Evaluation of the effect of preoperative chemotherapy in bone sarcomas

^{99m}Tc-HMDP scintigraphy in 34 cases

Yutaka Kobayashi[1], Toshifumi Ozaki[1], Yoshihiro Takeda[2], Akira Kawai[1] and Hajime Inoue[1]

We quantitatively analyzed images of ^{99m}Tc-HMDP bone scintigraphy in 34 bone sarcomas before and after preoperative chemotherapy. The isotopic uptake was calculated as tumor-to-background ratio (TBR), and the changes in TBR before and after chemotherapy were calculated as the alteration ratio. The histological effect of preoperative chemotherapy was classified in 4 grades, according to Huvos. We defined good scintigraphic responders as cases having decreased uptake after chemotherapy, with an alteration ratio ≥ 60%.

There was a positive correlation (Rho = 0.76, $p < 0.001$) between the histological effect and the alteration ratio. Of the 17 good histological responders, 13 showed a good scintigraphic response. The average alteration ratio in 17 cases with good response (68%) was higher than that in 17 cases showing poor response (–9.9%) ($p < 0.001$). 3 patients with pathologic fractures and 1 with primarily normal uptake showed false negative findings. The sensitivity of this method was 100% and the specificity was 81%.

Departments of [1]Orthopaedic Surgery and [2]Radiology, Okayama University Medical School, Okayama 700, Japan
Tel +81 86-235 7273 Fax -223 9727. Correspondence: Dr. Toshifumi Ozaki
Submitted 98-02-20. Accepted 98-06-09

Radionuclide bone scintigraphy with technetium-99m (^{99m}Tc) methylene diphosphonate (MDP) is very sensitive for the detection of primary and metastatic lesions of bone (Enneking et al. 1980, Menendez et al. 1993). However, its value for assessing the effect of preoperative chemotherapy remains unknown. In addition, no method of quantitative analysis that can predict tumor necrosis prior to surgery has yet been established. We performed ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) bone scintigraphy in patients with malignant bone tumors before and after preoperative chemotherapy, in order to evaluate the effects of chemotherapy. The images were analyzed quantitatively and compared with the histologic effects of treatment.

Patients and methods

34 patients with malignant bone tumor, diagnosed between 1985 and 1997, were studied with ^{99m}Tc-HMDP bone scintigraphy before and after preoperative chemotherapy (Table 1). The study group consisted of 12 women and 22 men with a median age of 16 (4–66) years. The diagnoses were osteosarcoma in 25 patients, Ewing's sarcoma in 6, and malignant fibrous histiocytoma (MFH) in 3. 17 tumors were in the femur, 10 in the tibia, 2 in the ilium, 1 in the fibula, 1 in the talus, 1 in the clavicle, 1 in the humerus, and 1 in the metacarpal bone. All patients had stage IIB tumors (Enneking et al. 1980) and none of the patients had metastases at diagnosis. 4 patients with osteosarcoma had a pathological fracture before or during chemotherapy. After starting preoperative chemotherapy, all patients walked without weight bearing on the affected limb.

25 patients with osteosarcoma and 3 with MFH received chemotherapy consisting of doxorubicin (60 mg/m^2), cisplatin (120 mg/m^2), high-dose methotrexate (10–12 g/m^2) with or without ifosfamide (14 g/m^2). 6 patients with Ewing's sarcoma received doxorubicin (30 mg/m^2), cyclophosphamide (1200 mg/m^2), actinomycin D (0.5 mg/m^2), vincristine (1.5 mg/m^2), and methotrexate (30 mg/m^2). All drugs were administered intravenously. 1 of the 6 patients with Ewing's sarcoma also underwent irradiation, 30 gray, of a hand tumor. After the preoperative chemotherapy, all patients were operated on.

