
Bone Lymphoma: ^{67}Ga Scintigraphy and CT for Prediction of Outcome After Treatment

Ora Israel, MD^{1,2}; Michal Mekel, MD¹; Rachel Bar-Shalom, MD¹; Ron Epelbaum, MD^{2,3}; Nirit Hermony, MD¹; Nissim Haim, MD^{2,3}; Eldad J. Dann, MD^{2,4}; Alex Frenkel, DSc¹; Myriam Ben-Arush, MD^{2,5}; and Diana Gaitini, MD^{2,6}

¹Department of Nuclear Medicine, Rambam Medical Center, Haifa, Israel; ²Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; ³Department of Oncology, Rambam Medical Center, Haifa, Israel; ⁴Department of Hematology, Rambam Medical Center, Haifa, Israel; ⁵Department of Pediatric Oncology, Rambam Medical Center, Haifa, Israel; and ⁶Department of Diagnostic Radiology, Rambam Medical Center, Haifa, Israel

The purpose of the present study was to evaluate the role of ^{67}Ga scintigraphy and CT in treatment monitoring of bone lymphoma.

Methods: Forty-four lymphoma patients with 91 sites of bone involvement were evaluated. Eight patients had Hodgkin's disease, and 36 patients had non-Hodgkin's lymphoma. Thirteen patients had primary lymphoma of the bone, and 31 patients had secondary lymphoma of the skeleton. ^{67}Ga and CT studies were performed at baseline, during and at the end of treatment, and during follow-up. Positive ^{67}Ga studies showed abnormal uptake in sites of lymphomatous involvement. Positive CT studies showed lesions with patterns of osteolysis, patterns of osteosclerosis, or a mixed pattern. A negative ^{67}Ga or CT study showed disappearance of all lymphoma-related abnormalities. The sensitivity and specificity of ^{67}Ga scintigraphy at presentation were calculated. Patterns of bone lymphoma on CT and their treatment-related changes were analyzed and recorded. Freedom-from-progression (FFP) curves were used to determine the prognostic value of positive and negative ^{67}Ga and CT findings for predicting outcome after treatment. **Results:** The sensitivity of ^{67}Ga for diagnosis of bone lymphoma was 93%, and the specificity was 91%. A CT pattern of osteolysis was seen in 70% of skeletal disease sites at diagnosis and in 21% during follow-up. Osteosclerosis was present in 23% of sites at diagnosis and in 38% during follow-up. ^{67}Ga findings became negative in 25% of patients during treatment, whereas only 1 patient showed negative CT findings. Forty-two percent of patients had negative ^{67}Ga findings at the end of treatment, compared with 18% who had negative CT findings. Sixty-one percent of patients had negative ^{67}Ga findings during follow-up, compared with 21% who had negative CT findings. A statistically significant difference in FFP was found between patients with positive and negative ^{67}Ga findings at all evaluated time points. No statistically significant difference in FFP was found at any time point between patients with positive and negative CT findings. **Conclusion:** ^{67}Ga scintigraphy has a high sensitivity and specificity for diagnosis of bone lymphoma. Bone lymphoma may show osteosclerotic and osteolytic CT patterns at diagnosis, during treatment, and after treatment. In most patients, CT studies do not become negative even 1 y after treatment. ^{67}Ga scintigraphy, however, may be used as a predictor of long-term outcome in patients with lymphoma of the skeleton.

Key Words: bone lymphoma; ^{67}Ga scintigraphy; CT

J Nucl Med 2002; 43:1295-1303

Diagnosis and treatment of lymphoma have improved significantly over the last several decades. Novel therapeutic options have been introduced. Developments in functional and anatomic imaging techniques now provide accurate diagnosis as well as good monitoring of response to treatment—the basis for successful management of lymphoma. ^{67}Ga scintigraphy plays an important role in serial assessment of the effect of therapy in both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). The advantages of ^{67}Ga scintigraphy over CT studies as an indicator of tumor viability are well documented (1-3). ^{67}Ga scintigraphy has the ability to discriminate between patients who achieve a complete response and those who show no or only partial response to induction therapy (2,3). Prognosis can be predicted during treatment, as soon as after 1 cycle of chemotherapy, and recurrent disease can be diagnosed early during follow-up (4-6). The value of ^{67}Ga scintigraphy has been assessed in patients with both nodal and extranodal lymphoma (7,8).

Involvement of the skeleton occurs in up to 20% of patients with HD. Approximately 3%-5% of all cases of NHL are primary disease of the skeleton; secondary involvement occurs in up to 25% of patients (9-11). With successful treatment, bone lymphoma has a good prognosis and a high survival rate, and accurate assessment of the response to treatment of lymphoma of the bone is therefore of high clinical significance (12-14). Anatomic imaging modalities, such as CT or MRI, are of value in the initial assessment of the extent of both soft-tissue and skeletal involvement and characterization of bone texture (15-18). Monitoring the response of bone lymphoma to treatment, however, is a diagnostic dilemma (15,19). Studies on the role of CT and MRI in assessing treated bone lymphoma consist usually of small patient series and have found variable imaging patterns (15,20). The value of ^{67}Ga scintigra-

Received Dec. 12, 2001; revision accepted Jun. 11, 2002.

For correspondence or reprints contact: Ora Israel, MD, Department of Nuclear Medicine, Rambam Medical Center, Haifa 35254, Israel.
E-mail: o_israel@rambam.health.gov.il

phy for assessing the response of bone tumors to treatment has also been questioned because of the bone-seeking properties of the radiopharmaceutical (11). Some studies have demonstrated that ^{67}Ga scintigraphy is of value in assessing bone lymphoma (7,18,21), whereas others have suggested that ^{67}Ga uptake in skeletal lesions after treatment may preferentially reflect bone healing, which may not be accurately differentiated from active disease (15,22–24).

