Validation of Gallium-67-Citrate Single-Photon Emission Computed Tomography in Biopsy-Confirmed Residual Hodgkin's Disease in the Mediastinum

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In a retrospective study of a series of 30 adult patients during restaging of Hodgkin's disease after therapy, computed tomography (CT) and biopsy results were correlated with ^{67}Ga SPECT in order to determine the value of SPECT imaging in monitoring recurrent mediastinal Hodgkin's disease. SPECT had an overall accuracy of 93% (28/30) and correctly identified active disease in 24 of 25, 96% of histopathologically proven recurrent Hodgkin's disease. Thus in this post-therapy setting, we have confirmed the high sensitivity of ^{67}GA SPECT scans in patients selected for biopsy. Gallium-67 may prove particularly useful in detecting residual disease activity in patients in whom biopsy was positive but the interpretations of the CT scans were uncertain in regard to presence of tumors [8/30 (27%)]. In this group of patients, we found SPECT particularly helpful. A larger prospective series is under way to assess this possibility.

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Treatment of Hodgkin's disease of the chest or mediastinum usually results in either complete or partial response to therapy, but commonly the clinical situation is complicated with residual mediastinal widening on x-ray and CT scans following the completion of therapy (*1*). These persistent residual abnormalities fall under a new category of unconfirmed/uncertain complete remission (CR[u]) (*2*), which has been recently introduced to accommodate the difficulty constituted by radiological abnormalities of uncertain significance in the restaging of Hodgkin's disease or consideration of further therapy. These radiographic modalities frequently fall short in differentiating fibrosis and infection from active disease (*1,3*).

Based on the pioneering work by Tumeh et al. (*4*) in the application of high-dose ^{67}Ga SPECT scanning, ^{67}Ga scanning has become a standard imaging modality in patients diagnosed with lymphoma, especially high-grade lymphomas and Hodgkin's disease. As no prior study of ^{67}Ga SPECT and CT scanning has been completely biopsy-controlled, we correlated biopsy results with SPECT and CT scans in all patients while realizing that the only definite way to discriminate mediastinal abnormality due to recurrent disease from that due to fibrosis is tissue diagnosis.

Gallium-67-citrate uptake is mediated by transferrin receptors on tumor cells and reflects an active metabolic process that is detectable by SPECT at a time when plain chest x-rays (CXR) or CT scans may not be definitely positive for the presence of tumor (*5–7*). In this setting, ^{67}Ga-citrate also has been used to determine when a CT abnormality is indicative of fibrosis and a negative gallium scan is thought to be helpful for excluding the presence of tumor (*8–11*). This current study supports the high sensitivity of ^{67}Ga for detecting Hodgkin's disease based on pathologic confirmation.

PATIENTS AND METHODS

We retrospectively reviewed the ^{67}Ga SPECT imaging findings and clinical histories of 30 patients who presented for restaging of Hodgkin's disease located in the mediastinum and/or neck. We reviewed 250 gallium scans performed between 1988 and 1991. Of this main population, we selected a group of patients with Hodgkin's disease who presented for restaging of the disease upon completion of treatment. A subgroup of patients were surveyed on the basis of availability of ^{67}Ga SPECT studies, concurrent CT scans and biopsy reports of relevant sites. The study group was comprised of 18 male and 12 female patients with an age range of 18–71 yr (mean 28 yr). We excluded 11 pediatric patients in order to eliminate the potential confusion brought about by post-therapy thymic hyperplasia (*12–14*).

The SPECT findings were compared with concomitant standard chest CT scans and histopathologic results in all patients. All patients completed combination chemotherapy and 16 received radiotherapy. The interval between completion of therapy and imaging ranged from 3 wk to 4 mo in our series, except in five patients who were off therapy for over a year.

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Contemporaneous histopathology reports were available in all patients for correlation with ^{67}Ga SPECT and CT scans. All CT examinations were performed on either a GE or Picker scanner with a scanning time of 2 sec. Contiguous axial images were obtained at 10 mm thickness from the lower neck region to the diaphragm on all patients. In addition, four patients whose disease was located in the region of the neck had CT scans, including the neck. CT scans were analyzed for the presence of mediastinal and/or neck masses and pulmonary nodules by one radiologist blinded to the previous ^{67}Ga SPECT, CT and biopsy results. Comparisons with the old CT scans were performed on all patients, if available.

