Staging and Monitoring of Malignant Lymphoma of the Bone: Comparison of ^{67}Ga Scintigraphy and MRI

Christian Stroszczynski, Johann Oellinger, Norbert Hosten, Guenther Spahn, Holger Amthauer, Jens Ricke, Karl-Titus Hoffmann, Herrmann Eichstaedt, Wolf-Dieter Ludwig and Roland Felix

The Strahlenklinik und Poliklinik, Medizinische Fakultät Charité der Humboldt Universität zu Berlin, Virchow-Klinikum, Berlin; and the Department of Hematology, Oncology and Tumor Immunology, Robert-Roessle-Klinik, Virchow-Klinikum, Humboldt Universität zu Berlin, Germany

The aim of this study was two-fold: to compare ^{67}Ga scintigraphy with MRI (a) for the staging of malignant lymphoma of the bone and (b) with regard to accuracy in detecting residual disease after first-line chemotherapy for restaging. **Methods:** Twenty-one patients with 36 malignant osseous lesions were examined, including 7 patients with primary or multifocal osseous lymphoma and 14 patients with malignant lymphoma and simultaneous or secondary involvement of the bone. After first-line therapy, MRI and ^{67}Ga scintigraphy were performed on 13 patients. The remission status based on all clinical and radiological findings during the follow-up was used as the gold standard. **Results:** The osseous lesions were located on the axial skeleton in 64% of patients and on the appendicular skeleton in 36%. ^{67}Ga scintigraphy detected 77% of the osseous lesions examined by MRI. For restaging after first-line therapy, MRI had a sensitivity of 90% and a specificity of 80% when dynamic MRI information was included. There were several false-positive results as a result of the pathologic increase in signal intensity ratios of reactive hematopoietic regions after chemotherapy. For ^{67}Ga scintigraphy, a sensitivity of 70% and a specificity of 93% were calculated. **Conclusion:** These data show that monitoring malignant lymphoma of the bone still presents diagnostic problems. Given the high sensitivity of MRI and the high specificity of ^{67}Ga scintigraphy but the limited specificity of MRI and sensitivity of ^{67}Ga scintigraphy, both methods are valuable but should be used as complementary diagnostic tools.

Key Words: bone neoplasms; lymphoma; radionuclide studies; MRI

J Nucl Med 1999; 40:387–393

Malignant lymphoma of the bone is uncommon and presents both diagnostic and therapeutic difficulties. Because the stage of development of the disease is the most important prognostic indicator of survival, a classification such as that proposed by Ostrowski et al. (*1*), which is based on stages, has proven useful in everyday clinical practice. According to this classification, malignant lymphoma can be divided into four groups: group I, primary lymphoma of the bone without nodal involvement; group II, multifocal osseous lymphoma without nodal involvement; group III, involvement of the bone with nodal involvement within 6 mo; and group IV, secondary involvement of the bone at least 6 mo after diagnosis of malignant lymphoma.

Although bone scintigraphy is widely used in the staging of malignant lymphoma for evaluating bone involvement, several studies suggest that the accuracy of bone scintigraphy for differentiating between residual activity and complete remission after first-line chemotherapy is unsatisfactory (*2–5*). The aim of this study was two-fold: to compare ^{67}Ga scintigraphy with MRI for the staging of malignant lymphoma of the bone and to compare the results obtained by the two imaging methods after first-line treatment for the detection of residual disease.

MATERIALS AND METHODS

Patients

This study comprised 21 patients (11 males, 10 females; age range 16–83 y). Although all patients with primary skeletal lymphoma (total, n = 7: group I, n = 5; group II, n = 2) had non-Hodgkin's lymphoma (NHL), 7 of 14 patients with secondary involvement of the bone (total, n = 14: group III, n = 10; group IV, n = 4) had Hodgkin's disease (HD) (Table 1). All patients were examined with MRI, and 14 patients were examined with ^{67}Ga scintigraphy. Of 36 malignant lesions detected by examinations used for staging, 23 were located in the axial skeleton and 13 in the appendicular skeleton (Table 2).

The diagnosis was confirmed by open biopsy results in all 7 patients with primary skeletal lymphoma, whereas in patients with secondary involvement, confirmation was obtained by CT-guided needle biopsy in 2 patients. In 10 patients, bone involvement was assumed because of positive biopsy of the iliac crest. In 2 patients, conventional radiographs showed typical signs of osseous involvement by malignant lymphoma.

After first-line therapy, MRI and ^{67}Ga scintigraphy were both performed in 13 of the original 21 patients. As the gold standard, the remission status based on all the clinical, radiological (including radiography, CT and bone scintigraphy) and histologic findings

Received Jan. 29, 1998; revision accepted Jun. 18, 1998.