The purpose of the present study was to evaluate the role of ^{67}Ga scintigraphy and CT for predicting outcome in treated bone lymphoma. CT patterns of bone lymphoma at baseline and their treatment-related changes are also described. In addition, the value of ^{67}Ga scintigraphy for the initial diagnosis of lymphomatous skeletal lesions was reassessed.

MATERIALS AND METHODS

Patient Population

Fifty-four lymphoma patients evaluated routinely using ^{67}Ga scintigraphy and CT had evidence of lymphoma involving the skeleton. Inclusion criteria into the study were confirmation of ^{67}Ga avidity of the lymphoma before treatment and availability of CT and ^{67}Ga follow-up examinations during and for the first year after completion of therapy. Ten of the 54 patients did not meet these criteria and were therefore excluded from the study. One patient had a non- ^{67}Ga -avid lymphoma, 1 patient had no follow-up examinations, 2 patients had surgical removal of a single bone lesion, and 6 patients died early during treatment. Four patients had bone biopsy of a single skeletal lymphoma site before baseline ^{67}Ga scintigraphy. ^{67}Ga avidity of the lymphoma could not be established in these 4 patients, and they were included only in the analysis of CT data. Thus, the final study population included 44 patients with data available for CT and 40 patients with data available for ^{67}Ga scintigraphy. Diagnosis of lymphomatous involvement of the bone was made by radiography and CT in all patients and was confirmed by biopsy in 27 patients.

The study included 19 female patients and 25 male patients with a median age of 38 y (range, 1–79 y). Eight patients had HD, all with secondary involvement of the skeleton. Thirty-six patients had NHL. Of those, 31 had aggressive NHL, 3 had low-grade NHL, and the histologic subclassification of 2 with NHL could not be precisely defined. Thirteen had primary lymphoma of the bone, and 23 had secondary involvement of the skeleton. There was a median of 2 skeletal lymphoma sites in each patient (range, 1–7 sites). The distribution of lymphomatous bone lesions in the peripheral and axial skeleton is shown in Table 1. Twenty-three patients had evidence of soft-tissue involvement in lymph nodes or extranodal sites, in addition to skeletal lymphoma lesions.

Six patients with HD received doxorubicin-containing chemotherapy regimens, and 2 patients received other treatment combinations. Chemotherapy of patients with NHL consisted of doxorubicin-containing regimens in 26 patients and other combinations in 10 patients. Radiation therapy was added to involved sites in 19 patients. The median duration of clinical follow-up of patients was 24 mo (range, 5–119 mo).

Imaging Studies

^{67}Ga scintigraphy and CT studies were performed at the time of the initial diagnosis, during treatment at a median of 3 chemother-

TABLE 1
Sites of Bone Involvement in Patients with NHL and HD

Site	n	NHL	HD
Spine	32	25	7
Pelvis	18	15	3
Thoracic cage	11	9	2
Skull	8	8	—
Long bones	22	21	1
Total	91	78	13

apeutic cycles (range, 1–7 cycles), at the completion of therapy, and twice during the first year of follow-up. The early follow-up study (FU1) was performed at a median of 4 mo after the end of treatment (range, 2–7 mo). The late follow-up study (FU2) was performed at a median of 11 mo (range, 8–19 mo) from the end of treatment.

^{67}Ga scintigraphy was performed using previously described techniques (3,7). Adult patients received 296–370 MBq (8–10 mCi) ^{67}Ga -citrate intravenously, and children received 2.77 MBq (75 μCi) per kilogram of body weight. Scintigraphy was performed at 48 h and 7 d after the injection of the radiopharmaceutical. The images were obtained using a dual-head camera (Helix; Elscint, Haifa, Israel, or VG; General Electric Medical Systems, Milwaukee, WI). Triple-energy ^{67}Ga peaks of 93, 184, and 300 keV and a parallel-hole, medium-energy collimator (APC-5 or HPC-5; Elscint) were used. SPECT was performed routinely for the whole torso after the planar study at 48 h.

CT studies earlier than 1994 were performed using a standard single-slice CT scanner (Elscint). Thereafter, CT was performed using a helical Twin Flash scanner (Elscint) or a multislice spiral scanner (Marconi Medical Systems, Haifa, Israel). Nonionic contrast medium (80–100 mL iopamidol, 300 mg iodine/mL) was delivered by an automatic injector into the median cubital vein at a flow rate of 2 mL/s, except when contraindicated in patients with allergy to iodine or with creatinine levels higher than 1.5 mg/100 mL. Scanning was performed using a 8.8-mm slice thickness after a 30-s delay for chest and a 60-s delay for abdomen and pelvis examinations. Dedicated examinations using 3- to 5-mm-thick contiguous sections were performed for highly suggestive or proven bone lesions of the axial and peripheral skeleton.

^{67}Ga scintigraphy findings at all evaluated time points were interpreted as positive if they showed 1 or more areas of abnormal uptake in the bone or soft tissues, outside the normal pattern of ^{67}Ga biodistribution. Negative ^{67}Ga findings showed uptake only in regions of normal, physiologic activity.

Findings considered positive for lymphomatous bone involvement on CT before and after treatment were either lytic lesions, seen as separate or coalescent areas of a mottled, permeative, moth-eaten pattern; discrete or diffuse sclerotic lesions; or sites showing a mixed pattern of lysis and sclerosis. Irregularities of the bone cortex, usually in association with osteolysis or osteosclerosis, were also recorded. Any abnormality (bone, soft-tissue, or both) was considered a positive CT finding at the time of the initial evaluation and at each time point related to treatment. CT findings were considered negative when all pathologic findings disappeared. After initiation of treatment, a test was considered positive in the presence of residual findings such as a persistent area of abnormal ^{67}Ga activity, even if decreasing in intensity, or a per-

sistent lesion on CT, even if decreasing in size or showing a change in pattern.