All scintiscans were obtained on a large field of view gamma camera with tomotographic capability 48–72 hr following the administration of high-dose ^{67}Ga (10 mCi, 370 MBq). A medium-energy collimator was used with 20% windows centered over 93, 184, 286 keV photon peaks. The scan intensity is set according to the data intensity (200 counts/pixel). Anterior and posterior whole-body images from vertex to mid-thighs were obtained at 48–72 hr postinjection. A SPECT acquisition is obtained over the area of interest using 64 stops with a matrix size of 64 × 64, an acquisition time of 30 sec/view in a step-and-shoot technique. SPECT projections are spatially smoothed and reconstructed using a filtered backprojection technique with a Butterworth filter of 0.50 cut-off frequency, order of 5, and a dampening factor of 0.50. Center of rotation correction was performed prior to the study. A three-dimensional display was used to display and create image sets one-pixel thick in the coronal, sagittal and transaxial planes. For the sagittal and coronal sets only, those slices which included the patient's activity were saved. In general, the entire set of transaxial slices was included. The three sets and the projections were then transferred for viewing and interpretation by the nuclear medicine physician. SPECT and planar images were interpreted separately by two nuclear physicians without knowledge of the final reports of both CT, SPECT and biopsy results. A consensus interpretation was reached by both nuclear physicians without knowledge of the name and final report of any patient.

We based our SPECT interpretation on the criteria indicated in Table 1. We interpreted the SPECT scans with the liver as the reference in comparing suspicious radiotracer uptake in the mediastinum. All the cases we selected were disease-free in the liver.

TABLE 1
Criteria for SPECT Interpretation

Nature of radiotracer uptake	^{67}Ga interpretation
Focal or multifocal RTU* equal to or higher than liver uptake	Positive scan for active disease
RTU lower than the liver and more than the background lung uptake	Equivocal scan c/w either active disease or inflammation
Focal or diffuse irregular RTU in the mediastinum which is not distinctly discernible from background uptake	Positive scan for inflammation or fibrosis; negative for active disease
No focal or diffuse RTU in the mediastinum	Negative scan for both active disease and inflammation or fibrosis

* RTU = radiotracer uptake.

The results were correlated with those of CT and pathologic results in all patients by one radiologist and two nuclear medicine physicians.

RESULTS

The results of SPECT ^{67}Ga scintigraphy and CT as compared with histopathologic results are shown in Table 2. Histopathologic data revealed 25 recurrent cases which were mostly positive for nodular sclerosing type (Table 3). All of these recurrent cases were unchanged in disease histologic type from the initial diagnosis.

We correctly identified recurrent disease in 24 of 25 (96%) of histopathologically proven active disease by

TABLE 2
Comparison of ^{67}Ga SPECT, CT, and Histopathologic Results

TABLE-2A

	Biopsy (+)	Biopsy (-) *
(+) SPECT	24	1
(-) SPECT	1	4

TABLE-2B

	Biopsy (+)	Biopsy (-) *
(+) CT	17	2
(-) CT	0	3

* 8 CT scans were of (CR[u]) (2)

TABLE 3
Histopathologic Results for Cases of Recurrent Hodgkin's Disease

Histopathologic data on initial diagnosis		Histopathologic data on restaging	
NSHD	27	NSHD	22
Mixed cellularity	1	Mixed cellularity	1
Lymph predom.	2	Lymph predom.	2
		Negative	5

SPECT studies, while CT scans revealed 17 cases of active disease. An additional eight CT scans were read as "suspicious or equivocal" in which possible soft-tissue masses were noted with no discernment between active disease, fibrosis and/or infectious process (Figs. 1B, 2B). In these eight equivocal cases, seven were positive for disease activity (Figs. 1A, 2A) and one was false-negative on SPECT imaging.

