

# Multifocal Primary Lymphoma of Bone: Scintigraphy and MR Findings before and after Treatment

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A case of multifocal primary lymphoma of bone is reviewed. Ga-67 citrate, Tc-99m HMDP, and Tl-201 scintigraphs all showed multifocal radiotracer accumulation. CT showed subtle osteolytic and osteosclerotic changes with surrounding soft tissue density mass. MRI clearly showed abnormal signal intensity in the bone marrow. After systemic chemotherapy and infield radiotherapy, the patient showed clinically complete remission. MRI showed reduction of the extraosseous components, but there was little signal change in the bone marrow despite the clinical response to the therapy. Scintigrams were more useful than MRI and CT for both staging and assessing the early response to therapy. The soluble interleukin-2 receptor level was found to be related to tumor cell activity.

*Key words:* malignant lymphoma, bone tumor, scintigraphy, magnetic resonance imaging (MRI)

### INTRODUCTION

PRIMARY LYMPHOMA of bone is a rare extranodal presentation of non-Hodgkin's lymphoma. Although patients with multifocal malignant bone lesions and accompanying surrounding soft tissue mass are thought to have an even worse prognosis, concurrent therapy has recently been effective.<sup>1,2</sup> Although MRI is useful for diagnosis and reflects tissue characterization, much time is required to improve the normal signal. Therefore, scintigrams are utilized to determine tumor distribution and reflect changes in tumor activity. The present case showed clinically complete remission after treatment, and the response to therapy was examined and compared using plain MRI, scintigraphy, and the soluble interleukin-2 receptor (sIL-2R) level before and after therapy.

