Dynamic bone scintigraphy for evaluation of tumor response after preoperative chemotherapy

A retrospective study of osteosarcoma and Ewing's sarcoma patients

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Dynamic bone scintigraphy with 2–second scintigrams for 6 minutes after the injection of Tc–99m–MDP, may be regarded as a kind of angiography. We investigated the vascularity and early uptake of MDP in 39 osteosarcoma and 12 Ewing sarcoma patients before and after preoperative chemotherapy, and compared them to the histological tumor response. Early appearance of activity in the feeding arteries and rapid clearance from the arterial to the venous side give a distinct early activity peak on histograms over the tumor region. We calculated a tumor–to–nontumor (t) ratio at 6 minutes after the injection. In osteosarcoma patients, a persistent peak or a Tratio decrease of less than 40%, without disappearance of the peak, identified 23 of the 24 poor responders. Peak disappearance occurred in 14 of the 15 good responders. In Ewing's sarcoma peak disappearance and a t-ratio decrease of more than 60% identified the good responders.

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In primary bone sarcoma, the histologic response of the resected tumor to preoperative chemotherapy is a strong prognostic variable (Rosen et al. 1983, Saeter et al. 1991). Modifications of postoperative chemotherapy in patients whose primary tumors showed a poor histological response have not resulted in the same survival rate as in good responders (Winkler et al. 1988). Early identification of poor responders and the possibility of changing chemotherapy preoperatively are important.

Angiography before and after preoperative chemotherapy has confirmed that bone sarcomas are usually very vascular and that rapid disappearance of tumor vessels is associated with a favorable response to chemotherapy, while persistent pathologic vascularity indicates a poor response. Thus, Carrasco et al. (1989) have reported that failure to show a reduction in tumor vascularity after two courses of chemotherapy preoperatively identified 91% of the poor responders, and after 4 courses only 50%. Dynamic bone scintigraphy with 2–second scintigrams for 6 minutes after the injection of Tc–99m–methylene diphosphonate (MDP) may be regarded as a type of angiography. The vascularity of the tumor and appearance of activity in the feeding arteries can be evaluated and compared to the opposite normal side, and a tumor to non–tumor ratio can be calculated. We performed this retrospective study to compare the results of the early vascular phase in bone scans before and after preoperative chemotherapy with the histopathological grading of tumor response in the resected primary tumor.

Patients and methods

39 osteosarcoma patients underwent a had dynamic scintigraphic examination before the initial biopsy and preoperatively after chemotherapy according to one of three consecutive

Scandinavian (SSG) protocols (Table 1). The patient population represents all patients who had had two dynamic bone scans in our institution.

12 patients with Ewing's sarcoma were evaluable, 2 patients with rib tumors had no increase in activity above the background in the dynamic studies and were not evaluable.

After intravenous injection of 7–10 MBq Tc–99m–MDP per kilo body weight, 200 scintigrams were obtained during the first 400 seconds (Gamma camera equipment from ADAC and Siemens). Regions of interest were drawn around the tumor and a reference area, usually the opposite normal limb, and time/activity curves for the regions were recorded. The tumor to nontumor (t) ratio was calculated by dividing the counts measured at 6 minutes in the tumor region by

Table 1. Response to preoperative chemotherapy in osteosarcoma as measured by dynamic bone scintigraphy and by histological evaluation of the resected tumor specimen