For correspondence or reprints contact: Christian Stroszczynski, MD, Strahlenklinik und Poliklinik, Medizinische Fakultät Charité der Humboldt Universität zu Berlin, Virchow-Klinikum, Augustenburger Platz 1,13353 Berlin, Germany.

TABLE 1
Overview of Histologic Types of 21 Patients with Malignant Lymphoma of Bone

Type	Group I	II	III	IV	Total
Hodgkin's lymphoma	—	—	4	3	7
Non-Hodgkin's lymphoma					
B-lymphoblastic	—	1	1	—	2
B-immunoblastic	—	—	—	1	1
B-centroblastic	3	—	2	—	5
B-centroblastic-centrocytic	—	—	2	—	2
B-centrocytic	1	—	1	—	2
T-cellular	—	1	—	—	1
Not classifiable	1	—	—	—	1
Total	5	2	10	4	21

Types of non-Hodgkin's lymphoma are according to the Kiel classification.

was used. The results of the restaging were classified as progression of disease (Parkinson's disease), no response (NR), partial remission (PR) and complete remission with residual focal alterations (CR-r) or without residual focal alterations (CR).

In cases of contradictory results of remission status and one of the examinations, MRI or ^{67}Ga scintigraphy, the diagnosis was confirmed by follow-up examinations. In 3 patients, a PR with "active" lesions was concluded because of ongoing clinical symptoms, elevated markers or a reduction of tumor size after second-line therapy that implicated a PR at the time of the examination. The diagnosis of CR was confirmed at the first follow-up examinations 3–5 mo after the restaging.

^{67}Ga Scintigraphy

^{67}Ga scintigraphy was performed at least 4 wk after chemotherapy or irradiation. Total-body ^{67}Ga scintigraphy was performed with a large-field-of-view or a double-head gamma camera (SP6 Helix; Elscint, Haifa, Israel) that used a medium-energy collimator. The dose was 155–217 MBq (4.2–5.9 mCi) and imaging was obtained 48–72 h later. SPECT reconstructions of the thoracic and abdominal region were usually performed after 48 h, followed by SPECT examinations the next day in cases of suspected infiltration of the skull, sinuses, facial bones or pelvis. Three independent pulse-height analyzers with a 20% window were used to detect the 93, 184 and 296 keV photon emissions of the radioisotope. The inherent spatial resolution was 3.5 mm full width at half maximum (FWHM) (SP6) or 3.2 mm FWHM (Helix). A minimum density of 300 counts/cm^2 was achieved in planar scans; the time limitation of the SPECT reconstructions was 60 min (360° rotation, 60 projections, step 6°). Laxatives were routinely used to optimize abdominal imaging.

TABLE 2
Overview of Skeletal Distribution of Osseous Lesions (n = 36) of 21 Patients

Site	Group I	II	III	IV	Total
Axial skeleton					
Skull, sinuses, facial bones	1	1	1	1	4
Spine and sacrum	—	—	8	3	11
Ribs	—	—	2	1	3
Sternum	—	—	—	1	1
Pelvis	1	—	2	1	4
Total	2	1	13	7	23
Appendicular skeleton					
Lower extremity	3	5	2	1	11
Upper extremity	—	—	—	2	2
Total	3	5	2	3	13
All	5	6	15	10	36

MRI

All MRI examinations were performed with a 1.5-T, superconducting high-field magnet (Gyroscan NT 15; Philips, Best, The Netherlands, or Magnetom SP 63; Siemens, Erlangen, Germany). The MRI restaging examinations were performed with the same imager as was used for the first examination. Static and dynamic gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)–enhanced MR images were obtained in all examinations.

Static studies included T1-weighted sequences with a repetition time (TR) of 550 ms and an echo time (TE) of 12 ms; the number of signals averaged (NSA) was 2. Although T2-weighted imaging provides no additional information concerning malignant infiltration of the bone, our choice of an opposed-phase gradient-echo (GE) sequence or a T1-weighted spinecho (SE) sequence with fat suppression depended on the location of the lesion. If the lesion was located in the spine, the pelvis, the sacrum or the skull, an opposed-phase GE sequence with a TR of 400 ms and a TE of 12 ms (flip angle 70°, acquisition matrix 256 × 256, NSA = 3) was used. A TE of 12 ms was found to minimize the signal intensity (SI) of normal bone marrow of the axial skeleton at 1.5 T. The slice orientation was sagittal for the spine and coronal for the pelvis, sacrum and skull. Patients with malignant lymphoma of the bone at other sites were examined with a fat-saturated T1-weighted SE sequence with identical parameters as previously described. The dynamic studies were performed in a transverse plane with a fast GE sequence (TR = 33 ms, TE = 7.0 ms, NSA = 2, flip angle 60°). After the acquisition of one plain image, a bolus Gd-DTPA injection (0.2 mmol/kg) was rapidly administered intravenously by means of an injector with a flow rate of 3 mL/s.