Statistical Analysis

The sensitivity and specificity of ^{67}Ga scintigraphy for detecting bone lymphoma at the time of diagnosis were calculated according to the equations $\text{TP}/(\text{TP} + \text{FN})$ for sensitivity and $\text{TN}/(\text{TN} + \text{FP})$ for specificity, where TP = true-positive, FN = false-negative, TN = true-negative, and FP = false-positive. TP studies showed ^{67}Ga uptake in skeletal lymphoma lesions. Patients showing no uptake of ^{67}Ga in sites of bone lymphoma were recorded as FN. TN studies showed no ^{67}Ga uptake when there was no evidence of lymphoma on CT, radiography, or biopsy. FP studies showed ^{67}Ga uptake in bone when CT, radiography, biopsy, or long-term clinical follow-up were negative for lymphoma. Data for sensitivity calculation (TP, FN) were taken from our group of lymphoma patients with proven bone involvement. Data for specificity calculation (TN, FP) were based on findings from the baseline ^{67}Ga studies of a randomly chosen group of 135 lymphoma patients from our institution without bone involvement. For the purpose of this study, the follow-up data from ^{67}Ga and CT performed on the patient group without bone involvement were not further analyzed.

Freedom-from-progression (FFP) curves were used to determine the prognostic value of positive and negative ^{67}Ga scintigraphy and CT findings during and after treatment. FFP was defined as the time from initiation of therapy until disease progression or until the last follow-up examination. Disease progression was defined either as worsening of the primary disease or as the appearance of new sites of lymphoma after the patient had achieved a complete response. Subsets of positive and negative ^{67}Ga scintigraphy and CT findings were compared at each evaluated time point to assess their impact as predictors of FFP. FFP curves for positive and negative ^{67}Ga and CT findings were calculated using the Kaplan–Meier method. Differences in FFP curves were compared using the log-rank test, with statistical significance defined as $P < 0.05$.

RESULTS

The sensitivity and specificity of ^{67}Ga scintigraphy for the initial diagnosis of bone lymphoma were calculated using a combination of CT, radiography, and biopsy results as the gold standard. A group of 40 patients with known involvement of the skeleton and 135 lymphoma patients of a randomly chosen group with no skeletal involvement were assessed. There were 37 TP studies, 3 FN studies, 123 TN studies, and 12 FP studies. The sensitivity of ^{67}Ga scintigraphy for diagnosis of lymphoma of the bone was 93%, and the specificity was 91%.

^{67}Ga scintigraphy findings were negative for 25% of studies performed during treatment and for 42% of studies performed at the end of treatment. At FU1, 68% of ^{67}Ga studies had negative findings. At FU2, ^{67}Ga scintigraphy findings were negative in 61% of the patients. In 12 of the 23 patients showing soft-tissue involvement in addition to bone lymphoma, changes in ^{67}Ga uptake occurred at the same time points both for involved lymph nodes and for skeletal lesions. In the other 11 patients, disappearance of ^{67}Ga uptake in sites of nodal involvement preceded changes

in bone lymphoma lesions. CT findings were negative in 3% of studies (1 patient) during treatment, in 18% of studies at the end of treatment, in 17% of studies at FU1, and in 21% of studies at FU2. The number of ^{67}Ga and CT studies with negative and positive results in relation to treatment is shown in Table 2. The 3-y FFP rate for the entire group of patients was 73.6%. There was a statistically significant difference in the 3-y FFP between patients with positive and negative ^{67}Ga scintigraphy at all evaluated time points: $P < 0.05$ during treatment, $P < 0.03$ at the end of treatment, $P < 0.0001$ at FU1, and $P < 0.002$ at FU2. CT results were not predictive for FFP. There was no statistically significant difference in the 3-y FFP between patients with positive and negative CT at all evaluated time points (Figs. 1–4; Table 3).

At diagnosis, CT of skeletal lymphoma lesions showed a predominant osteolytic pattern at 70% of sites. Predominant osteosclerotic lesions were seen in 23% of cases, whereas 7% of disease sites showed a mixed lytic and blastic pattern. CT studies performed during treatment, at the end of chemotherapy, and during follow-up showed a decrease in the percentage of osteolytic lymphoma lesions, from 70% at baseline to 21% at FU2; an increase in the number of lymphoma sites with osteosclerotic features, from 23% at presentation to 38% at 1 y after completion of treatment; and an increase in the number of lymphoma sites with a mixed lytic and sclerotic pattern, from 7% before treatment to 20% at FU2. The distribution of various CT patterns of lymphoma bone lesions in relationship to treatment and the correlation between the presence of these patterns and ^{67}Ga avidity are shown in Table 4.

DISCUSSION

Primary lymphoma of the bone is rare and represents about 3%–5% of bone tumors and of extranodal lymphomas (9–11,19). It has been described in patients with NHL and

TABLE 2
Number of Patients with Negative and Positive ^{67}Ga Scintigraphy and CT Findings During, at End of, and After Treatment

Time of evaluation	Test	Total no. patients	No. patients with negative test	No. patients with positive test
During treatment	^{67}Ga	36	9 (25)	27 (75)
	CT	30	1 (3)	29 (97)
End of treatment	^{67}Ga	31	13 (42)	18 (58)
	CT	28	5 (18)	23 (82)
FU1	^{67}Ga	31	21 (68)	10 (32)
	CT	24	4 (17)	20 (83)
FU2	^{67}Ga	23	14 (61)	9 (39)
	CT	19	4 (21)	15 (79)

Numbers in parentheses are percentages.