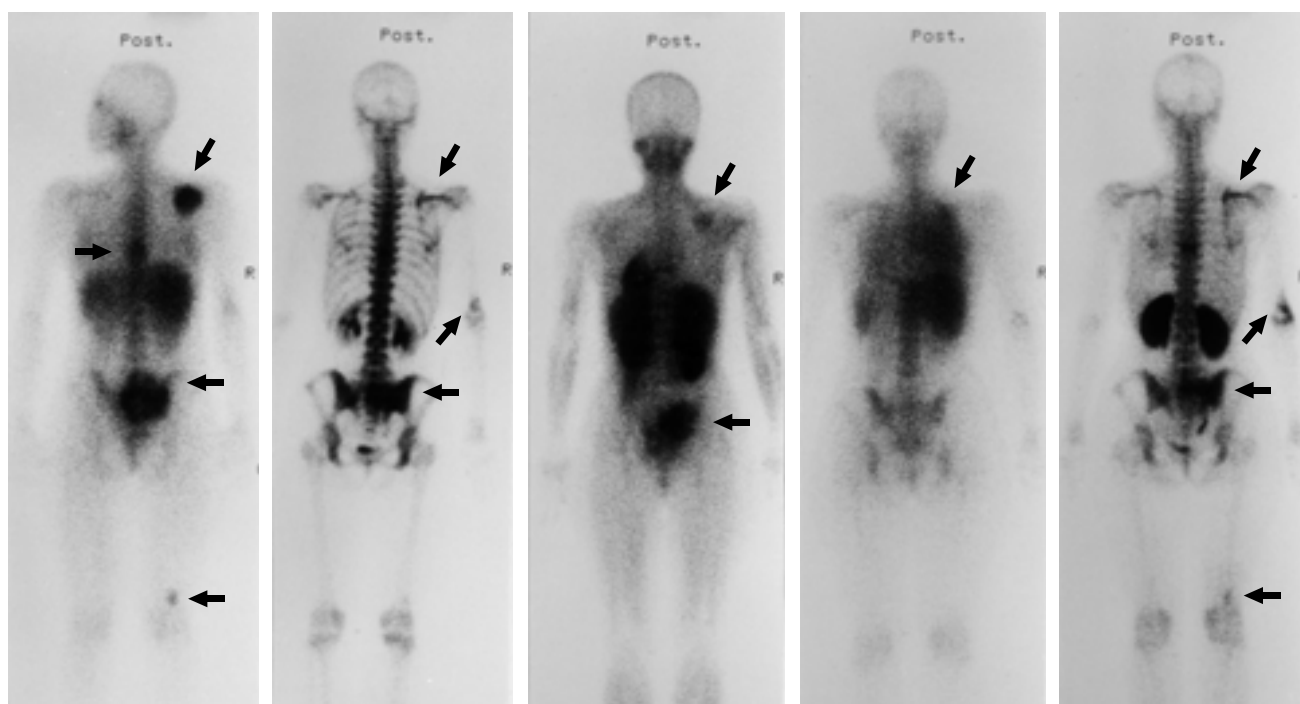
### CASE REPORT

A 25-year-old woman presented with a four-month history of lumbago. The pain worsened day by day, and severe gait disturbance appeared, until finally she was hospitalized in August 1996. Both WBC and CRP levels were within the normal range. Both the ATLA test and Bence-Jones protein were negative. The sIL-2R level was elevated to 825 U/ml (normal range: 145-519 U/ml).

Gallium-67 citrate (74 MBq intravenous injection; whole-body images obtained 2 days postinjection) (Fig. 1a), Tc-99m hydroxymethylene diphosphonate (HMDP) (555 MBq intravenous injection; whole-body images obtained 3 hours postinjection) (Fig. 1b), and thallium-201 (111 MBq intravenous injection; whole-body images obtained 15 minutes postinjection) (Fig. 1c), imaging studies were performed. Both Ga-67 citrate and Tc-99m HMDP scintigraphy performed pretreatment showed high radiotracer uptake in the right sacroiliac joint and right scapula, and moderate uptake in the 8th thoracic vertebra (Th8), right femur, and right elbow. Tl-201 scintigraphy showed high radiotracer accumulation in the right sacroiliac joint and moderate accumulation in the right scapula.

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Received December 6, 1999, revision accepted May 24, 2000.  
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**Fig. 1. Whole body scintigraphy.**

Both Ga-67 citrate scintigraphy of pretreatment (a) and Tc-99m HMDP scintigraphy (b) show high RI accumulation in the right sacroiliac joint and right scapula, and moderate radiotracer accumulation in Th8, the right femur, and right elbow. Tl-201 scintigraphy (c) shows high radiotracer accumulation in the right sacroiliac joint moderate accumulation in the right scapula. After three courses of chemotherapy, high radiotracer uptake on Ga-67 citrate scintigraphy (d) disappeared, but no remarkable change is seen on Tc-99m HMDP scintigraphy (e) except increased uptake in the right elbow because irradiation was not performed. Irradiation caused high radiotracer accumulation in the right lung (d), and chemotherapy caused radiotracer accumulation in both kidneys (e).

Pelvic CT imaging (Fig. 2a, b) showed subtle osteolytic and osteosclerotic change associated with a soft tissue mass in the region of the sacroiliac joint. Lymphadenopathy was not seen. Pelvic MRI showed a large mass lesion involving the right ilium with an extraosseous compartment. The mass showed low signal intensity on T1-weighted images (Fig. 2c) and heterogeneous iso to high signal intensity on T2-weighted images (Fig. 2d). It was irregularly enhanced after the intravenous injection of Gd-DTPA. The right femur region could not be pointed out on plain radiography, but MRI clearly revealed the abnormal lesions in the right femur (Fig. 3a). MRI also showed areas of high signal intensity on T2-weighted images in the surrounding muscle of the right scapula, which were the levator scapulae and infraspinatus muscles (Fig. 4), and areas of low signal intensity on T1-weighted imaging of in Th8 and the right humerus.