A total sequence of 40 images was made, with a delay of 2 s between the images. The imaging time per image was 5 s. The SI of the tumor and, in cases of varying regional uptake, of different areas within the tumor were measured by using an irregular region of interest (ROI) for each image. The SIs of adjacent normal bone marrow, fatty tissue and muscle were also determined in the same images.

The values derived from each image were plotted against time as proposed by Erlemann et al. (*6*), who introduced the measuring of the SI ratio for the follow-up of malignant bone tumors. For each type of tissue, the signal increase over the baseline SI was calculated as follows: SI ratio = SI_{max} / SI_{plain}. The lesions were considered active if the SI ratio was >2 and inactive if the SI ratio was <2. T1-weighted SE and opposed-phase GE or T1-weighted SE imaging with fat saturation were repeated using identical parameters as for the plain images.

Methods of Comparison

The MR images were read independently by two radiologists highly specialized in the interpretation of musculoskeletal imaging. MRI was considered positive (MR+) in cases of progression of

disease, NR or PR. Progression of disease was concluded when bone marrow infiltration or paraosseous involvement increased. NR was concluded if the diameter of the paraosseous involvement changed by <50% or if the size and maximal signal increase of the bone lesion did not change noticeably. PR on MRI was concluded if the diameter of the paraosseous infiltration decreased by >50% and the SI ratio decreased compared with the SI value at the pretreatment staging.

The remission status for MRI was considered negative (MR−) if morphologic signs of a CR with normal SI of the bone marrow appeared in all images or in cases of so-called CR-r, including hypointense lesions of the bone marrow on T1-weighted SE images with or without a slight signal increase (SI ratio < 2).

Gallium scans were independently interpreted by two physicians experienced in nuclear medicine, with a consensus being reached for equivocal lesions. Any gallium uptake outside the normal distribution that could not be attributed to some other pathologic process was regarded as positive (Ga+). A gallium scan was considered to be unsuspicious (Ga−) if it showed a normal distribution of the radioisotope for the skeleton.

RESULTS

Staging of Malignant Lymphoma of the Bone

MR images of 21 patients with 36 osseous lesions were available. Bone marrow lesions were hypointense on plain, T1-weighted SE images with respect to the adjacent bone marrow, with a high contrast in the case of involvement of the appendicular skeleton (13 of 13 lesions). When the axial skeleton was infiltrated (n = 23), the detection of malignant infiltration by plain, T1-weighted SE imaging was difficult or impossible in those 4 of the 23 cases in which the osseous lesions were located in the femur.

All lesions were identified after intravenous administration of Gd-DTPA using an opposed-phase GE or a fat-saturated SE sequence (Fig. 1). Both ^{67}Ga scintigraphy and MRI were available in 14 patients with 22 osseous lesions. ^{67}Ga scintigraphy detected 77% of all lesions that involved bone infiltration. When located in the axial skeleton, 69% of the lesions were visible on ^{67}Ga scintigraphy, whereas 89% of the lesions in the appendicular skeleton were detected (Table 3).

^{67}Ga scintigraphy detected all manifestations of malignant lymphoma of the bone without nodal involvement (groups I and II), whereas in cases of simultaneous or secondary involvement of the bone (groups III and IV), scintigraphy yielded 38% false-negatives. Soft tissue was involved in 9 of the osseous lesions, with ^{67}Ga scans being positive in 89% of the lesions (8 of 9).

Restaging of Malignant Lymphoma of the Bone

After first-line therapy, 13 patients underwent both MRI and ^{67}Ga scintigraphy for restaging. All 25 malignant lesions documented in these patients in the staging examinations were analyzed (Table 4). Ten lesions showed residual activity and 15 lesions were classified as inactive on the basis of the gold standard. ^{67}Ga scintigraphy identified all lesions (n = 7) in groups I and II correctly, with 3 true-positive and 4 true-negative results. In groups III and IV, 14 of 18 lesions were identified correctly: There were 4 true-positives, 10 true-negatives, 3 false-negatives and 1 false-positive in a patient with nodular sclerosing HD involving the spine. This gives a sensitivity for ^{67}Ga scintigraphy of 70% and a specificity of about 93%.

Sensitivity of MRI was 90% and specificity was 80%. MRI of 14 of 15 malignant lesions with CR according to the gold standard showed residual alterations in SI of the examined bone marrow, usually visible as areas with lower SI on T1-weighted SE images compared with the adjacent bone marrow. One patient with extranodal NHL of the pleura involving the spine showed normal SI of the bone marrow on all MR images and no enhancement after Gd-DTPA administration (^{67}Ga true-negative).