Treatment protocol	Age	Sex	Local. of tumor	Peak dis–appearance	t-ratio %decrease or increase	Histopat. Grade [a]
ISGI	19	M	femur	yes	–55	III
	17	F	femur	yes	–62	III
	13	M	femur	yes	–35	III
	18	M	humerus	yes	–57	II
	16	M	femur	no	–18	I
	51	F	femur	yes	+90	I
SSG VIII	17	M	femur	yes	–65	IV
	6	F	femur	yes	–43	III
	18	F	femur	yes	–48	III
	12	F	femur	yes	0	III
	21	F	femur	yes	–39	III
	18	F	tibia	yes	–66	III
	13	F	femur	yes	–39	III
	16	F	tibia	yes	–33	III
	18	M	tibia	yes	–2	II
	18	F	femur	yes	–22	II
	16	F	tibia	no	–7	II
	19	M	femur	no	–39	II
	16	F	tibia	no	+10	II
	17	F	humerus	no	+73	II
SSG II	20	M	humerus	no	+49	III
	19	M	tibia	yes	–59	III
	14	F	tibia	yes	–45	III
	20	M	humerus	yes	–30	III
	11	F	tibia	no	–23	II
	15	F	femur	no	+43	II
	19	M	femur	no	+103	II
	12	F	femur	yes	–19	II
	14	F	tibia	no	+11	II
	15	M	femur	yes	+16	II
	16	M	tibia	no	+18	II
	19	M	femur	yes	–12	I
	17	M	tibia	yes	+88	I
	27	M	femur	no	+27	I
	12	M	femur	no	+92	I
	19	M	humerus	no	+55	I
	23	M	femur	no	+7	I
	17	M	femur	yes	+20	I
	17	M	femur	no	+44	I

[a] Histopat. response according to Huvos.

the counts measured in the reference region. Three criteria were evaluated: 1) the earliest phase, whether or not an initial peak occurred, which was usually the case preoperatively, especially in patients with osteosarcoma, 2) the slope of the curve, and 3) the t-ratio.

The histopathologic grading of the resected tumor was performed according to the guidelines of Huvos (5): Grade IV—no histologic evidence of remaining viable tumor cells; Grade III—predominant areas of acellular osteoid tumor, necrotic and/or fibrotic material attributable to the effects of chemotherapy, with only scattered foci of histologically viable tumor cells; Grade II—areas of acellular tumor osteoid, necrotic and/or fibrotic material attributable to the effects of chemotherapy, with other areas of histologically viable tumor; Grade I—little if any identified effects. Grades IV and III are classified as good responders, whereas grades II and I are poor responders.

Results

All patients with osteosarcoma showed increased activity in the feeding arteries to the tumor resulting in an initial peak (Figure 1 and Table 1). All good responders except one, a 20-year-old man, showed disappearance of the peak after preoperative chemotherapy. In this man the peak remained and the t-ratio increased by 49% despite a good histopathologic response. He relapsed with lung metastases 19 months after the primary diagnosis and died 10 years later. In another patient with a good histopathologic response (12-year-old girl), a pathologic fracture occurred during the preoperative chemotherapy. The peak disappeared, but no change in the t-ratio was seen, probably because of bone repair. Five other good responders showed a reduction in the t-ratio of less than 40%, but with a peak disappearance.

Of the poor responders, 15 of 24 patients had a persistent peak, 23 a reduction in the t-ratio below 40% and 14 patients an increase in the t-ratio. Sensitivity and specificity for the peak disappearance and t-ratio are listed in Table 3 for the osteosarcoma patients.

In Ewing's sarcoma, all patients who were considered as good responders histologically showed a disappearance of the initial activity peak and the t-ratio decreased by more than 60%. Patients with a good response, grade IV, may have a normalization of blood flow (Figure 2). Of the 8 poor responders, 4 had an initial peak before chemotherapy and the peak disappeared in only 1 of these. The poor responders showed a reduction in the t-ratio of less than 60%. Evaluation of the slope gave no further information compared with the t-ratio.

Discussion

In 14 of 15 patients with osteosarcoma, receiving preoperative chemotherapy, a good vascular scintigraph-

Table 2. Evaluation of treatment response in Ewing sarcoma. Changes from the first to the second preoperative investigation and compared to the histopathologic response of the resected specimen.

Age	Sex	Local. of tumor	Peak dis–appearance	t-ratio %decrease	Histopat. Grade
21	F	fibula	yes	–63	IV
14	F	humerus	yes	–65	IV
25	F	humerus	yes	–77	IV
10	M	tibia	yes	–64	III
36	M	tibia	no peak	–57	II
15	M	pelvis	no peak	–43	II
14	M	head	no	–40	II
23	F	femur	no	–5	II
18	M	humerus	no peak	–15	I
39	M	femur	no	–24	I
22	F	ulna	yes	–48	I
13	M	pelvis	no peak	–35	I

Table 3. Sensitivity and specificity of dynamic bone scintigraphy for prediction of tumor response in osteosarcoma