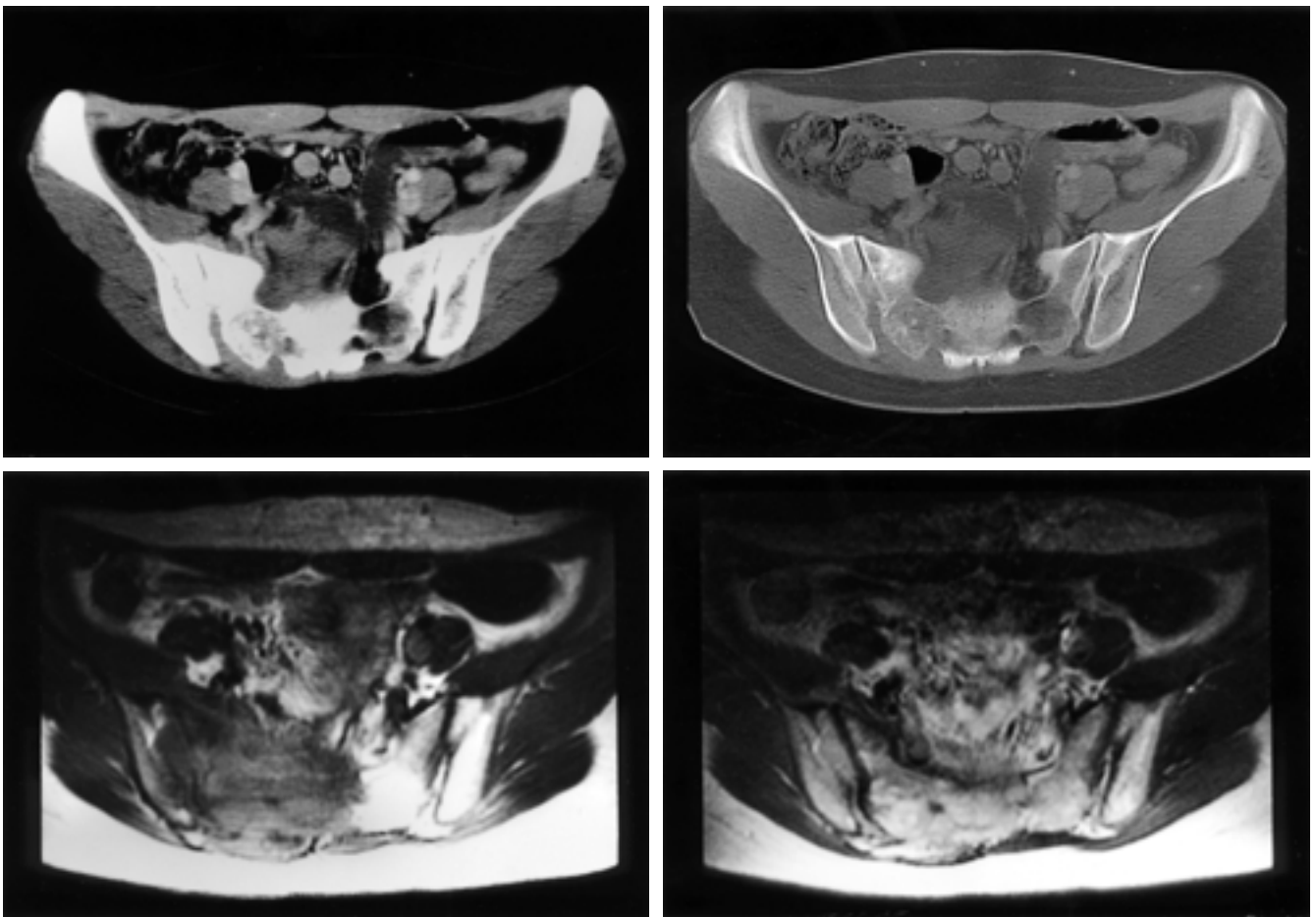
Neither definite tumor stain nor tumor vessel encasement was noted at pelvic angiography.

An open bone biopsy of the sacrum was performed. Histopathological study with immunohistological staining indicated small round-cell tumors representing

T-cell-type malignant lymphoma (Fig. 5). Ewing's sarcoma was excluded because glycogen was negative. Based on the clinical history and foci of the tumor localized in bone and surrounding soft tissue, the diagnosis of bone lymphoma stage IV was made on the basis of the Ann-Arbor classification.