There was no evidence of active disease on biopsy in five cases, three of which were detected by both SPECT and CT, and one was detected only by SPECT on which the CT was false-positive. In order to exclude the possibility of biopsy sampling errors, these five patients whose biopsies were negative for Hodgkin's disease were followed clinically and by repeated gallium and CT scans for 3 mo

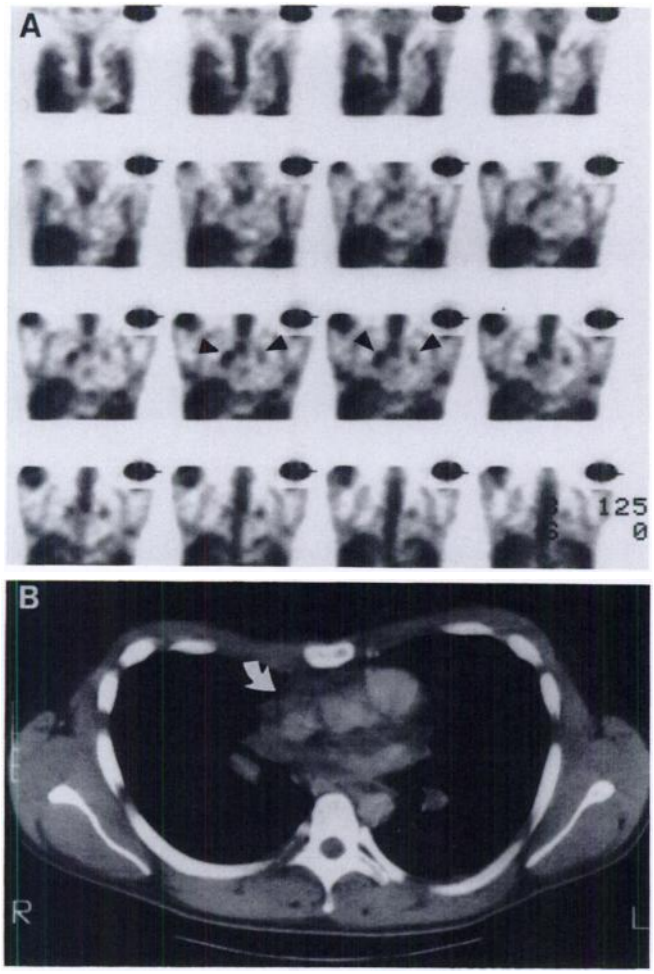

FIGURE 1. (A) A 36-yr-old male with mediastinal Hodgkin's disease treated with chemotherapy, which was completed 2 mo prior to imaging. SPECT images depict increased radiotracer uptake in both hilar regions (arrows), compatible with residual disease. Irregular lung uptake, attributable to chemotherapy, is also visible. (B) CT scan on the same patient demonstrates a subtle focus of residual mass in the right anterior mediastinum (arrow) indiscernible from active disease and interpreted as consistent with either fibrosis or residual mass, whereas biopsy of a right hilar lymph node revealed nodular sclerosing Hodgkin's disease.