In 12 of the above-mentioned 15 malignant lesions, an SI ratio <2 was measured and the negative MRI assessment was correct, but in patients with CR, 3 lesions showed an SI ratio >2, which resulted in false-positive findings (Fig. 2). Clinical determination of the remission status showed residual activity in 10 of the lesions. MRI detected almost all the lesions with residual activity (9 of 10). Three lesions, all with extensive soft tissue involvement, showed morphologic signs of progression of disease or NR, including persistence of soft tissue involvement and a strong signal increase (the SI ratios were 3.8, 4.2 and 4.4).

All 7 bone lesions classified as PR were hypointense on T1-weighted SE images and hyperintense on fat-saturated or opposed-phase GE images. Although the average SI ratio was 2.4 (SD = 0.2), 1 lesion was incorrectly judged to be negative because the SI ratio was 1.4.

All patients with PR and 13 of 15 lesions in patients with CR and CR-r had no residual soft tissue infiltration, whereas soft tissue was involved before treatment in 4 of 7 lesions in patients with PR and in 5 of 15 lesions in patients with CR-r (Table 5). Bone marrow infiltration showed a reduction in size in 3 of 7 lesions in patients with PR and in 7 of 15 lesions in patients with CR-r.

DISCUSSION

Lymphomatous involvement of the bone is an uncommon disease. In up to 15% of patients with HD, secondary spread from nodal sites has been reported. If primary HD of the bone without extraosseous manifestations occurs at all, it is extremely rare (*7*). In NHL, secondary bone involvement may occur in up to 25% of cases, whereas less than 1% of all NHLs are primary lymphomas of the bone (*1,3,8–11*).

Primary lymphoma of the bone tends to be localized on the appendicular skeleton and has a better prognosis than secondary involvement of the bone, which often infiltrates the axial skeleton, reflecting extensive disease (*12,13*). Bone scintigraphy is routinely used for the screening of skeletal involvement during staging of HD and high-grade NHL because of its ability to give an overview of the whole skeleton. In several studies, bone scintigraphy was compared with ^{67}Ga scintigraphy for the staging of secondary bone involvement in lymphoma (*3,14–16*).