The patient was treated with both radiotherapy and systemic chemotherapy. Radiotherapy was performed with 50 Gy to the sacrum, right scapula, right femur, Th8, and right humerus, one by one. Six courses of chemotherapy using the modified CHOP regimen (cyclophosphamide 800 mg/m<sup>2</sup>, farnorubicin 40 mg/m<sup>2</sup>, vindesine 3 mg/m<sup>2</sup>, prednisolone 60 mg/body) were completed. In the third to sixth course the dosage was decreased to 60-80% because of neutropenia, which was treated with G-CSF.

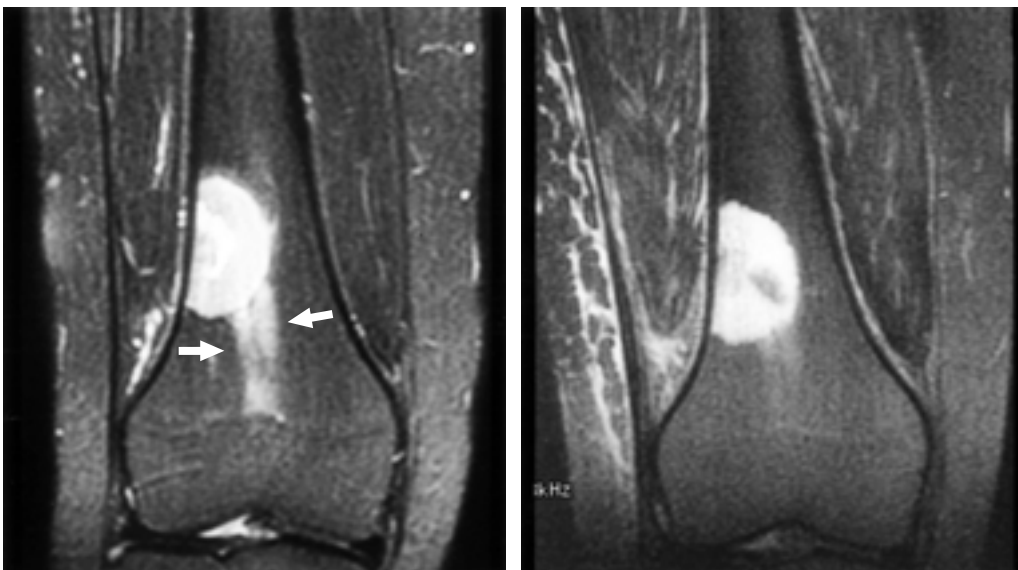
The therapeutic effects were assessed after three courses and at the end of the sixth course. After three courses of therapy, no uptake was seen in the irradiated field on Ga-67 citrate scintigraphy (Fig. 1d). MRI showed a decrease of soft tissue mass, but almost no size or signal change was seen in the bone marrow. Further, uptake continued on both Tc-99m HMDP (Fig.



**Fig. 2.** CT of the pelvis.

CT shows abnormal alignment with soft tissue density in the sacroiliac lesion (a). Mild osteolytic and osteosclerotic change are mixed (b). MRI shows hypo-signal intensity on the T1-weighted image (SE 500/20) (c), and heterogeneous hyper-signal intensity on the T2-weighted image (2000/20) (d).

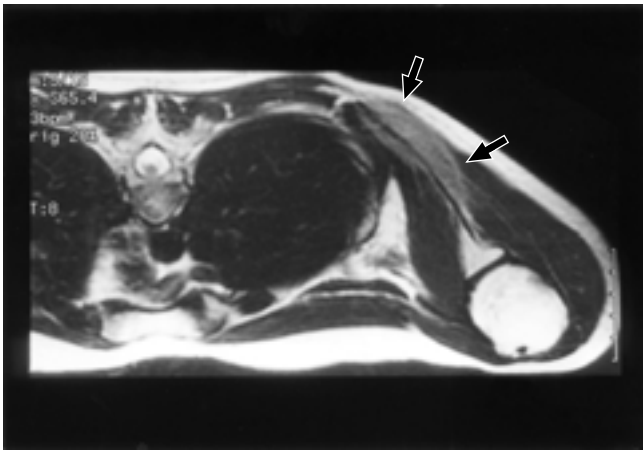
a	b
c	d



a | b

**Fig. 3.** MR imaging of the right femur.

The tumor, with a plain boundary, is located in the distal metaphysis of the right femur (a). T1WI shows low signal intensity and T2WI (FSE 4000/98) high signal intensity. The linear high signal of the epiphyseal line is seen (arrows). No periosteal reaction accompanies the tumor. After treatment, the linear high signal disappeared and a low signal spot appears in the mass (b).