Scintigraphy

740 MBq ^{99m}Tc-HMDP was administered intravenously, and images were obtained after 3 hours. Scin-

Table 1. Comparison of scintigraphic and histologc results after chemotherapy

No.	Age	Sex	Histologic diagnosis	Tumor site	Tumor necrosis (%)	Histologic grade	Alteration ratio (%)	Abnormal uptake	Site	Other clinical findings
1	14	M	osteosarcoma	femur	0	I	-134	+	tibal shaft	
2	21	M	osteosarcoma	fibula	30	I	-72	–		
3	21	F	Ewing's sarcoma	clavicle	0	I	-62	–		
4	66	F	osteosarcoma	tibia	0	I	-50	–		
5	14	F	osteosarcoma	tibia	0	I	-42	+	talus	
6	24	F	osteosarcnma	femur	0	I	-18	–		
7	13	F	osteosarcoma	femur	0	I	-10	–		
8	15	M	osteosarcoma	tibia	0	I	-8	–		
9	57	M	MFH	femur	10	I	-7	–		
10	48	M	osteosarcoma	femur	0	I	5	–		
11	21	M	Ewing's sarcoma	ilium	0	I	7	–		
12	21	M	osteosarcoma	femur	40	I	20	–		
13	16	M	osteosarcoma	femur	0	I	30	–		
14	14	M	osteosarcoma	femur	20	I	31	+	distal tibia, talus	
15	17	F	osteosarcoma	tibia	85	II	40	–		
16	23	M	osteosarcoma	tibia	70	II	49	+	distal femur, distal tibia, talus	
17	16	F	osteosarcoma	femur	70	II	54	+	talus, distal tibia	
18	11	M	osteosarcoma	femur	90	III	20	–		
19	15	M	osteosarcoma	tibia	95	III	43	+	distal femur	
20	14	M	osteosarcoma	femur	95	III	44	+	distal tibia, talus	
21	17	M	osteosarcoma	femur	90	III	64	–		pf
22	16	M	osteosarcoma	tibia	98	III	75	+	talus, calcaneus	pf
23	11	F	osteosarcoma	femur	95	III	76	+	femur shaft	pf
24	10	F	osleosarcoma	femur	90	III	93	+	ilium	
25	28	M	MFH	tibia	95	III	94	–		
26	28	M	MFH	femur	95	III	96	–		
27	13	F	Ewing's sarcoma	metacarpal	100	IV	-30	–		
28	4	M	Ewing's sarcoma	tibia	100	IV	62	–		
29	10	M	Ewing's sarcoma	humerus	100	IV	65	–		
30	19	M	osteosarcoma	femur	100	IV	81	–		
31	9	M	osteosarcoma	tibia	100	IV	82	–		pf
32	25	M	osteosarcoma	ilium	100	IV	88	–		
33	11	F	osteosarcoma	femur	100	IV	92	+	distal tibia, talus	
34	10	F	Ewing's sarcoma	talus	100	IV	110	–		

MFH malignant fibrous histiocytoma, pf pathologcal fracture

tigraphic images were printed on film and then imported to a computer using an image scanner. Images before and after chemotherapy were analyzed with NIH IMAGE, an image analysis program (National Institute of Health, Bethesda, MD, USA) (Ma et al. 1997) as follows: 2 regions of interest (ROI) that were equal in size were placed on each image, the first ROI was placed on the tumor and the second one on the corresponding site on the contralateral side of the body to check the background. The position and size of the ROIs in each patient were kept identical before and after preoperative chemotherapy. For each ROI, the average density per pixel was calculated. The initial scintigraphy was done before treatment and the second was done at the end of preoperative treatment: at 3 months after the initiation of treatment and 3 weeks after the last administration of antitumor drugs.

The tumor-to-background ratio (TBR) was calculated by dividing the average density per pixel of the tumor (T) by that of the background (BG). Excluding background activity, the TBR was determined as follows: TBR = (T–BG)/BG. We compared the TBR before chemotherapy (TBR1) with that after chemotherapy (TBR2), and the change was defined as the alteration ratio: alteration ratio (%) = (TBR1–TBR2)/TBR1 × 100 (Ohtomo et al. 1996, Imbriaco et al. 1997). We defined a good scintigraphic response as an alteration ratio ≥ 60%, because this gave the fewest false positives and no false negatives.