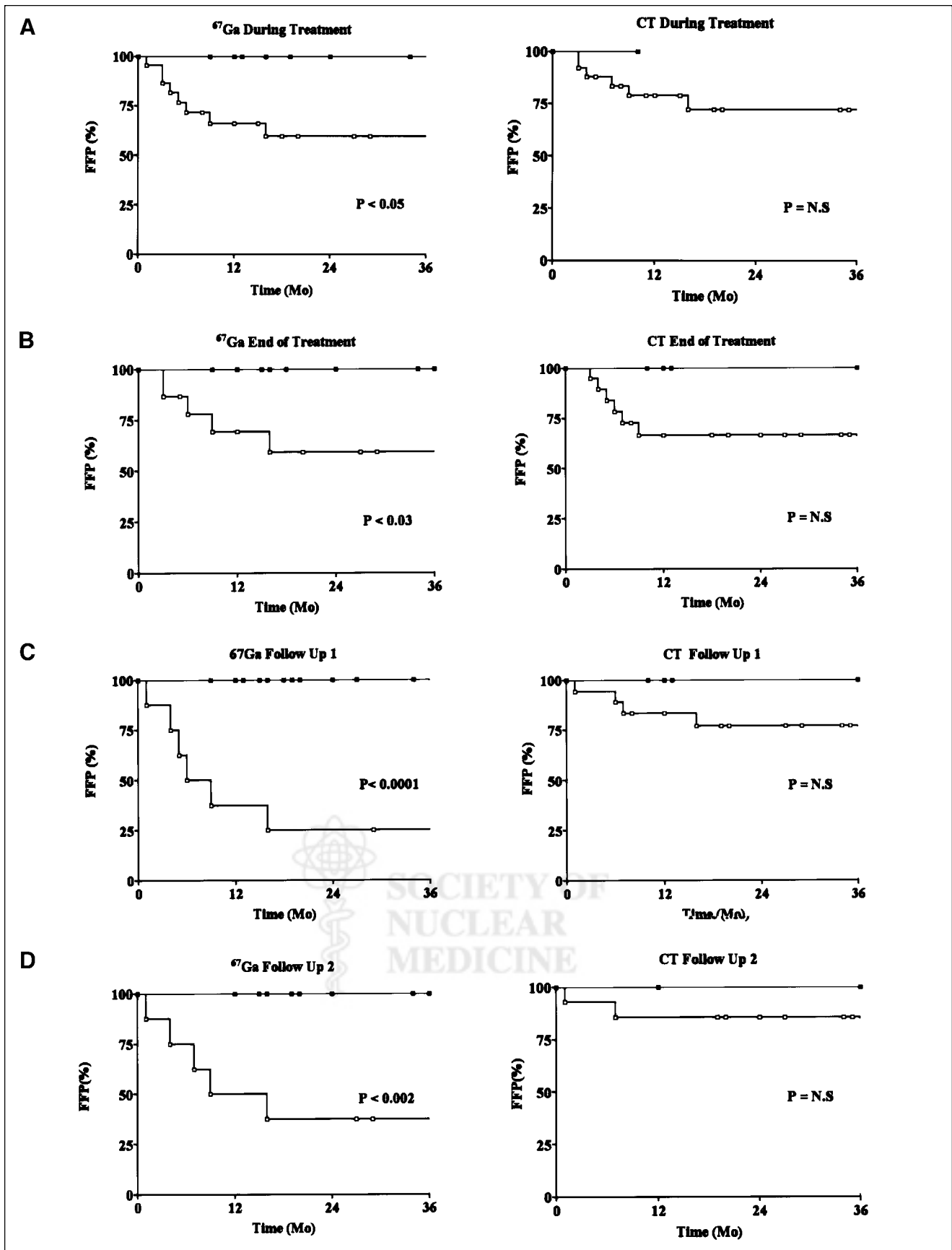


FIGURE 1. Three-year FFP in patients with positive (□) and negative (■) ⁶⁷Ga scintigraphy and CT findings. Graphs show findings during treatment (A), at end of treatment (B), at FU1 (C), and at FU2 (D).

