AND CT IN NSCLC

cation of CT-SPECT fusion is in the evaluation of mediastinal lymphadenopathy. Surgical resection offers the only chance of cure for this large group of patients. Accurate mediastinal staging is critical for selecting patients for surgery, and the information provided by immunoscintigraphy could improve significantly on the evaluation of mediastinal lymphadenopathy currently provided by CT. In eight of our patients, fusion enhanced the ability to assess uptake at the site of lymphadenopathy. Application of fusion to patients with primary NSCLC would be useful for noninvasive staging prior to surgery.

We have used image registration to further enhance the quality of information provided by CT and immunoscintigraphy SPECT imagining in NSCLC. In particular, the accurate differentiation of metastatic nodal involvement from hyperplastic adenopathy and the precise anatomical localization of areas of abnormal radioactivity on SPECT make future applications of fusion in NSCLC staging appear quite promising. In the future, thresholding techniques and three-dimensional image manipulation may improve the algorithm. It is anticipated that this methodology will not only contribute to our understanding of immunoscintigraphy SPECT but also to the quantitation of tumor size and activity and will play an important role in planning radioimmunotherapy.

Acknowledgments

We thank Carol Scoppe for her invaluable assistance in organizing the image data and Djenane Racine and Evelyn Millan for technical assistance.

References


Fusion of Immunoscintigrapy Single Photon Emission Computed Tomography (SPECT) with CT of the Chest in Patients with Non-Small Cell Lung Cancer


Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/55/23_Supplement/5759s

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.