To assess the effect of preoperative chemotherapy, the largest plane of longitudinal sections of the specimen was examined microscopically. We classified the histological response after preoperative chemotherapy in 4 grades, according to Huvos et al. (1977): grade I, necrosis < 50%; grade II, 50% ≤ necrosis < 90%; grade III, necrosis ≥ 90%; and grade IV, 100% necrosis. Grade III or IV was defined as a good response.

The relation between the histological effect and the alteration ratio on the bone scan was evaluated by the Spearman rank correlation test. Differences between proportions were evaluated by the chi-square test with

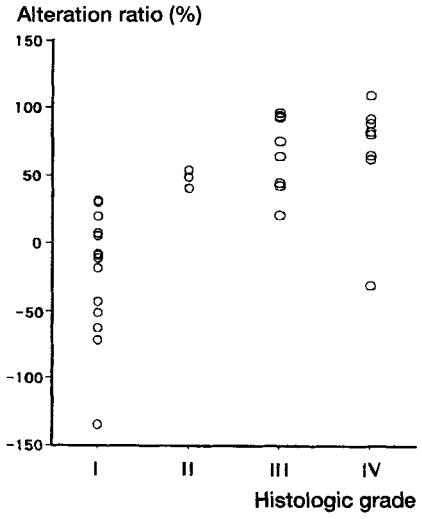


Figure 1. Alteration ratio and histologic grade. The histological grade and alteration ratio showed a significant correlation.

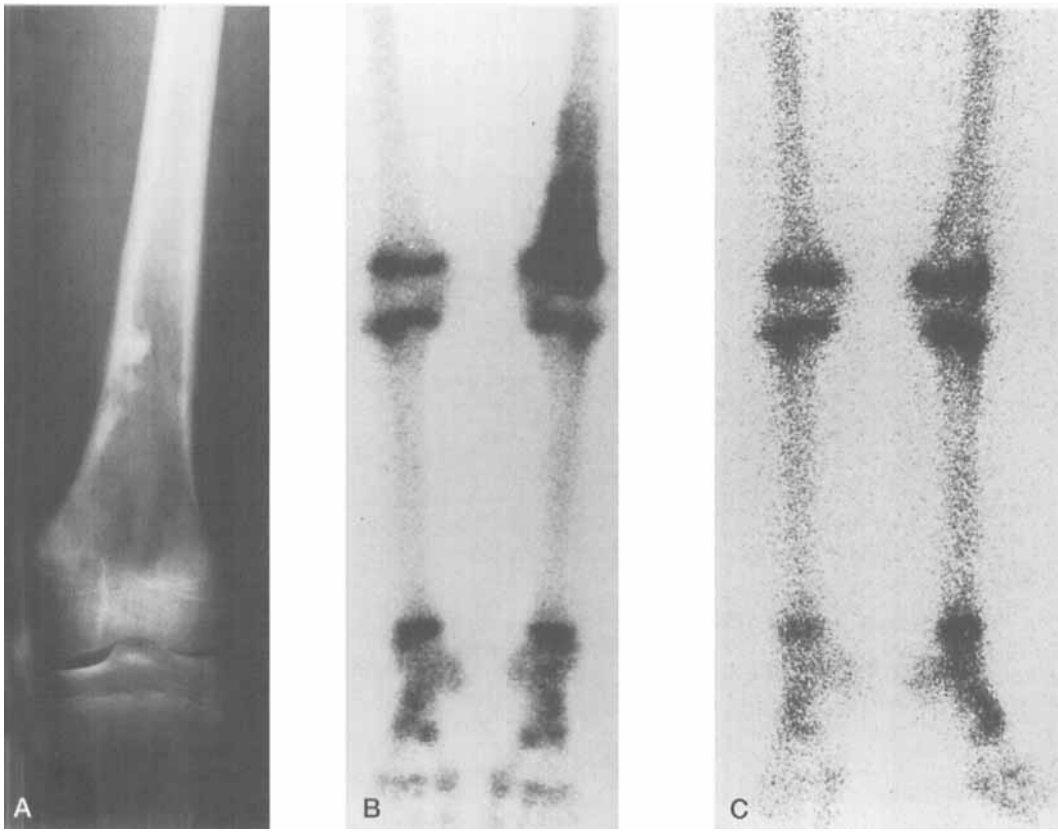
Fisher's correction. The differences in the mean rank between 2 continuous variables were evaluated by the Mann-Whitney U-test. A p-value of less than 0.05 was considered significant.