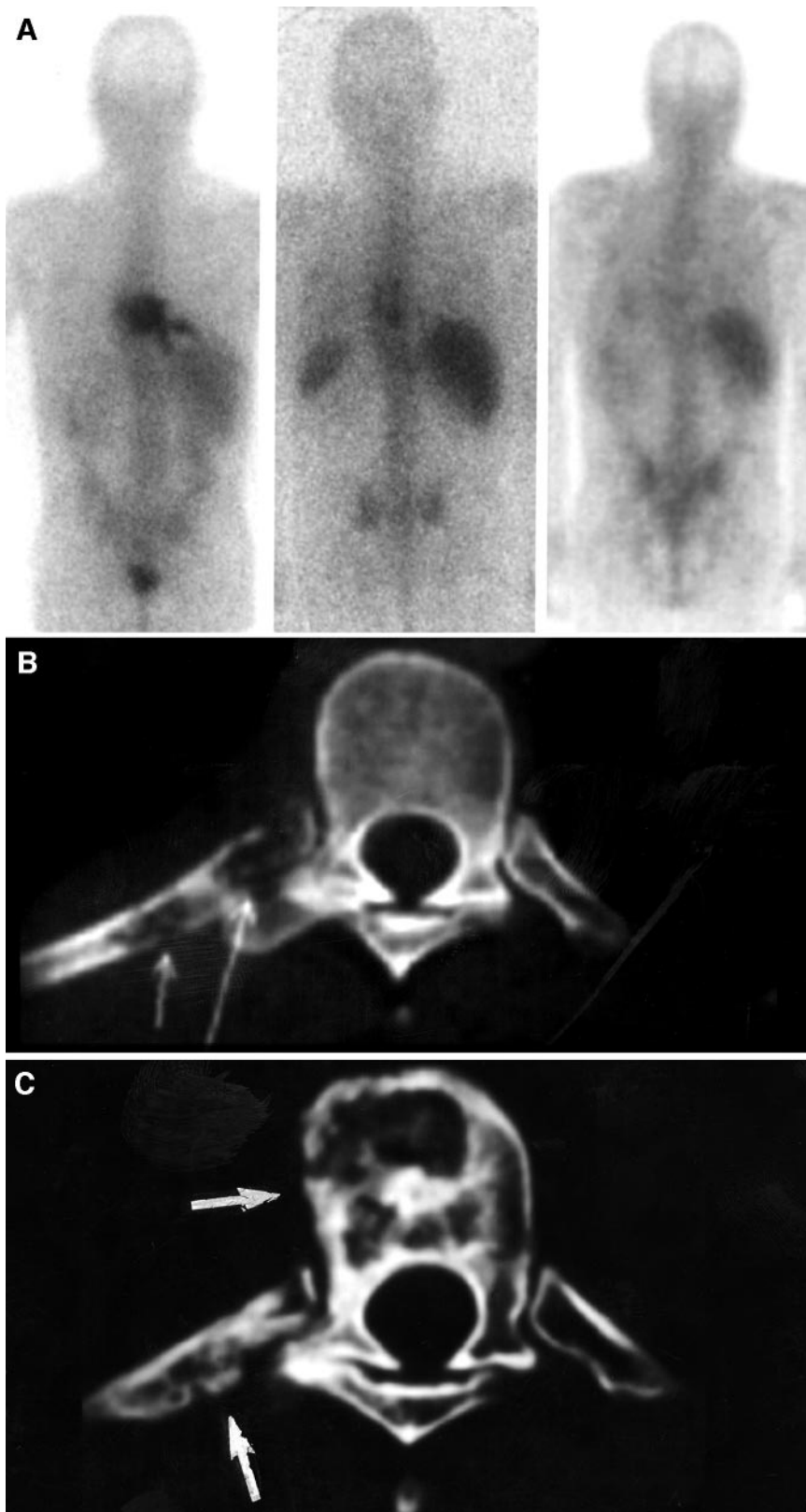


FIGURE 2. Negative ^{67}Ga scintigraphy and abnormal CT findings at end of treatment in 37-y-old man with diffuse large cell B-type NHL, stage I EA, involving posterior arch of 9th and 10th right ribs and T9 and T10 vertebrae. (A) ^{67}Ga scintigraphy at diagnosis (left) shows pathologic uptake at involved sites of disease. Marked improvement is seen at mid treatment (center), with residual abnormal ^{67}Ga activity in lower thoracic spine. ^{67}Ga scintigraphy findings at end of treatment (right) are negative. (B) CT at diagnosis shows infiltrative osteolytic lesion with cortical disruption of posterior arch of 9th right rib (arrows) and surrounding soft-tissue involvement. Moth-eaten pattern is seen in vertebral body of T9. (C) CT at end of treatment shows mixed sclerotic and lytic pattern in 9th rib and T9 vertebral body (arrows). Patient had no evidence of disease for 30 mo.

involves mostly the appendicular skeleton. Secondary lymphomatous involvement of the skeleton is the result of hematogenous spread or direct extension from regional soft-tissue masses and may occur in both HD and NHL (9–11).

Initial diagnosis of skeletal lymphoma lesions may be delayed because of a paucity of symptoms (12). At presentation, lymphoma of the bone may show several radiologic findings such as a moth-eaten osteolytic pattern, predomi-

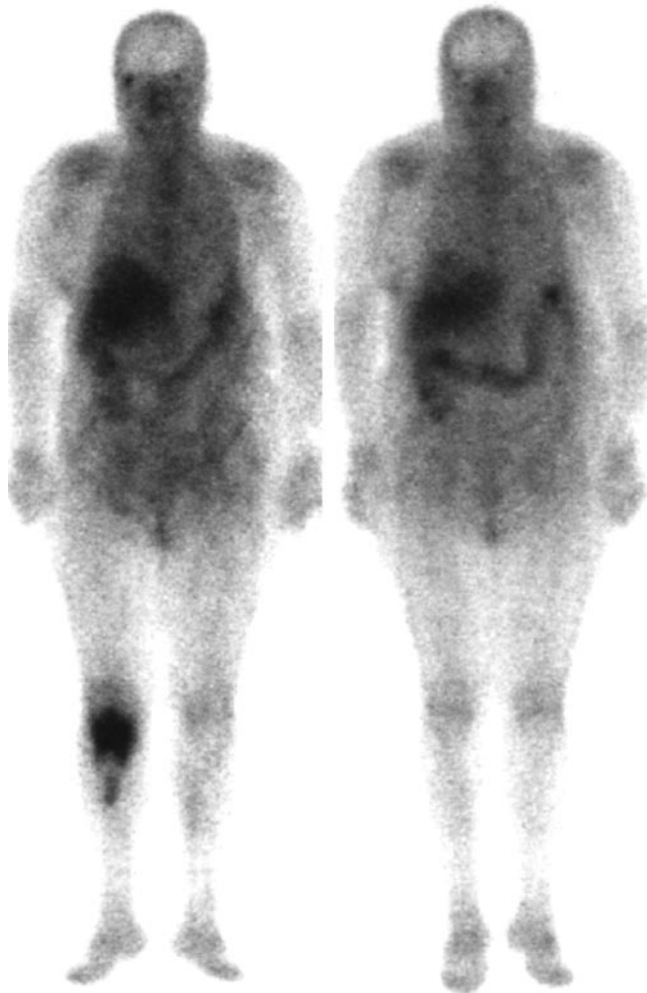


FIGURE 3. Negative ^{67}Ga scintigraphy findings during chemotherapy in 68-y-old woman with follicular mixed low-grade lymphoma involving right inguinal lymph nodes and right tibia. ^{67}Ga scintigraphy at baseline (left) shows abnormal uptake in proximal right tibia. Repeated ^{67}Ga scintigraphy after 4 cycles of chemotherapy (right) shows negative findings, which remained unchanged at end of treatment and during follow-up. Disease has been in complete remission for 12 mo.

nantly osteoblastic characteristics, or a mixed pattern of bone destruction and formation (15,25,26). MRI is highly sensitive for detection of bone lesions but lacks specificity, showing variable patterns of disease (11). Both CT and MRI provide, however, a good assessment of bone texture and of the relationship between bony lesions and their adjacent structures such as soft tissues and bone marrow, therefore allowing for accurate definition of the extent of the tumor (15–18,20).