**Fig. 4.** MR imaging of the right scapula. In the muscle surrounding the right scapula, the tumor is seen as a crescent-shaped high signal on T2WI (FSE 4615/80) (arrows).

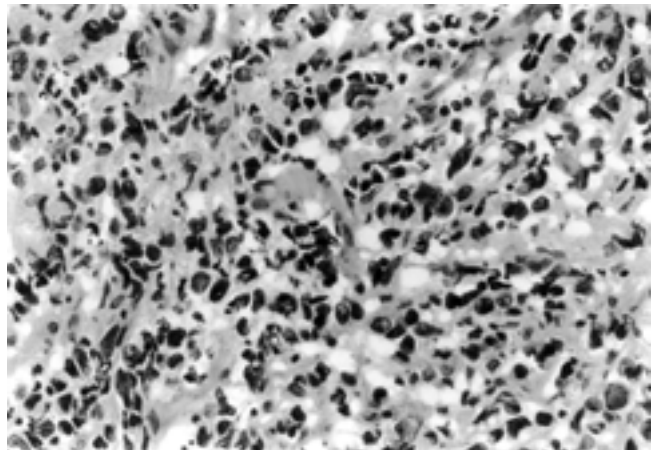
le) and Tl-201 scintigraphy. After six courses, no abnormality was seen in any scintigraphs; however, MRI still showed abnormal signal in the bone marrow (Fig. 3b). The level of sIL-2R decreased to 404 after three courses, then decreased further to 232 at the end of the sixth course. The patient showed clinically complete remission, and neither relapse nor metastasis has been recognized in the four years since treatment.

#### DISCUSSION

Primary lymphoma of bone accounts for approximately 5% of extranodal non-Hodgkin's lymphomas and 3-5% of all primary osseous malignancies. The criteria that must be met to establish the diagnosis of primary lymphoma of bone are: (1) only a single bone is initially affected; (2) there is unequivocal histologic evidence of lymphoma of the bone lesion; and (3) there is metastasis to only regional areas on presentation, or the primary tumor precedes the metastasis by at least six months.<sup>3</sup> Even if the foci are localized to a bone and the surrounding soft tissue simultaneously, these cases are considered primary lymphoma of bone.<sup>4,5</sup>

In radiographic appearance, the bone lesions are usually permeative osteolytic (77%), osteosclerotic in 4.3%, and mixed in 16% of cases.<sup>6</sup> In this case, the osteolytic lesions except for the sacrum were hardly revealed on radiographs.

The MR imaging features of primary lymphoma of bone have been described.<sup>7-11</sup> Primary lymphoma of bone has been characterized as hypointense on T1-weighted imaging, and as showing various patterns on T2-weighted imaging and moderate homogeneous enhancement. Observations in the present study showed



**Fig. 5.** Histopathological findings with H.E. stain. Tumor cells are present between bone trabeculae. They are small to medium in size, and there is ruggedness in the nuclear membrane. The collagen fibers in the interstitial tissue were hyperplastic (not shown). Immunohistological staining revealed a few positive cells at UCHL-1 and LCA, and very few positive cells at MIC2.

various signal intensities on T2-weighted imaging with fat saturation. Especially in the study concerning T2-weighted imaging of lymphoma of bone, it showed lower signal intensity than other small round-cell tumors.<sup>10</sup> The reason is the high content of fibrous tissue. The pathologic features of lymphoma of bone are generally thought to show high cellularity and proliferation of collagen fiber with few necroses. The high fibrosity is a result of the restorative processes that occur after the destruction caused by the tumor. However, another report suggests that the T2-weighted imaging characteristics of primary lymphoma of bone vary.<sup>8</sup> The variable T2-weighted imaging of highly fibrotic processes may be attributed to other factors such as internal cellularity, maturity of fibrous tissue, and internal vascularity. It does not appear to be a simple reflection of histologic findings of intralesional vascularity or fibrosis. Further, enhancement is not useful for the differentiation of bone tumor owing to the overlap between highly vascular benign and hypovascular malignant lesions.<sup>7,12</sup> Thus the MR signal pattern of bone lymphoma is non-specific, so other diagnostic modalities are needed.