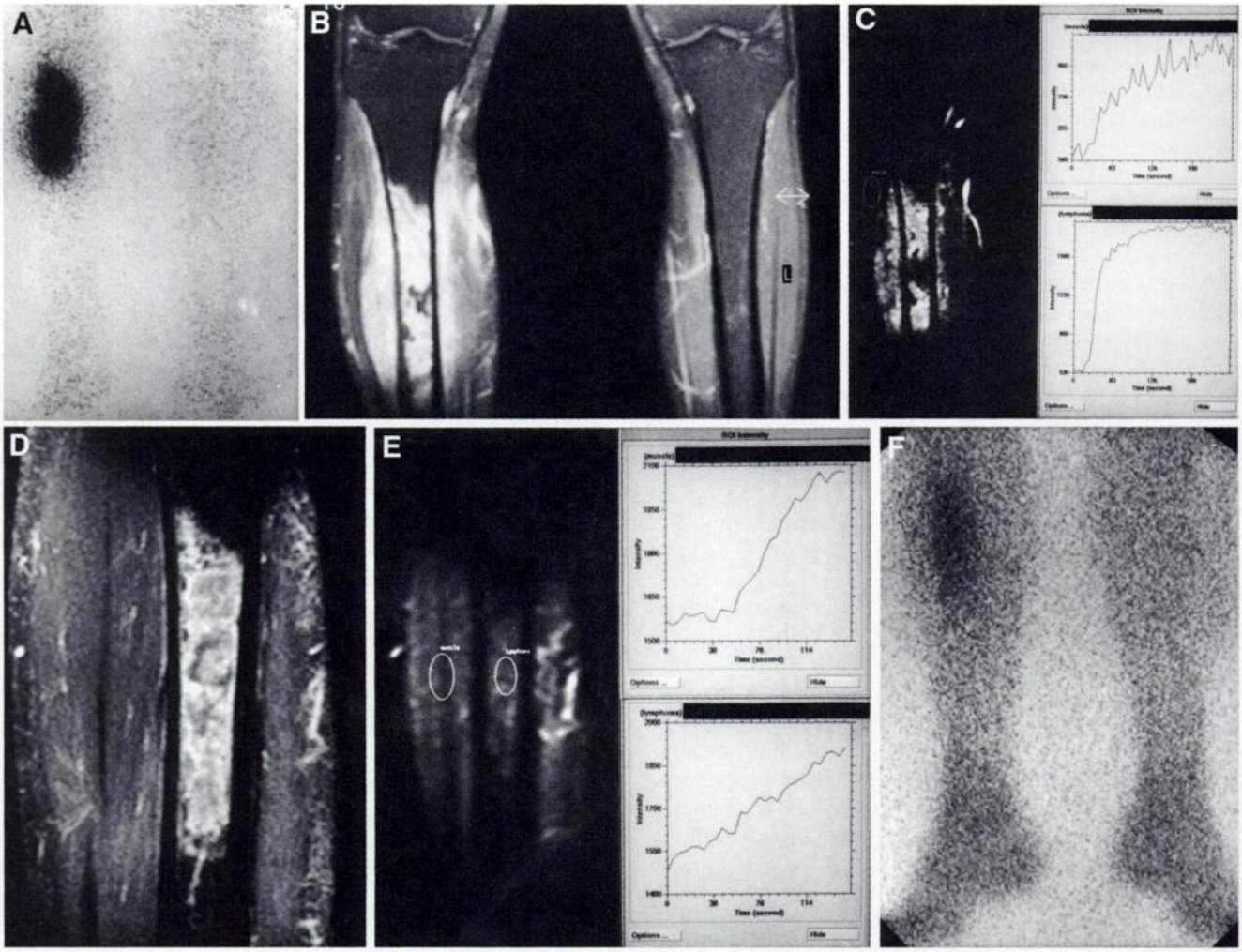

FIGURE 1. Staging and monitoring of 36-y-old patient with immunoblastic NHL and simultaneous involvement of nodules and right tibia who presented with fever, weight loss and pain. (A) Planar ^{67}Ga scintigram (anterior view) shows high activity on proximal right tibia. (B) MR image (fat saturation, contrast-enhanced, coronal view) shows hyperintense bone marrow lesion and permeative infiltration of compacta, which was still detectable as hypointense line, combined with extensive, hyperintense soft tissue involvement. (C) SI ratio of lymphomatous osseous lesion (right tibia) was about 3.5 (lower curve) compared with two-fold signal increase for normal muscle (upper curve). (D) After first-line therapy, patient achieved PR. Static MR image (T1-weighted, enhanced, fat saturation) still demonstrates hyperintense bone marrow lesion, although soft tissue involvement was gone. (E) Dynamic MR image shows minor increase of signal intensity. (F) In agreement with MRI, ^{67}Ga scintigram shows reduced activity of lesion on planar view. Patient died of early relapse several months later.

Most of these research groups reported a high sensitivity of both scintigraphic methods on the basis of clinical examination and conventional radiography as a gold standard. In our investigations, ^{67}Ga scintigraphy detected 89% of the malignant lesions when they were located on the appendicular skeleton, 89% when there was soft tissue involvement and all lesions in cases of primary or multiosseous lymphoma of the bone. On the other hand, sensitivity was 62% in cases of secondary bone involvement and 69% in cases of location on the axial skeleton.

To date, MRI has proven to be the most sensitive technique for the detection of bone involvement in lymphoma (*17–22*). This is the reason why in our clinic MRI was performed in cases of suspected bone infiltration. Several studies reported excellent results in the staging of

TABLE 3
Staging of Malignant Lymphoma of the Bone

	Gold standard	^{67}Ga+	^{67}Ga−
Groups I and II	9	9/9	—
Soft tissue involvement	4	4/4	—
Groups III and IV	13	8/13	5/13
Soft tissue involvement	5	4/5	1/5
All lesions	22	17/22 (77%)	5/22 (23%)
Soft tissue involvement	9	8/9 (89%)	1/9 (11%)
Location			
Axial	13	9/13 (69%)	4/13 (31%)
Appendicular	9	8/9 (89%)	1/9 (11%)

Results of ^{67}Ga scintigraphy of 14 patients with 22 osseous lesions.

TABLE 4
Restaging of 13 Patients with 25 Osseous Lesions After First-Line Therapy

	True-positive	False-positive	True-negative	False-negative	All
^{67}Ga					
Groups I and II	3	—	4	—	7
Groups III and IV	4	1	10	3	18
All	7	1	14	3	25
MRI					
Groups I and II	3	1	3	—	7
Groups III and IV	6	2	9	1	18
All	9	3	12	1	25
Gold standard					
Groups I and II	3	—	4	—	7
Groups III and IV	7	—	11	—	18
All	10	—	15	—	25

Comparison of ^{67}Ga scintigraphy and MRI.

malignant lymphoma with ^{18}F-fluorodeoxyglucose PET, but results as to bone involvement with a large group of patients are not yet available (*23,24*).

Because MRI focuses on only one region of the skeleton at a time, it is impossible as a result of time considerations to obtain an overview of the whole skeleton with this technique. MRI is considered to be superior to other techniques for investigating the bone marrow because of its ability to distinguish clearly between fat and other types of tissue (*20*). For imaging the axial skeleton, we used an opposed-phase GE sequence in which the magnetization vectors of fat and water protons were antiparallel during signal sampling. Pathologic changes in cell composition result in a disturbance of the equilibrium between fat and water protons, yielding a higher SI (*21*).