^{67}Ga has been used for imaging of bone lymphoma (7,11,15,21–24). Some authors have reported a high sensitivity and specificity of ^{67}Ga scintigraphy for diagnosis of lymphoma of the skeleton (7,15,21), whereas other studies showed somewhat poorer results (22). These discordant data may have been the result of differences in radiophar-

maceutical dosage and equipment used for scanning. Increased ^{67}Ga uptake in bone may be due to skeletal lymphoma but may also occur in other areas of increased bone turnover such as epiphyseal growing plates in children, sites of previous bone biopsy, or nonlymphomatous skeletal lesions. The present study reports, however, a high sensitivity and specificity of ^{67}Ga scintigraphy for diagnosis of bone lymphoma. Because lymphoma may involve both the axial and the peripheral skeleton, whole-body ^{67}Ga scintigraphy including the limbs provides an additional clinical advantage. Documenting ^{67}Ga avidity in skeletal lymphoma lesions at diagnosis is the basis for further assessment of treatment response during and after therapy.

Bone lymphoma is a tumor with a significant rate of remission and cure after treatment (12–14). Treatment options of bone lymphoma include chemotherapy, radiotherapy, or a combined multimodality approach. Knowledge of the value of the different imaging modalities in monitoring response to treatment and in predicting outcome is therefore important in clinical decision making. Early assessment of treatment response may result in an early change in the therapeutic strategy if necessary. Short- and long-term treatment-related toxicity is relatively common, especially in the pediatric patient population, and accurate and timely determination of the effect of a particular treatment is therefore of clinical significance (27,28).

Monitoring response to treatment of skeletal lesions is problematic (19,24). Although radiography and CT may show bone remodeling with reossification of lytic lesions (25), radiologic techniques have been found unreliable in assessing the effect of therapy (23). MRI may show prolonged T1 values in treated skeletal lesions (15) but has a low specificity for assessing the response of bone lymphoma to therapy (18). CT and MRI abnormalities may persist long after completion of treatment, and the differential diagnosis between residual disease and healing bone tissue is difficult (19). The definitive diagnosis of lymphomatous involvement of the skeleton at baseline is made by bone biopsy. Multiple biopsies could theoretically also represent the gold standard for evaluating response to treatment. Biopsy is, however, an invasive procedure and cannot be used repeatedly in the routine clinical work-up of patients (18,19,29).

The value of ^{67}Ga scintigraphy for monitoring the response to treatment in lymphoma involving the lymph nodes and other soft tissues is well documented (2,30). Negative ^{67}Ga findings at the end of treatment indicate a good response and outcome, regardless of the presence or absence of a residual mass on CT. Persistent ^{67}Ga uptake at the end of treatment indicates the presence of active disease. ^{67}Ga scintigraphy provides a means for early diagnosis of recurrence (6), and recent studies have shown that ^{67}Ga scintigraphy performed early during treatment is a good predictor of prognosis and outcome (4,5).

The present data further demonstrate the role of ^{67}Ga scintigraphy in the assessment of lymphoma involving the

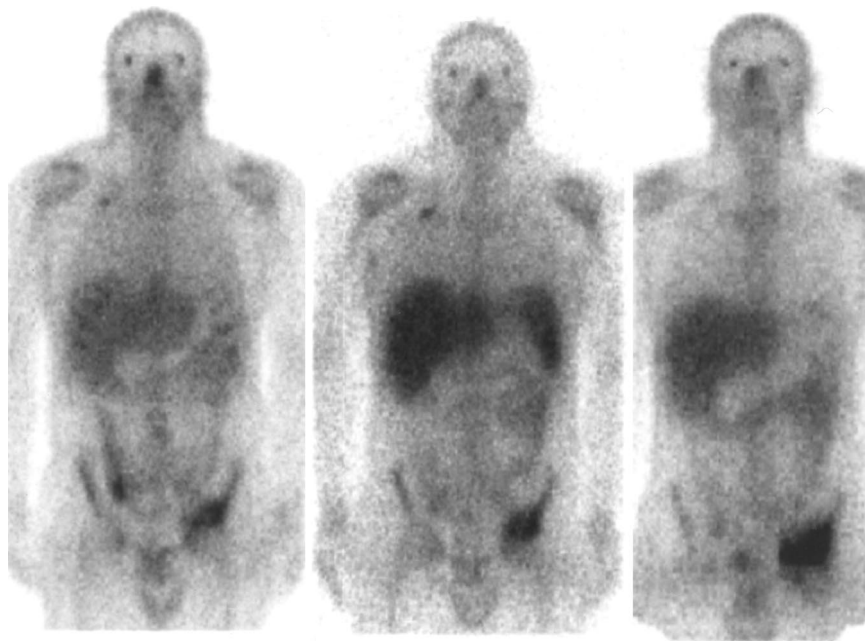


FIGURE 4. Abnormal ^{67}Ga scintigraphy findings during and after chemotherapy in 33-y-old man with biopsy-proven recurrent HD involving left acetabulum. ^{67}Ga scintigraphy before treatment (left) shows area of pathologic uptake in left acetabulum. Chemotherapy including dexamethasone, ifosfamide, cisplatin, and etoposide was initiated. ^{67}Ga scintigraphy during treatment (center) and at completion of chemotherapy (right) shows increase in size and intensity of pathologic uptake. Repeated bone biopsy indicated presence of active HD. (Note also abnormal ^{67}Ga uptake in involved right supraclavicular lymph node.) Tumor progression was diagnosed, and patient died 6 mo later.