	Sensitivity (%)	Specificity (%)
Good response		
Peak disappearance	93	63
Tdecrease > 40%	53	96
Poor response		
Persisting peak	63	96
Tdecrease < 40%	96	47
Persisting peak, or Tdecrease < 40% without peak disappearance	96	93

ic response, as measured by disappearance of the peak, was associated with a favorable histologic response and, in 8 of these 14, the t-ratio decreased by more than 40%. One of the histologically good responders was judged to be poor responder scintigraphically. He relapsed after 19 months with lung metastases and died 10 years later. A persistent peak reflects the presence of tumor vessels and rapid clearance from the arterial to the venous side. A persistent peak or a reduction in the t-ratio of less than 40% or even an increase without peak disappearance occurred in 23 of 24 patients with a poor histological response. The patient who showed a good response scintigraphically and a poor histological response had a tumor with large areas of chondroblastic differentiation. The central part of the tumor did not show uptake of Tc–99m–MDP or increased blood flow. This remained unchanged the two investigations. The reductions in blood flow and t-ratio occurred in the peripheral part of the tumor. Our results agree with those previously found by angiography after two courses of chemotherapy (Carrasco et al. 1989). Using dynamic bone scintigraphy a persistent peak indicates poor responders with a sensitivity of 63%, but with a specificity of 96%. For the decreased t-ratio (<40%) the sensitivity is 96% and the specificity 47%. Our results for the poor responders are not so good as those seen with dynamic MR (Erleman et al. 1990), where a slope reduction of less than 60% showed a sensitivity of 80% and a specificity of 91%, 63% and 100%, respectively, for a slope reduction <40%. MR is superior to bone scintigraphy in spatial resolution and for detection of areas with viable tumor cells. However, dynamic MR is time–consuming and expensive, while dynamic bone scintigraphy is easily performed in routine work.

Bone scintigraphy before and after preoperative chemotherapy, comparing the regional tumor blood pool, and regional Tc–99m–MDP clearance during the first hour after injection is an excellent method for evaluating histological tumor response (Knop et al. 1990). A reduction in the tumor blood pool of more than 20% showed a sensitivity of 94% and a specificity of 80% for detection of tumor regression and, halfway during preoperative chemotherapy of 100% and 80%, respectively. For the Tc–99m–MDP clearance from the tumor preoperatively the sensitivity was 94% and specificity 100%, while at the halfway stage specificity and sensitivity was 100%. One disadvantage of this method is that 7 blood samples must be taken during the one–hour gamma camera acquisition. Color Doppler ultrasonography (CDUS) is the only non–invasive method that can simultaneously assess blood flow, velocity and flow direction. However, it is an accurate tool for monitoring chemotherapy only if a soft tissue mass is present with the bone (van det Woude et al 1988, 1994).

With Thallium–201 scintigraphy, the uptake of thallium is correlated to the blood flow in the tumor and it can predict a good histologic response and prognosis (Rosen et al. 1993). Serial thallium scintigraphy can identify poor responses within two weeks after initiation of treatment. Thallium is cyclotron–produced and not readily available in the nuclear medicine departments.

Technetium–labeled radiopharmaceuticals (MIBI and Tetrofosmin), used for cardiac perfusion, like thallium, have been assessed to evaluate the preoperative response to chemotherapy. The variations were too large to permit conclusions in individual patients, but a correlation was found between the reduction in the radiopharmaceutical uptake and the histological response in the entire series (Söderlund et al. 1997).

In patients with Ewing's sarcoma, the disappearance of a peak and a t-ratio of more than 60% were