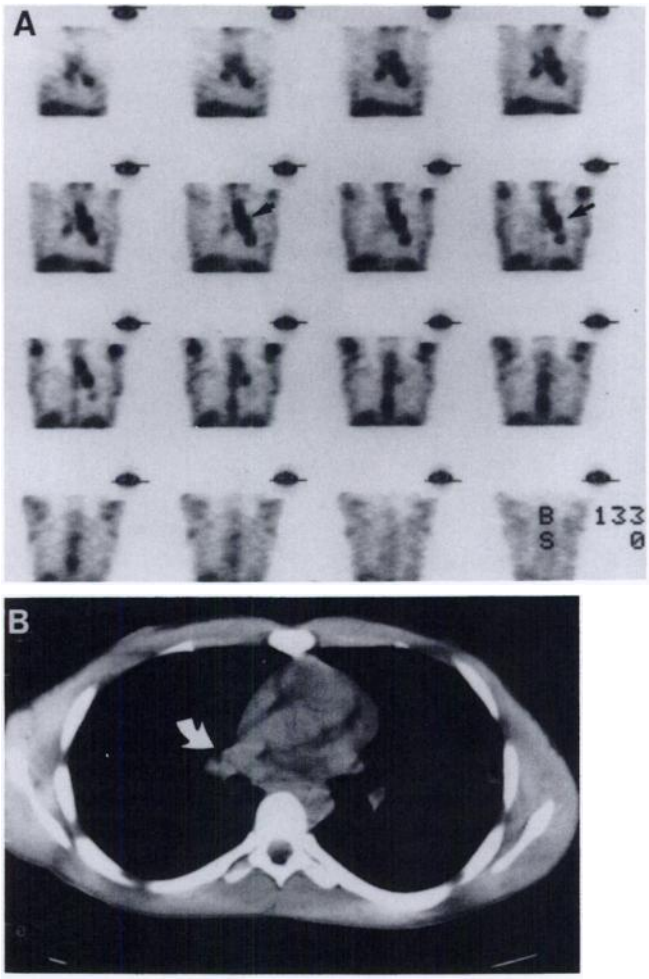

FIGURE 2. (A) A 21-yr-old male with nodular sclerosing Hodgkin's disease completed chemotherapy 10 wk prior to imaging and was then referred for restaging of the disease. SPECT images on coronal sections depict diffuse increased ^{67}Ga uptake in distribution of left paratracheal, hilar and anterior mediastinal lymph nodes, representing recurrent Hodgkin's disease. (B) CT scan of the same patient displays suggestion of enlarged lymph nodes in the right hilar region (arrow). However, this finding could not be differentiated from fibrosis and therefore could not be precisely interpreted as recurrent disease. Subsequent biopsy of the corresponding lymph nodes revealed recurrent Hodgkin's disease.

on a monthly basis. The ^{67}Ga SPECT studies and CT scans were both unchanged at the end of the 3-mo period, from the prior scans performed at the time of the biopsy. There was neither clinical evidence nor laboratory evidence of recurrent disease for at least a 3-mo interval. Following this initial 3-mo follow-up period, the patients were continually followed up to 6 mo on a bimonthly basis and were still disease-free by laboratory and clinical data. Also, repeated ^{67}Ga and CT scans did not show any interval change. There were two false-positive CT scans and one of these patients also had a false-positive SPECT study in which the disease was anatomically located in the anterior mediastinal region (Fig. 4A). The two false-positive CT scans were interpreted as mediastinal soft-tissue prominences in the anterior mediastinum, highly suggestive of recurrence or residual disease. Relevant biopsies revealed fibrotic tissue in the mediastinum (Figs. 3B and 4B). One of the aforementioned cases which was false-positive in the mediastinum on CT scan was true-negative on SPECT imaging (Fig. 3A).

There was one false-negative SPECT scan on which CT was equivocal in showing poorly-defined soft-tissue prominence in the left hilum and biopsy was positive for Hodgkin's disease.

Statistical Analysis

Thirty cases were examined by both CT and SPECT imaging in order to compare the sensitivity and specificity of these scanning methods. There were eight equivocal cases on CT scan. All eight cases were positive by biopsy. For CT, the "worst" sensitivity (considering the eight equivocal cases as false-negatives) is 68% (17/25), the conditional sensitivity (omitting the equivocal cases) and the best sensitivity (considering the eight equivocal cases as true-positives) are 100% (17/17 and 25/25, respectively) (*15*). There were no equivocal cases that were disease-negative based on biopsy; therefore, the specificity for CT is 60% (3/5) without ambiguity. For SPECT, the sensitivity and specificity are 96% (24/25) and 80% (4/5) without ambiguity since there were no equivocal cases. The differences in these results between CT and SPECT cannot be tested statistically due to an inadequate number of discordant pairs (i.e., positive on SPECT and negative on CT or positive on CT and negative on SPECT) (*16*).

However, there is significant association between scanning methods and equivocal results ($p < 0.01$; McNemar's test). The data strongly suggest that CT is inferior to SPECT with respect to equivocal outcomes.