Results

There was no clear difference in isotope uptake between osteosarcoma, Ewing's sarcoma, and MFHs. There were no remarkable differences between the peripheral and central areas of the tumors before treatment; however, the difference became slightly clearer after chemotherapy.

10 of 34 patients were classified as grade I histologic response (average scintigraphic alteration ratio: –22% (SE 12)), 3 as grade II (average alteration ratio: 48% (SE 4.1)), 9 as grade III (average alteration ratio: 68% (SE 8.9)), and 8 as grade IV (average alteration

Figure 2. Case 33. An 11-year-old girl with osteosarcoma of the left distal femur.



A. Plain radiogram showing an osteoblastic area with periosteal reaction in the femur.
B. Bone scan before preoperative chemotherapy showed abnormal high uptake in the same region.
C. After preoperative chemotherapy, abnormally high uptake disappeared and it was at almost the same level as that on the opposite limb. Note that there was slight diffuse uptake in the left foot and distal growth plate of the distal tibia, but no abnormalities were detected on the plain radiograph.

ratio: 69% (SE 15)) (Table 1; Figure 1). There was a strong positive correlation (Rho = 0.76, $p < 0.001$) between the histological effect and the alteration ratio (Figure 1).

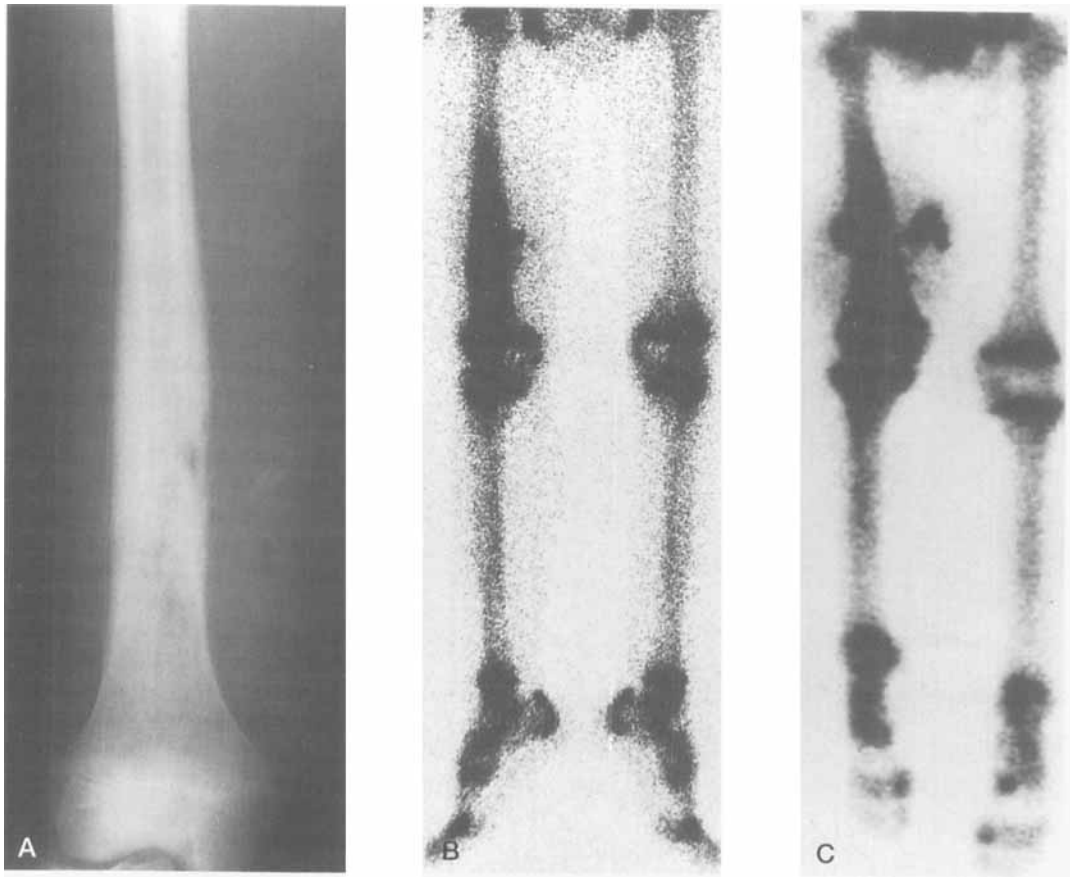
Among the 17 good histological responders, 13 cases showed a good scintigraphic response (alteration ratio ≥ 60%). The average alteration ratio in cases with a good histologic response (68%) was (Figure 2) higher than that in cases with poor response (–9.9%) ($p < 0.001$) (Figure 3). 4 patients with good chemotherapy response showed an alteration ratio < 60% (Table 2). 3 of these 4 patients had a pathologic fracture during preoperative chemotherapy. The fourth patient with a fracture did not show abnormally high uptake before preoperative chemotherapy, but uptake increased slightly after chemotherapy. The sensitivity as regards identification of a good chemotherapy response of this method was 76.5% and the specificity was 100%.