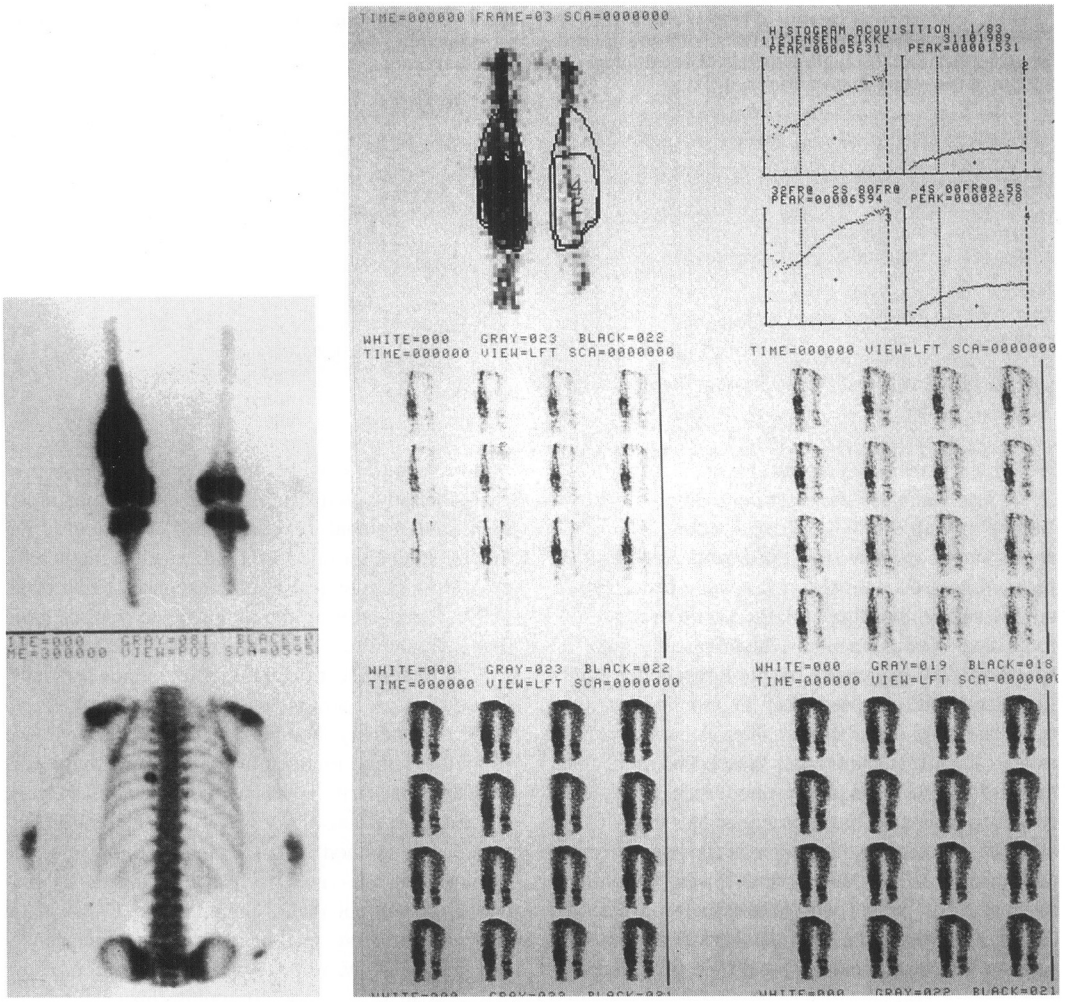

Figure 1. a. Bone scintigraphy in a 6-year-old girl with osteosarcoma in the distal end of the right femur and a metastatic lesion in the 7th left rib.

b. Dynamic scintigrams with two second scans starting at the lower row from left to right. Asymmetric activity appearance and visualization of the tumor activity before activity is seen on the normal side, resulting in a peak on the time/activity curves.

associated with a good response. Normalization of the t-ratio to 1 or less indicated a good histological response. 4 of the 8 poor responders showed no peak and the vascularization was usually less distinctive than in patients with osteogenic sarcoma. A reduction in the t-ratio of less than 60% indicated a poor response to preoperative chemotherapy.

Conclusions

Dynamic bone scintigraphy is useful in the evaluation of tumor response to preoperative chemotherapy in sarcoma patients. In osteosarcoma patients, poor responders can be identified by a sensitivity of 96% and specificity of 93% regarding a persistent activity peak or a reduction in the t-ratio of less than 40% without peak disappearance. In Ewing's sarcoma, good responders show a peak disappearance and a reduction in the t-ratio of more than 60%.