Contrast agents like Gd-DTPA increased the accuracy of MRI in the detection of malignant infiltration of the bone marrow in lymphoma, because there is no SI increase in the bone marrow of healthy adults, either in areas of fatty marrow or in red marrow, whereas contrast enhancement of malignant infiltration in lymphoma is a constant finding (*20,21,25*).

Given the high sensitivity of bone scintigraphy in screening for bone involvement in the staging of malignant lymphoma and the high accuracy of MRI in detecting bone infiltration in suspected areas, ^{67}Ga scintigraphy seems to be of negligible benefit for the staging of malignant lymphoma of the bone. However, a baseline scan before treatment is required to avoid misinterpretations in cases of non-^{67}Ga-avid bone lymphomas.

After first-line therapy, differentiation between progression of disease, NR, PR and CR becomes increasingly important for the decision between palliative strategies or second-line therapies with curative options such as high-dose chemotherapy with stem cell support.

Several studies suggest that ^{67}Ga scintigraphy is more accurate than bone scintigraphy in monitoring the therapeutic response of patients with malignant lymphoma of the bone (*13,14,26–28*). In agreement with our findings, false-negative results may occur, whereas false-positive ^{67}Ga scans in cases of CR are extremely rare. Residual activity can be overlooked, especially when it is located in the spine and pelvis, because of physiologic accumulation of the radioisotope in the liver, spleen and bowel (*2,14,29*).

In this study, the results of ^{67}Ga scintigraphy corresponded with the clinical remission status for all cases of primary lymphoma. This agrees with the results of Furman et al. (*13*), who obtained a higher correlation between response and ^{67}Ga scintigraphy than for bone scintigraphy in nine children with primary lymphoma of the bone. In patients with secondary involvement of the bone, 3 of 10 lesions with residual activity were false-negative on ^{67}Ga scans. This result might be explained by the predominant location of secondary bone lymphoma on the axial skeleton and, possibly, by a difference in histologic subtype between primary and secondary bone lymphoma, which results in a

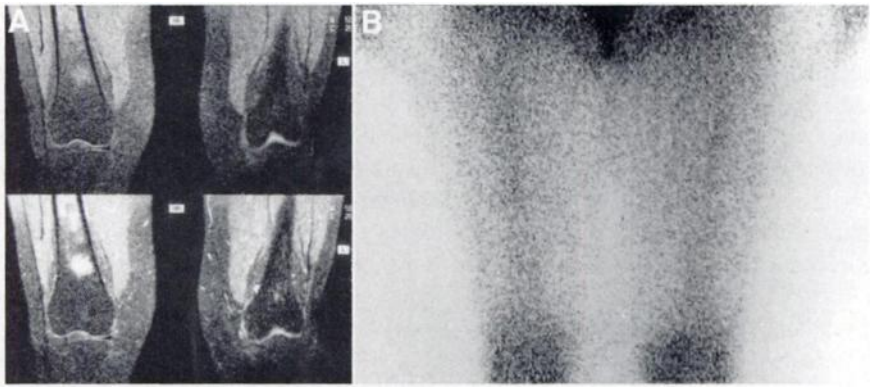

FIGURE 2. ^{67}Ga scintigraphy and MRI of 45-y-old woman with clinical signs of CR after chemotherapy of centroblastic lymphoma of right femur. (A) Native MR image with fat saturation shows heterogeneous SI for bone marrow of right femoral metaphysis and diaphysis (upper image), but there was high signal increase after intravenous injection of contrast agent (lower image), which was incorrectly interpreted as residual activity. (B) ^{67}Ga scintigram (anterior view) shows normal activity on both femoral bones, reflecting true-negative result. This was confirmed by follow-up examinations 3 and 6 mo later.

TABLE 5
Remission Status, ^{67}Ga Scintigraphy and MRI with Regard to Soft Tissue Involvement and Bone Infiltration in Patients with Bone Lymphoma After First-Line Therapy

Patient no.	Remission status*	Size reduction of soft tissue involvement	Size reduction of bone infiltration	MRI	^{67}Ga	Comments
1	PD	Progression	Progression	+	+	Progression of pain, fever, tumor size
		Progression	No	+	+	
2	NR	No	No	+	+	Pain, tumor size
3	PR	Not involved	No	+	−	Fever, LDH elevated
		Not involved	No	+	−	
4	PR	Yes	No	−	+	Pain, BSR elevated
5	PR	Yes	Yes	+	+	Follow-up (reduction of tumor size under second-line therapy)
		Yes	Yes	+	+	
		Not involved	Yes	+	+	
6	PR	Yes	No	+	−	Follow-up (reduction of tumor size under second-line therapy)
7	CR-r	Not involved	Yes	+	−	Follow-up (6 mo)
8	CR-r	Yes	No	+	−	Follow-up (9 mo)
		Not involved	No	+	−	
9	CR-r	Not involved	Yes	−	+	Follow-up (8 mo)
		Not involved	Yes	−	−	
		Not involved	Yes	−	−	
10	CR-r	Yes	Yes	−	−	Follow-up (5 mo)
		Yes	No	−	−	
		Not involved	No	−	−	
		Not involved	No	−	−	
11	CR-r	Not involved	No	−	−	Follow-up (15 mo)
		Not involved	No	−	−	
		Not involved	No	−	−	
12	CR-r	Yes	Yes	−	−	Follow-up (13 mo)
13	CR	Yes	Yes	−	−	Follow-up (6 mo)