Table 2. Summary of results

Chemotherapy effect	Poor	Good
Group 1 (< 60%)	17	4
Group 2 (≥ 60%)	0	13

11 patients showed heterogeneous isotope uptake in the primary lesion before and/or after preoperative chemotherapy. 8 cases showed higher uptake in the region distal to the affected site (Figures 2 and 3), while 3 showed higher uptake proximal to the affected site (Table 1). MR imaging of these areas revealed no abnormalities.

Figure 3. Case 1. A 14-year-old boy with osteosarcoma of the right distal femur.



A. Plain radiogram showing osteosclerotic and osteolytic findings, with a small osteolytic area. Periosteal reaction was noted. Even after multidrug chemotherapy, the tumor showed evident malignant progression.
B. Bone scan before preoperative chemotherapy, with abnormally high uptake in the right femur.
C. Bone scan after preoperative chemotherapy. Abnormal uptake was increased. The alteration ratio was -134% (group 1). Histologic analysis showed that remnants of viable tumor were widespread in both the intra- and extramedullary tumor components. This patient was classified as a grade I response.

Discussion

For diagnosis, evaluation of treatment, and postoperative follow-up of patients with bone sarcoma, several imaging methods are used, such as conventional radiographs, CT (Wellings et al. 1994), MRI (Erlmann et al. 1989, Sanchez et al. 1990, Fletcher et al. 1992), angiography (Carrasco et al. 1989), scintigraphy with ^{201}Tl (Menendez et al. 1993, Rosen et al. 1993, Ohtomo et al. 1996, Imbriaco et al. 1997), or ^{99m}Tc-HMDP (Simon and Kirchner 1980, Sommer et al. 1987, Knop et al. 1990, Hicks 1997). MRI can clearly show the change in the tumor size and is useful for evaluating the extent of tumor, but this technique is of less value for estimating the effect of treatment (de Baere et al. 1992, Hanna et al. 1992, Holscher et al. 1992, Ozaki et al. 1992). Contrast-enhanced MRI can detect residual viable tumor after chemothrapy (van der Woude et al.1994, van der Woude et al. 1995). Angiography can assess tumor vascularity, but treatment effect cannot be quantified by vascularity (Carrasco et al. 1989).

Thallium-201 (^{201}Tl) is a potassium analogue that accumulates in tumor cells and its uptake reflects blood flow, capillary permeability, ATPase activity in the cell membrane, and the number of viable tumor cells. A few articles reported that the alteration ratio between before and after treatment correlated well with the histologic response of the osteosarcoma (Menendez et al. 1993, Ohtomo et al. 1996, Imbriaco et al. 1997). The mechanism of ^{99m}Tc-HMDP accumulation in bone imaging differs from that of ^{201}Tl scintigraphy.

Uptake in bone after intravenous administration of ^{99m}Tc-HMDP is based on both blood flow and ion exchange (a chemical rather than metabolic process), which occurs on the bone surface in contact with the circulating fluids (Genant et al. 1974, Siegel et al. 1976). Areas of increased uptake correspond to areas of accelerated bone turnover (Rosenthall and Lisbona 1982, Seeger et al. 1991).