skeleton. During treatment, 25% of patients with bone lesions had normal ^{67}Ga findings, whereas only 1 patient had normal CT findings. Most patients with lymphoma of the skeleton showed abnormal findings on CT even as late as 1 y after completion of treatment. At that time, 61% of patients had negative ^{67}Ga findings, compared with only 21% of patients showing normal CT findings. Assessment of the rapidity of response using ^{67}Ga scintigraphy for bone lymphoma is not as good as that previously reported for nodal disease (4,5). ^{67}Ga scintigraphy is, however, a better predictor of the long-term outcome of patients with lymphoma of the skeleton than are anatomic imaging modalities such as CT. A statistically significant difference in FFP between patients with positive and negative ^{67}Ga scintigraphy findings was found as soon as at mid treatment and thereafter. In contrast, no statistically significant difference in FFP at any time point was found between patients with positive and negative CT results. Patient outcome expressed as 3-y FFP was used as the indicator of efficacy for both

^{67}Ga scintigraphy and CT for treatment monitoring. The significant difference in FFP between patients with positive and negative ^{67}Ga findings early during treatment as well as during follow-up may be used in the future to tailor treatment according to the results of functional imaging modalities. Repeated bone biopsy sampling cannot be routinely performed.

Because of the variability found in CT patterns of skeletal lymphoma after treatment, the strict criterion of complete normalization of CT images was used for comparison of FFP. The lack of specific CT features in treated bone lymphoma is a diagnostic challenge further demonstrated by the present results. Although there was a decrease in the percentage of osteolytic lesions over time and an increase in the incidence of osteoblastic patterns, 1 in every 5 lymphoma lesions in the skeleton at 1 y after treatment still presents predominant features of bone destruction. At all evaluated time points, similar numbers of lytic and blastic skeletal lymphoma lesions showed ^{67}Ga avidity despite an

TABLE 3
Three-Year FFP Rate in Lymphoma Patients with Negative and Positive ^{67}Ga Scintigraphy and CT Findings

Time of test	^{67}Ga			CT		
	Negative	Positive	<i>P</i>	Negative	Positive	<i>P</i>
During treatment	100	48	0.05	100	72	NS
End of treatment	100	59	0.03	100	67	NS
FU1	100	25	0.0001	100	77	NS
FU2	100	38	0.002	100	86	NS

NS = not statistically significant.

P is based on Kaplan–Meier curves and shows significance of difference in 3-y FFP rate between patients with negative and positive ^{67}Ga scintigraphy and CT findings.

Data are percentages.

TABLE 4
Treatment-Related Distribution of CT Patterns and Their Correlation with ⁶⁷Ga Avidity

CT pattern	Baseline	During treatment	End of treatment	FU1	FU2
Osteolysis*					
CT sites	70	49	26	31	21
⁶⁷ Ga-positive lytic sites	68	32	63	30	—
Osteosclerosis*					
CT sites	23	27	29	25	38
⁶⁷ Ga-positive sclerotic sites	83	50	67	13	11
Mixed†					
CT sites	7	21	27	24	20
⁶⁷ Ga-positive mixed-pattern sites	75	38	33	38	20
Normal					
CT sites	—	3	18	20	21
⁶⁷ Ga-positive normal-CT sites	—	—	—	—	—

*Predominant feature.

†Mixed pattern of osteolysis and osteosclerosis without clear predominance of 1 characteristic.

Data are percentages.

expected preferential ⁶⁷Ga positivity in areas of bone repair. The fact that both osteosclerotic and osteolytic lymphoma lesions take up ⁶⁷Ga in a similar fashion supports the hypothesis that the lymphoma-seeking properties, rather than the bone-seeking properties, of ⁶⁷Ga play the primary role in uptake of this tracer in sites of active bone involvement.

PET using ¹⁸F-FDG is evolving as a sensitive and accurate method of assessing lymphoma (31). It has proven accurate for the initial diagnosis and staging of bone lymphoma (32,33). Having fewer bone-seeking properties, ¹⁸F-FDG has the potential of improving the assessment of patients with skeletal lymphoma lesions, especially for the prediction of outcome early during treatment. Possible drawbacks may be related to bone marrow uptake and its differential diagnosis from bone involvement, particularly in the axial skeleton (32,33). The development of new hybrid imaging devices combining nuclear medicine techniques with sequential CT acquisition may represent a further step in optimizing simultaneous evaluation of functional and morphologic characteristics of bone lymphoma before and after treatment (34). The role of ¹⁸F-FDG PET and hybrid imaging for monitoring the response of bone lymphoma to treatment still needs to be assessed.

CONCLUSION

⁶⁷Ga scintigraphy has a high sensitivity and specificity for the diagnosis of bone lymphoma. CT may show variable patterns in patients with lymphomatous skeletal lesions at presentation, during treatment, and after treatment. In most patients with lymphoma involving the skeleton, CT findings do not become negative even at 1 y after treatment. ⁶⁷Ga scintigraphy, however, may be used as a predictor of long-term outcome in patients with bone lymphoma. Tailoring and optimization of treatment in patients with bone lymphoma based on functional data provided by nuclear med-

icine procedures should increase the rate of successful therapy and decrease treatment-related toxicity.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Gerald M. Kolodny for his many useful suggestions during the revision of the manuscript. This study was supported by a grant from the Israel Cancer Association and the L. Rosenblatt Technion Fund for Research in Cancer.