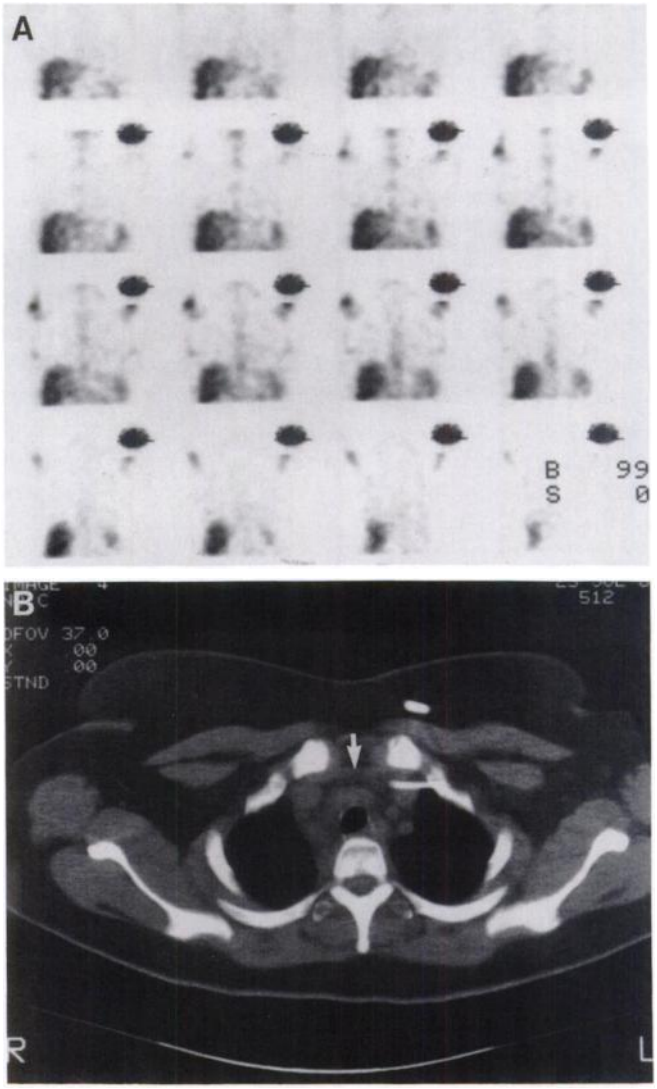

FIGURE 3. (A) A 20-yr-old female with Hodgkin's disease, Stage IIB, was treated with chemotherapy which was completed 2 mo prior to imaging. The patient was referred for restaging upon completion of therapy. Coronal images on the SPECT study demonstrate normal distribution of radiotracer throughout the visualized thoracic structures with no evidence of recurrent or residual disease. (B) CT scan of the same patient demonstrates residual disease in the anterior mediastinum (arrow). Biopsy of the anterior mediastinal lymph nodes was negative for Hodgkin's disease. The biopsy material was fibrotic in part.

DISCUSSION

Gallium-67 SPECT images should play a crucial role when CT depicts a subtle focus of mass indistinguishable from active disease, especially in cases where further therapeutic steps are to be taken in the management of patients.

At least 60% of patients with Hodgkin's disease have mediastinal involvement and this is associated with a high risk of relapse when the mass is bulky (*17*). Because of this risk, such patients are often submitted for combination therapy. Mediastinal abnormalities are preset in as many as 64% of patients following the completion of treatment (*18*). It is usually not clear whether persistence of mediastinal widening indicates a need for more extensive chemo- or radiotherapy. Based on clinical assessment, Anderson and Kaplan found an overall accuracy of 96% and a specificity of 90% or greater for both Hodgkin's disease and non-Hodgkin's lymphoma (NHL) for planar ^{67}Ga scanning (*19*). A more recent study confirmed these findings (*9*). Improved technology in gamma cameras and the