We performed Ga-67 citrate, Tc-99m HMDP, and Tl-201 scintigraphy. The appearance of each type of scan was different. High uptake in soft tissue mass was seen in Ga-67 citrate and Tl-201 scintigraphs, but whole body Tl-201 scans did not describe bone abnormality. Ga-67 citrate scintigraphy represented the earlier reduction of uptake compared with the other exams. Lymphoma cells may have a slight influence on osteoid formation.

Furthermore, T2 signal of MRI did not show radiotracer uptake.

Interpreting the radiological follow-up status for patients who have been treated for lymphoma of bone is often challenging. In most survivors, there was little or no change in the abnormal radiographic bone findings despite clinical response to therapy.<sup>2</sup> In the present case, the soft tissue masses in the areas surrounding the sacrum and scapula was diminished, but little change was observed in the signal intensity of bone marrow. In the lesion of the femur, the low signal intensity spot appeared as a high signal intensity lesion on T2-weighted imaging. It was difficult to differentiate without enhancement because the lesion might have reflected the fibrous change of the tumor. The linear high signal to the epiphyseal line disappeared. It also was difficult to diagnose whether this lesion reflected tumor invasion or reflective edema. The MR findings of decreased soft tissue mass and reduction of radiotracer uptake were correlated. Scintigraphy was superior in terms of rapid change of bone marrow, and it was useful for clarifying lesional activity even when it showed poor spatial resolution. Further, scintigraphy may be more useful than Gd-DTPA enhanced MRI with regard to time and cost of whole body examination if the lesions are multifocal.

In the scintigraphy of bone lymphoma, both Tc-99m HMDP and Ga-67 citrate scintigraphy are reported to have high sensitivity for the detection of lymphomatous lesions in bone.<sup>13</sup> However, they may also reflect bone healing and remodeling instead of the presence of a tumor. They showed almost the same lesional distribution, but the decrease in Ga-67 citrate scintigraphy accumulation was earlier than that of Tc-99m HMDP. Bone scintigraphy most likely reflects reparative osteoid formation rather than tumor activity. In some cases, the scan shows a malignant pattern on the reduction of bone metastasis after chemotherapy or irradiation, which is called the flare phenomenon. The flare phenomenon can be identified by the concomitant appearance of increased sclerosis in previously osteolytic or mixed metastatic lesions.<sup>14</sup> This may be the same appearance as the maturity of fibrosis, tissue remodeling, and new bone formation on MRI. In this case, however, it might not have been the flare phenomenon because the uptake did not increase remarkably.

It is highly uncertain as to whether MRI recovers to a normal signal for tissue restoration with fibrous change and new bone formation. However, Ga-67 citrate scintigraphy reflects changes in tumor activity more rapidly, and it may be considered useful for evaluating the effects of treatment and in-progress observation. The sIL-2R levels correlate with Ga-67 citrate scintigraphy, and may be the most ideal examination for outpatients

with lymphoma.

Tl-201 scintigraphy may be the most ideal radiopharmaceutical agent because it reflects tumor burden more accurately than either Tc-99m HMDP or Ga-67 citrate scintigraphy.<sup>15</sup> In this study, Tl-201 scanning showed marked uptake only of soft tissue mass and reflected rapid tumor response, similar to Ga-67 citrate scintigraphy, whereas it revealed little uptake in bone disorder. Ga-67 citrate scintigraphy was superior to Tl-201 for both tumor detection and early response to therapy.