REFERENCES

1. Iosilevsky G, Front D, Bettman L, et al. Uptake of gallium-67 citrate and [2-H3] deoxyglucose in the tumor model, following chemotherapy and radiotherapy. *J Nucl Med.* 1985;26:278–282.
2. Israel O, Front D, Lam M, et al. Gallium-67 imaging in monitoring lymphoma response to treatment. *Cancer.* 1988;61:2439–2443.
3. Front D, Israel O, Epelbaum R, et al. Gallium-67 SPECT in patients with lymphoma before and after treatment. *Radiology.* 1990;175:515–519.
4. Front D, Bar-Shalom R, Mor M, et al. Hodgkin's disease: prediction of outcome with Ga-67 scintigraphy after one cycle of chemotherapy. *Radiology.* 1999;210:487–491.
5. Front D, Bar-Shalom R, Mor M, et al. Aggressive Non-Hodgkin's lymphoma: early prediction of outcome with Ga-67 scintigraphy. *Radiology.* 2000;214:253–257.
6. Front D, Bar-Shalom R, Epelbaum R, et al. Early detection of recurrence by Ga-67 scintigraphy. *J Nucl Med.* 1993;34:2101–2104.
7. Bar-Shalom R, Israel O, Epelbaum R, et al. Gallium-67 scintigraphy in lymphoma with bone involvement. *J Nucl Med.* 1995;36:446–450.
8. Ben-Haim S, Bar-Shalom R, Israel O, et al. Liver involvement in lymphoma: role of Ga-67 scintigraphy. *J Nucl Med.* 1995;36:900–904.
9. Ozdemirli M, Mankin HJ, Aisenberg AC, et al. Hodgkin's disease presenting as a solitary bone tumor: a report of four cases and review of the literature. *Cancer.* 1996;77:79–88.
10. Bragg DG, Colby TV, Wand JH. New concepts in the non-Hodgkin lymphomas: radiologic implications. *Radiology.* 1986;159:289–304.
11. Stroszczyński C, Oellinger J, Hosten N, et al. Staging and monitoring of malignant lymphoma of the bone: comparison of Ga-67 scintigraphy and MRI. *J Nucl Med.* 1999;40:387–393.
12. Schmidt AG, Kohn D, Bernhards J, et al. Solitary skeletal lesions as primary manifestations of non-Hodgkin's lymphoma. *Arch Orthop Trauma Surg.* 1994;113:121–128.

13. Guermazi A, Brice P, de Kerviler EE, et al. Extranodal Hodgkin's disease: spectrum of disease. *Radiographics*. 2001;21:161-179.
14. Mulligan MNE, McRae GA, Murphey MD. Imaging features of primary lymphoma of bone. *AJR*. 1999;173:1691-1697.
15. Edeiken-Monroe B, Edeiken J, Kim EE. Radiologic concepts of lymphoma of bone. *Radiol Clin North Am*. 1990;28:841-864.
16. Mulligan ME, Kransdorf MJ. Sequestra of primary lymphoma of bone: prevalence and radiologic features. *AJR*. 1993;160:1245-1248.
17. Melamed JW, Martinez S, Hoffman CJ. Imaging of primary multifocal osseous lymphoma. *Skeletal Radiol*. 1997;26:35-41.
18. Moon TY, Kim E, Kim YC, et al. Comparison of nuclear bone and gallium scans in the therapeutic evaluation of bone lymphoma. *Clin Nucl Med*. 1995;20:721-724.
19. Baar J, Burkes RL, Bell R, et al. Primary non-Hodgkin's lymphoma of bone. *Cancer*. 1994;73:1194-1199.
20. Cook MA, Manfredi OL, Kasaw S, et al. Primary skeletal lymphoma imaging and pathologic correlation. *J Am Osteopath Assoc*. 1996;96:610-612.
21. Mouratidis B, Gilday DL, Ash JM. Comparison of bone and Ga-67 scintigraphy in the initial diagnosis of bone involvement in children with malignant lymphoma. *Nucl Med Commun*. 1994;15:144-147.
22. Orzel JA, Sawaf NW, Richardson ML. Lymphoma of the skeleton: scintigraphic evaluation. *AJR*. 1988;150:1095-1099.
23. Roach PJ, Janicek MJ, Kaplan WD. Bone lymphoma, comparison of Tl-201 and Ga-67 scintigraphy in assessment of treatment response. *Clin Nucl Med*. 1996;21:689-694.
24. Ramanna L, Waxman A, Binney G, et al. Thallium-201 scintigraphy in bone sarcoma: comparison with gallium-67 and technetium-MDP in the evaluation of chemotherapeutic response. *J Nucl Med*. 1990;31:567-572.
25. Braunstein EM, White SJ. Non-Hodgkin lymphoma of bone. *Radiology*. 1980;135:59-63.
26. Malloy PC, Fishman EK, Magid D. Lymphoma of bone, muscle and skin: CT findings. *AJR*. 1992;159:805-809.
27. Haddy TB, Keenan AM, Jaffe ES, et al. Bone involvement in young patients with non-Hodgkin's lymphoma: efficacy of chemotherapy without local radiotherapy. *Blood*. 1988;72:1141-1147.
28. Furman WL, Fitch S, Hustu HO, et al. Primary lymphoma of bone in children. *J Clin Oncol*. 1989;7:1275-1280.
29. Baar J, Burkes RL, Gospodarowicz M. Primary non-Hodgkin's lymphoma of bone. *Semin Oncol*. 1999;26:270-275.
30. Front D, Ben-Haim S, Israel O, et al. Lymphoma: predictive value of Ga-67 scintigraphy after treatment. *Radiology*. 1992;182:359-361.
31. Bar-Shalom R, Valdivia AY, Blafox MD. PET imaging in oncology. *Semin Nucl Med*. 2000;30:150-185.
32. Moog F, Bangerter M, Diederichs CG, et al. Extranodal malignant lymphoma: detection with FDG PET versus CT. *Radiology*. 1998;206:475-481.
33. Moog F, Kotzerke J, Reske SN. FDG PET can replace bone scintigraphy in primary staging of malignant lymphoma. *J Nucl Med*. 1999;40:1407-1413.
34. Israel O, Keidar Z, Iosilevsky G, et al. The fusion of anatomic and physiologic imaging in the management of patients with cancer. *Semin Nucl Med*. 2001;31:191-205.