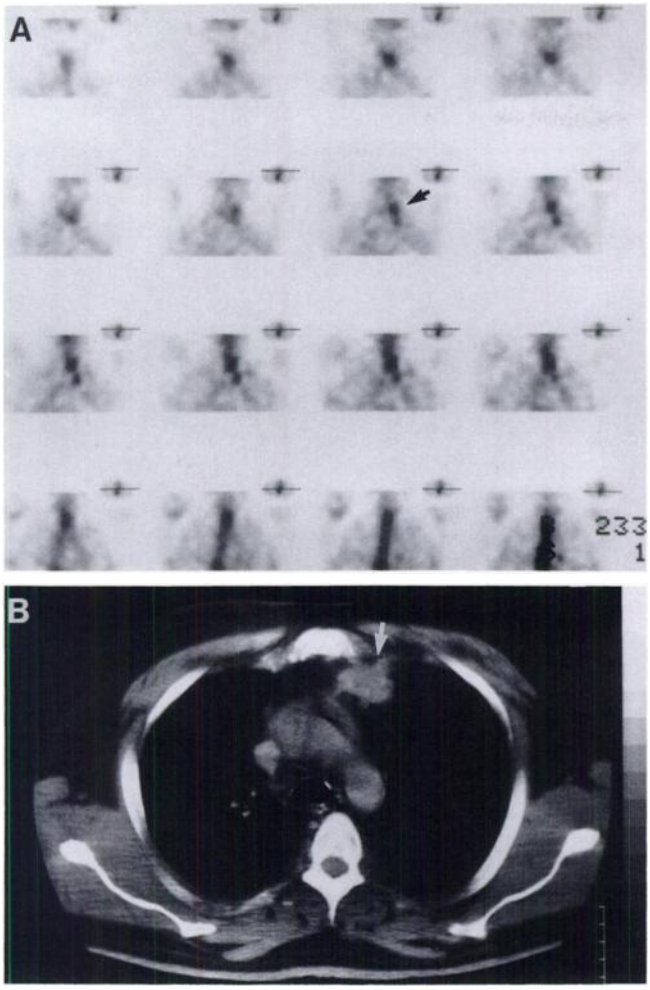

FIGURE 4. (A) A 30-yr-old male with Hodgkin's disease underwent SPECT imaging for reevaluation of the extent of disease 9 wk following the cessation of treatment. Coronal sections of the SPECT study reveal intense radiotracer uptake in the left paratracheal and hilar regions (arrow) which were all highly suggestive of active disease. (B) CT scan at the same corresponding level as SPECT images shows residual disease with subtle calcification, contained within the left anterior mediastinum (arrow). Biopsy of the mediastinal lymph nodes showed dense sclerotic fibrosis with evidence of old hemorrhage and a few nests of thymic tissue and no evidence of active disease.

availability of SPECT have improved gallium scanning, specifically for mediastinal imaging. In addition, the use of a dose of 10 mCi of ^{67}Ga in adults has increased the count density, thereby eliminating false-negative results, often recorded in prior studies (*20–25*). However, Hagemister et al. compared the ^{67}Ga planar images performed with 3–5 mCi without SPECT imaging with those carried out by a newer technology in which a dose of 7–10 mCi of ^{67}Ga was administered (*26*). In this study, although a trend toward improved results in peripheral nodal sites at higher doses appeared, there was no improvement in the overall accuracy. Again it should be noted that this study was performed only with a planar technique. On the other hand, SPECT techniques and precision are greatly improved by increasing count rate. Increasing the amount of administered radioactivity enhances image contrast and may depict additional disease foci. The ability to use SPECT imaging to create transaxial, coronal, and sagittal image planes may also improve detection of lesions in the mediastinum and aids greatly in locating abnormalities. Residual abnormalities remaining after treatment confounds diagnostic and clinical decisions. In one series, only 18% of the patients with residual mediastinal abnormalities relapsed and in the same study 45% of patients who were considered to have incomplete remissions eventually achieved a complete remission in 1 yr (*27*).

Since the main purpose of this study is to compare primarily the sensitivity of both CT and SPECT studies in biopsy-controlled patients, we studied a subgroup of Hodgkin's disease patients on the basis of availability of concurrent CT scans and biopsy results. However, this selected group of patients might not reflect the actual recurrence rate of Hodgkin's disease due to the fact that negative CT and SPECT scans readily obviate the need for biopsy, whereas positive scans on either modality might prompt biopsy depending on the clinical indication and decision. Therefore, the results derived from this particular study appear to have a high recurrence rate and would tend to select those patients with active disease. The true-negative gallium scan is the most difficult to document. Repeated delayed imaging is suggested to enhance the tumor-to-background ratio for detecting subtle sites of recurrent or residual disease (*28*). However, as this is a retrospective study, we did not have the opportunity to carry out this approach. Instead, we had the advantage of evaluating tumor localization with a SPECT technique that is a well-established nuclear medicine imaging approach for increasing image contrast.

In the evaluation of newly diagnosed patients with Hodgkin's disease, CT is currently the imaging method of choice for staging in clinical application. However, following treatment for monitoring response to treatment or early relapse, ^{67}Ga SPECT imaging may be particularly useful in assessing disease activity status in residual mass(es) on CT as suggested by our study. Gallium-67 SPECT is also useful in determining when a CT positive or equivocal lesion can be negative.

CONCLUSION

The main finding in this biopsy-controlled group study was that ^{67}Ga SPECT was highly sensitive for detecting recurrent Hodgkin's disease in patients selected for biopsy. There was also a trend for SPECT to be more sensitive as well as more specific than CT. In particular, CT had a statistically significant higher rate of equivocal results in patients with positive biopsies. For those times when a CT scan is non-conclusive in terms of disease activity, we believe that SPECT is a most helpful noninvasive modality in differentiating recurrence/residual disease from fibrosis in the mediastinum.

However, the anatomic information supplied by CT is always needed to direct scintigraphic images in cases of bulky disease and for this reason we believe these studies provide complementary information.

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