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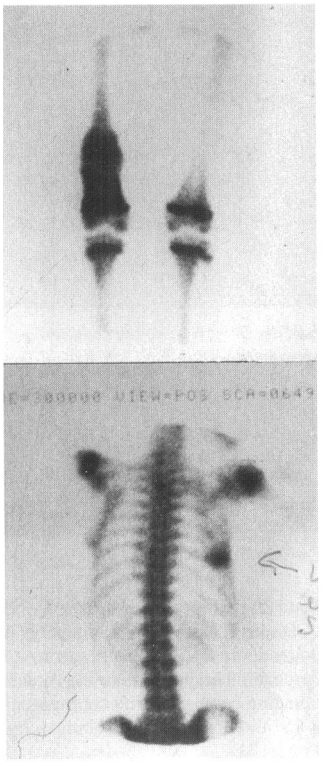
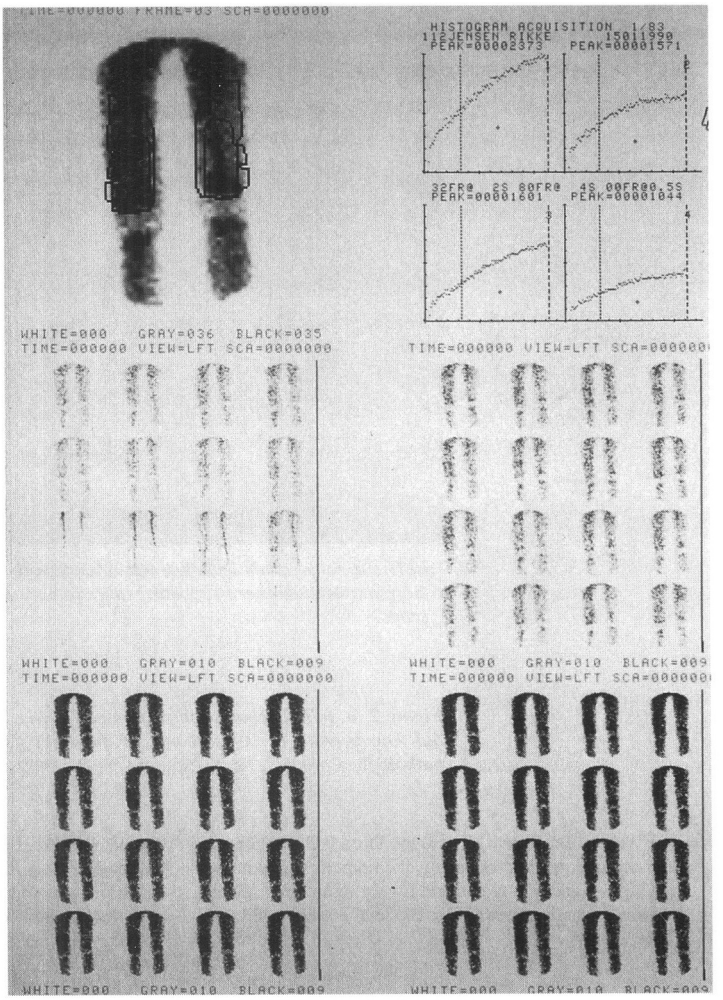


c. After preoperative chemotherapy the metastatic lesion can barely be seen and the tumor activity has decreased.



d. On the dynamic study peak has disappeared and the curve is not so steep compared to the normal side and the first investigation resulting in a decreased t-ratio by 43%, findings typical for a good response.

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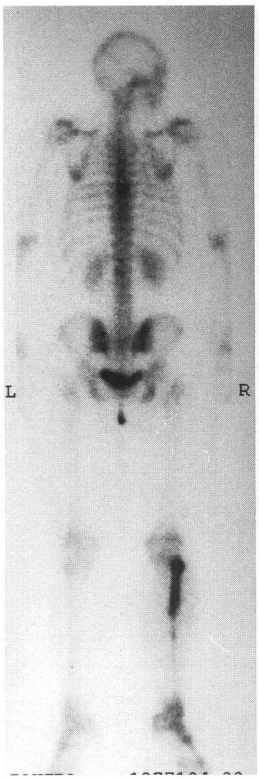