In our study, we defined a good scintigraphic response as an alteration ratio ≥ 60%, because this cut-off minimized the number of false positive or negative cases. 4 patients had false negative findings on bone scan. In patients with pathological fracture or primary normal uptakes, the scintigraphic assessment of chemotherapy may not be suitable. When remodeling of bone becomes evident after preoperative chemotherapy, uptake will increase as a consequence of activating bone turnover. Therefore, we anticipated that the timing of the second scanning by ^{99m}Tc-HMDP may be important for precise evaluation of treatment effect, but in this study, the 4 false negative cases were related to other factors. A cut-off value of 60% is thought to be an appropriate alteration ratio for evaluating the effect of chemotherapy by ^{99m}Tc-HMDP bone scan.

The increase in ^{99m}Tc-HMDP uptakes observed in areas outside the tumor in the affected extremities was not always the result of tumor extension. This was most frequently observed around the ankle. Such an extended pattern of uptake has not been definitively elucidated (Thrall et al. 1975). One of the reasons may be related to increased blood flow on the affected side, produced by the tumor (Goldman and Braunstein 1975). In addition, increased blood flow caused by an inflammatory response and an increased turnover of bone, due to acute osteoporosis, may be related to each other (Thrall et al. 1975). If these findings are noted on bone scintigraphy, further MR study should be performed, to evaluate the possibility of tumor extension.

The authors thank I. Nagaya, Department of Nuclear Medicine, Okayama University Hospital, Okayama, Japan, for technical assistance and Dr.H. Yamamoto for statistical assistance. This stuyd was supported in part by a Grant-in-Aid for Cancer Research (No. 200) from the Japanese Ministry of Health and Welfare.

Carrasco C H, Charnsangavej C, Raymond A K, Richili W R, Wallace S, Chawla S P, Ayala A G, Murray J A, Benjamin R S. Osteosarcoma: angiographic assessment of response to preoperative chemotherapy. Radiology 1989; 170: 839-42.

de Baere T, Vanel D, Shapeero L G, Charpentier A, Terrier P, di Paola M. Osteosarcoma after chemotherapy: evaluation with contrast material-enhanced subtraction MR imaging. Radiology 1992; 185: 587-92.

Enneking W F, Spanier S, Goodmann M A. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980; 153: 106-20.

Erlmann R, Reiser M F, Peters P E, Vasallo P, Nommensen B, Kusnierz-Glaz C R, Ritter J, Rossener A. Musculoskeletal neoplasms: static and dynamic Gd-DTPA-enhanced MR imaging. Radiology 1989; 171: 767-73.

Fletcher B D, Hanna S L, Fairclough D L, Gronemeyer S A. Pediatric musculoskeletal tumors: use of dynamic, contrast-enhanced MR imaging to monitor response to chemotherapy. Radiology 1992; 184: 243-8.

Genant H K, Bautovich G J, Singh M, Lathrop K A, Harper P V. Bone-seeking radionuclides: An in vivo study of factors affecting skeletal uptake. Radiology 1974; 113: 373-82.

Goldman A B, Braunstein P. Augmented radioactivity on bone scans of limb-bearing osteosarcoma. J Nucl Med 1975; 16: 423-4.

Hanna S L, Parham D M, Fairclough D L, Meyer W H, Le A H, Fletcher B D. Assessment of osteosarcoma response to preoperative chemotherapy using dynamic FLASH gadolinium-DTPA-enhanced magnetic resonance mapping. Invest Radiol 1992; 27: 367-73.

Hicks R J. Nuclear medicine techniques provide unique physiologic characterization of suspected and known soft tissue and bone sarcomas. Acta Orthop Scand 1997; 68: 25-36.

Holscher H C, Bloem J L, Vanel D, Hermans J, Nooy M A, Taminiau A H M. Osteosarcoma: chemotherapy-induced changes at MR imaging. Radiology 1992; 182: 839-44.

Huvos A G, Rosen G, Marcove R C. Primary osteogenic sarcoma. Arch Pathol Lab Med 1977; 101: 14-8.