The treatment for advanced lymphoma is generally combination chemotherapy, but concurrent therapy with involved field radiation has recently been reported.<sup>12</sup> The 3-year Kaplan-Meier event-free survival rate was 73%, and recurrence in the local irradiated field was rare. However, marginal or distant relapses occurred in about 50% of patients who received radiation alone, suggesting that combination chemotherapy and involved field radiation therapy, even if the tumor spreads as a multifocal lesion, prolonged event-free survival.<sup>2</sup> The outcome of advanced primary lymphoma of bone has been better remission.

However, this type of therapy it might increase the risk of infarction, secondary bone malignancies, bone infarction, or insufficiency fracture after irradiation to bone.<sup>5</sup> The pattern of bone scans in the radiation field shows a decrease in radiotracer uptake, whereas bone fracture can be revealed as high accumulation spots. Therefore, enhanced MRI or CT scan is necessary to distinguish recurrent tumor from fracture.

In conclusion, a case of multifocal primary lymphoma of bone treated by concurrent therapy was reviewed. MRI was useful for diagnosis and tissue characterization, and scintigrams were useful to recognize tumor distribution. Ga-67 citrate scintigraphy reflected the change in tumor activity more rapidly, and both Ga-67 citrate scintigraphy and the sIL-2R level were useful for assessing the response to therapy and in-progress observation.

#### REFERENCES

- 1) Okajima Y, Amano Y, Hayashi H, *et al.* Primary malignant lymphoma of the ischium. *Jpn J Diagnostic Imaging*, 15: 803–806, 1995.
- 2) Rapoport AP, Constine LS, Packman CH, *et al.* Treatment of multifocal lymphoma of bone with intensified promacecytobom chemotherapy and involved field radiotherapy. *Am J Hematol*, 58: 1–7, 1998.
- 3) Coley BL, Higenbotham NL, Groesbeck HP. Primary reticulum-cell sarcoma of bone: summary of 37 cases. *Radiology*, 55: 641–658, 1950.
- 4) Ueda T, Aozasa K, Ohsawa M, *et al.* Malignant

- lymphoma of bone in Japan. *Cancer*, 64: 2387–2392, 1989.
- 5) Uchida T, Horikoshi N, Aiba K, *et al.* Primary lymphoma of bone – a clinical study of 9 patients. *Jpn J Cancer Clin*, 40: 596–601, 1994.
  - 6) Edeiken-Monroe B, Edeiken J, Kim EE. Radiologic concepts of lymphoma of bone. *Radiol Clin North Am*, 28: 841–864, 1990.
  - 7) Haussler MD, Fenstermacher MJ, Johnston DA, *et al.* MRI of primary lymphoma of bone. Cortical disorder as a criterion for differential diagnosis. *JMRI*, 9: 93–100, 1999.
  - 8) White LM, Schweiter M.E, Khalili K, *et al.* MR imaging of primary lymphoma of bone; T2-weighted signal intensity. *AJR*, 170: 1243–1247, 1998.
  - 9) Melamed JW, Martinez S, Hoffman CJ. Imaging of primary multifocal osseous lymphoma. *Skeletal Radiol*, 26: 35–41, 1997.
  - 10) Stiglbauer R, Augustin I, Kramer J, *et al.* MRI in the diagnosis of primary lymphoma of bone: correlation with histopathology. *J Comput Assist Tomogr*, 16: 248–253, 1992.
  - 11) Hermann G, Klein MJ, Abdelwahab IF, *et al.* MRI appearance of primary non-Hodgkin's lymphoma of bone. *Skeletal Radiol*, 26: 629–632, 1997.
  - 12) Verstraete KL, Vanzieleghem B, De Deene Y, *et al.* Static, dynamic and first-pass MR imaging of musculoskeletal lesions using gaddiamide injection. *Acta Radiol*, 36: 27–36, 1995.
  - 13) Braustein EM, White SJ. Non-Hodgkin's lymphoma of bone. *Radiology*, 135: 59–63, 1980.
  - 14) Milos JJ, Daniel FH, William DK. Healing flare in skeletal metastases from breast cancer. *Radiology*, 192: 201–204, 1994.
  - 15) 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*, 21: 689–694, 1996.