*PD = progression of disease; NR = no response; PR = partial remission; LDH = lactate dehydrogenase; BSR = blood sedimentation rate; CR-r = complete remission with residual alterations; CR = complete remission.

In cases of contradictory results of remission status, MRI or ^{67}Ga scan, the gold standard included the results of the follow-up that confirmed a CR-r in patients 7, 8 and 9. Patients 3 and 4 still had clinical symptoms and elevated markers after first-line therapy, which implicated residual activity; patient 6 had a reduction of tumor size after second-line therapy.

difference of sensitivity to ^{67}Ga scanning. The data should be interpreted with caution because of the small number of lesions investigated. The injected dose of 155–217 MBq (4.2–5.9 mCi) is lower than the dose used in several studies in which "high-dose gallium scintigraphy" was performed (*2,14,26–28*). On the other hand, a minimum density of 300 counts/cm^2 was achieved on planar scans that correlates well with other published data.

Only a few reports evaluated the diagnostic accuracy of MRI in assessing treatment response (*6,22*). To our knowledge, this is the first study that compares the accuracy of MRI and ^{67}Ga scintigraphy for the restaging of malignant lymphoma of the bone.

After first-line therapy, all but 1 patient had residual signal alterations of the bone marrow on MRI, reflecting lymphomatous tissue, fibrosis or inactive necrosis. In cases of response to treatment, differentiation by MRI between "active" lesions, which usually require further treatment by more aggressive second-line therapies, and "inactive" lesions, reflecting a so-called CR-r is difficult. Dynamic Gd-DTPA-enhanced MRI enables the quantification of the signal increase in malignant lesions, which reflects perfusion and interstitial edema as accompanying phenomena of lymphoproliferative activity. On the other hand, we observed high signal increase in 3 of 15 lesions in patients with CR, negative ^{67}Ga scan and no sign of residual activity on follow-up examinations, which induced false-positive interpretations of the MRI examinations. Hypercellularity of reactive hematopoetic regions with high vascularization or inflammation that is found on histologic examination of such cases might explain these findings (*6,25,30*). MRI allowed a separate analysis of response of soft tissue infiltration and bone infiltration because of a spatial resolution superior to that of ^{67}Ga scintigraphy.

CONCLUSION

In this study, soft tissue involvement after first-line therapy was exclusively detected in patients with clinical signs of progression of disease or NR, but it is not clear whether soft tissue residual disease should be interpreted as

an indicator of residual bone disease because of the limited number of patients evaluated.

If the size of the osseous lesion decreases under therapy, a response to treatment can be concluded, but the majority (55%) of lesions in patients with response did not demonstrate a reliable reduction of the size.

With regard to monitoring the response to therapy for restaging, both MRI and ^{67}Ga scintigraphy are valuable, but they should be used as complementary diagnostic tools because of the lower sensitivity of ^{67}Ga scintigraphy (70%) but a higher specificity (93%) compared with MRI (90% sensitivity, 80% specificity). If the malignant lesions are located on the appendicular skeleton, in cases of primary lymphoma or of soft tissue involvement, ^{67}Ga scan results correlated well with the clinical remission status and tended to be similar or even superior to MRI. In cases of secondary involvement of the bone or location of the malignant lesion on the axial skeleton, MRI tended to be more accurate.