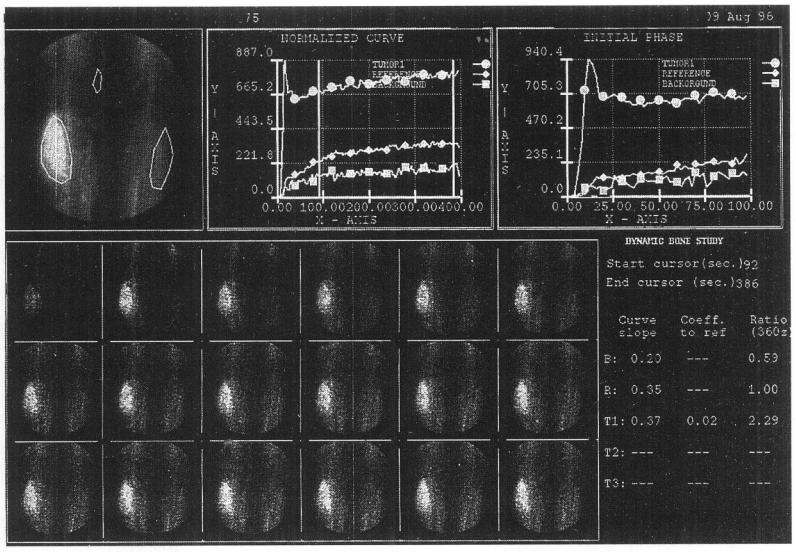

b. The dynamic study demonstrates an unusually high peak, however the curve is not so steep as it usually is seen in osteogenic sarcoma. Each box with scintigrams consists of 10 scans.

Figure 2. a. Initial scintigraphic examination in a 21-year-old woman with Ewing sarcoma in the right fibula and pathological processes in the spines.

van der Woude H J, Bloem J L, Hogendoorn P C W. Preoperative evaluation and monitoring chemotherapy in patients with high–grade osteogenic and Ewing's sarcoma: review of current imaging modalities. Skeletal Radiol 1988; 27: 57–71.

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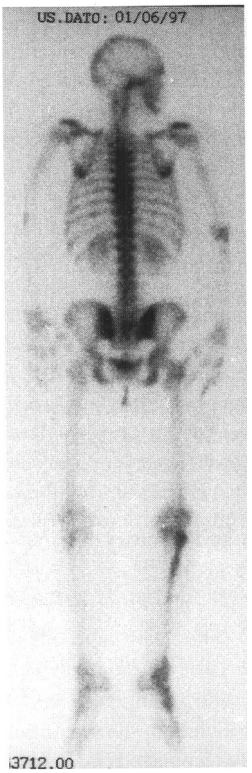

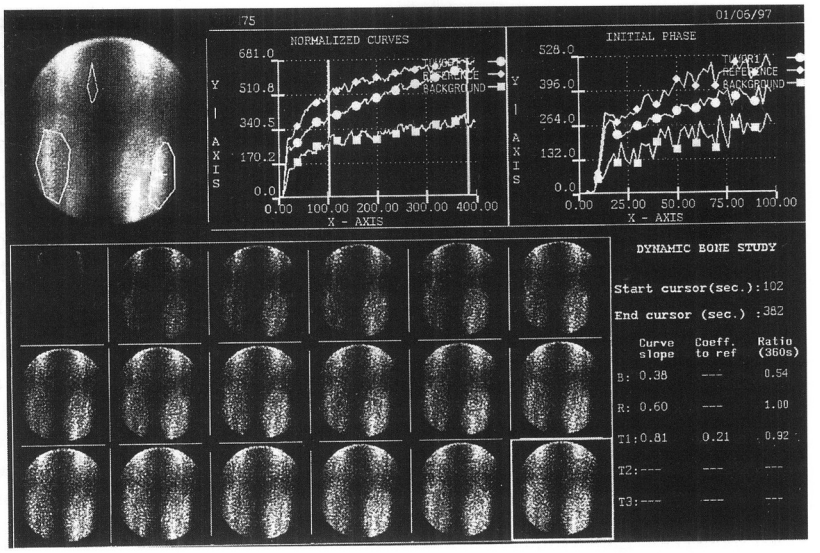

d. The activity on the tumor side is lower than on the normal reference side. The peak has disappeared and the blood flow is normalized. The findings are typical for good response.

c. Still, but lower uptake in fibula on bone scan.

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