Imbriaco M, Yhe S D, Yeung H, Zhang J J, Healey J H, Meyers P, Huvos A G, Larson S M. Thallium-201 scintigraphy for the evaluation of tumor response to preoperative chemotherapy in patients with osteosarcoma. Cancer 1997; 80 (8): 1507-12.

Knop J, Delling G, Heise U, Winkler K. Scintigraphic evaluation of tumor regression during preoperative chemotherapy of osteosarcoma. Correlation of 99mTc-methylene diphosphonate parametric imaging with surgical histopathology. Skeletal Radiol 1990; 19: 165-72.

Ma L D, Frassica F J, McCarthy E F, Blumke D A, Zerhouni E A. Benign and malignant musculoskeletal masses: MR imaging differentiation with rim-to-center differential enhancement ratios. Radiology 1997; 202: 739-44.

Menendez L R, Fideler B M, Mirra J. Thallium-201 scanning for the evaluation of osteosarcoma and soft-tissue sarcoma. J Bone Joint Surg (Am) 1993; 75: 526-31.

Ohtomo K, Terui S, Yokoyama R, Abe H, Terauchi T, Mazda G, Beppu Y, Fukuma H. Thallium-201 scintigraphy to assess effect of chemotherapy in osteosarcoma. J Nucl Med 1996; 37: 1444-8.

Ozaki T, Inoue H, Taguchi K, Sugihara S. Gadolinium-DTPA enhanced magnetic resonance imaging of bone and soft tissue sarcomas in comparison with pathological findings. Acta Med Okayama 1992; 46: 471-7.

Rosen G, Loren G J, Brien E W, Ramana L, Waxman A, Lowenbraun S, Eckardt J J, Eilber F, Menendez L, Mirra J M. Serial thallium-201 scintigraphy in osteosarcoma. Clin Orthop 1993; 293: 302-6.

Rosenthall L, Lisbona R. Radionuclide bone and joint imaging. In: Radiology of bone tumors and allied disorders (Ed. Wilner D). W. B. Saunders Co., Philadelphia 1982; 4: 4162-3.

Sanchez R B, Quinn S F, Walling A, Estrada J, Greenberg H. Musculoskeletal neoplasms after intraarterial chemotherapy: correlation of MR images with pathologic specimens. Radiology 1990; 174: 237-40.

Seeger L L, Gold R H, Chandnani V P. Diagnostic imaging of osteosarcoma. Clin Orthop 1991; 270: 254-63.

Siegel B A, Donovan R L, Alderson P O, Mack G R. Skeletal uptake of 99mTc-diphosphonate in relation to local bone blood flow. Radiology 1976; 120: 121-3.

Simon M A, Kirchner P T. Scintigraphic evaluation of primary bone tumors. J Bone Joint Surg (Am) 1980; 62: 758-64.

Sommer H J, Knop J, Heise U, Winkler K, Delling G. Histomorphometric changes of osteosarcoma after chemotherapy. Correlation with 99mTc methylene diphosphonate functional imaging. Cancer 1987; 59: 252-8.

Thrall J H, Geslien G E, Corcoron R J, Johnson M C. Abnormal radionuclide deposition patterns adjacent to focal skeletal lesions. Radiology 1975; 115: 659-63.

van der Woude H-J, Bloem J L, Schipper J, Hermans J, van Eck-Smit B L F, van Oostayen J, Nooy M A, Taminiau A H M, Holscher H C, Hogendroon P C W. Changes in tumor perfusion induced by chemotherapy in bone sarcomas: color Doppler flow imaging compared with contrast-enhanced MR imagings and three-phase bone scintigrphy. Radiology 1994; 191: 421-31.

van der Woude H-J, Bloem J L, Verstraete K L, Taminiau A H M, Nooy M A, Hogendroon P C W. Osteosarcoma and Ewing's sarcoma after neoadjuvant chemotherapy: value of dynamic MR imaging in detecting viable tumor before surgery. AJR 1995; 165: 593-8.

Wellings R M, Davies A M, Pynsent P B, Carter S R, Grimer R J. The value of computed tomographic measurements in osteosarcoma as a predictor of response to adjuvant chemotherapy. Clin Radiol 1994; 49: 19-23.