REFERENCES

1. Ostrowski ML, Unni KK, Banks PM, et al. Malignant lymphoma of bone. *Cancer.* 1986;58:2646–2655.
2. Moon TY, Kim EE, 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.
3. Mouratidis B, Gilday DL, Ash JM. Comparison of bone and 67-Ga scintigraphy in the initial diagnosis of bone involvement in children with malignant lymphoma. *Nucl Med Commun.* 1994;15:144–147.
4. Schechter JP, Jones SE, Woolfenden JM, Lilien DL, O'Mara RE. Bone scanning in lymphoma. *Cancer.* 1976;38:1142–1148.
5. White LM, Gray BG, Ichise M, Kirsh JC, Burkes R. Scintigraphic flare in skeletal lymphoma. *Clin Nucl Med.* 1994;19:661–664.
6. Erlemann R, Sciuk J, Bosse A, et al. Response of osteosarcoma and Ewing sarcoma to preoperative chemotherapy: assessment with dynamic and static MR imaging and skeletal scintigraphy. *Radiology.* 1990;175:791–796.
7. Ozdemirli M, Mankin HJ, Aisenberg AC, Harris NL. Hodgkin's disease presenting as a solitary bone tumor. A report of four cases and review of the literature. *Cancer.* 1996;77:79–88.
8. Bragg DG, Colby TV, Ward JH. New concepts in the non-Hodgkin lymphomas: radiologic implications. *Radiology.* 1986;159:289–304.
9. Braunstein EM, White SJ. Non-Hodgkin lymphoma of bone. *Radiology.* 1980;135:59–63.
10. Chin HW, McGuire MH, Block M, Frank AR, Boman BM, Mailliard JA. Primary lymphoma of bone. *Nebr Med J.* 1990;75:303–306.
11. Phillips WC, Kattapuram SV, Doseretz DE, et al. Primary lymphoma of bone: relationship of radiographic appearance and prognosis. *Radiology.* 1982;144:285–290.
12. Farres MT, Dock W, Augustin I, et al. The radiological features of primary bone lymphomas. *Fortschr Rontgenstr.* 1993;158:589–593.
13. Furman WL, Fitch S, Hustu OH, Calliman T, Murphy SB. Primary lymphoma of bone in children. *J Clin Oncol.* 1989;7:1275–1280.
14. Bar-Shalom R, Israel O, Epelbaum R, et al. Gallium-67 scintigraphy in lymphoma with bone involvement. *J Nucl Med.* 1995;36:446–450.
15. Haddy TB, Keenan AM, Jaffe ES, Magrath IT. Bone involvement with non-Hodgkin's lymphoma: efficacy of chemotherapy without local radiotherapy. *Blood.* 1988;72:1141–1147.
16. Kluin-Nelemans HC, Noordijk EM. Staging of patients with Hodgkin's disease: what should be done? *Leukemia.* 1990;4:132–135.
17. Stiglbauer R, Augustin I, Kramer J, Schurawitzki H, Imhof H, Radaszkiewicz T. MRI in the diagnosis of primary lymphoma of bone: correlation with histopathology. *J Comput Assist Tomogr.* 1992;16:248–253.
18. Melamed JW, Martinez S, Hoffman CJ. Imaging of primary multifocal osseous lymphoma. *Skeletal Radiol.* 1997;26:35–41.
19. Linden M, Zankovich R, Theissen P, Diehl V, Schicha H. Malignant lymphoma: bone marrow imaging versus biopsy. *Radiology.* 1989;173:335–339.
20. Steiner RM, Mitchell DG, Rao VM, Schweitzer ME. Magnetic resonance imaging of diffuse bone marrow disease. *Radiol Clin North Am.* 1993;31:383–409.
21. Hosten N, Sander B, Schörner W, et al. MR tomographic screening studies of the bone marrow with gradient echo sequences: (1) the contrast relations of phase-identical and phase-shifted gradient echo sequences. Studies on probands and pathological-anatomical preparations [in German]. *Fortschr Rontgenstr.* 1991;154:614–620.
22. Lang P, Grampp S, Vahlensieck M, et al. Primary bone tumors: value of MR angiography for preopreative planning and monitoring response to chemotherapy. *AJR.* 1995;165:135–142.
23. Okada J, Yoshikawa K, Imazeki K, et al. The use of FDG-PET in the detection and management of malignant lymphoma: correlation of uptake and prognosis. *J Nucl Med.* 1991;32:686–691.
24. Rodriguez M, Rehn S, Ahlström H, et al. Predicting malignancy grade with PET in non-Hodgkin's lymphoma. *J Nucl Med.* 1995;36:1790–1796.
25. Amano Y, Hayashi H, Kumazaki T. Gd-DTPA enhanced MRI of reactive hematopoietic regions in marrow. *J Comput Assist Tomogr.* 1994;18:214–217.
26. McLaughlin AF, Magee MA, Greenough R, et al. Current role of gallium scanning in the management of lymphoma. *Eur J Nucl Med.* 1990;16:755–771.
27. Roach PJ, Janicek MJ, Kaplan WD. Bone lymphoma. Comparison of Tl-201 and Ga-67 citrate scintigraphy in assessment of treatment response. *Clin Nucl Med.* 1996;21:689–694.
28. Israel O, Front D, Lam M. Gallium-67 imaging in monitoring lymphoma response to treatment. *J Nucl Med.* 1990;31:365–368.
29. Salloum E, Brandt DS, Caride VJ, et al. Gallium scans in the management of patients with Hodgkin's disease: a study of 101 patients. *J Clin Oncol.* 1997;15:518–527.
30. Stroszczynski C, Hosten N, Amthauer H, et al. Dynamic computed tomography of the bone marrow in normal and pathological vertebrae. *Fortschr Rontgenstr.* 1997;167:240–246.