J Orthop Sci (2002) 7:304–312

Journal of
Orthopaedic Science

Clinical significance of thallium-201 scintigraphy in bone and soft tissue tumors

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Abstract We evaluated sequential thallium scans on both early images (EI) and delayed images (DI) for 62 patients who had bone and soft tissue lesions. The purpose was to determine whether this technique could be used to ascertain accurately whether lesions were malignant or benign and to predict the response to chemotherapy. The thallium-201 chloride (^{201}Tl) accumulation in malignant tumors and benign lesions was statistically different. Sensitivity, specificity, and accuracy for ^{201}Tl scans in detecting malignant tumors was 94%, 65%, and 82%, respectively, for EI, and 94%, 85%, and 90%, respectively, for DI. On multivariate analysis, significant independent factors for ^{201}Tl uptake were malignant lesions on EI and DI and high cellularity on EI. Thirteen patients with malignant bone and soft tissue tumors underwent ^{201}Tl scans before and after preoperative chemotherapy. There was a good correlation between percentage of tumor necrosis and percentage change of accumulation in lesion-to-normal tissue ration, and the correlation coefficient was higher on EI (r = 0.801) than on DI (r = 0.664). These results support the notion that ^{201}Tl scintigraphy, although showing some false-positive and false-negative findings, is a useful tool in the evaluation of either malignant tumors or benign lesions. Furthermore, ^{201}Tl scans on EI provide benefit concerning the evaluation of chemotherapeutic response in patients with malignant bone and soft tissue tumors.

Key words Thallium-201 · Malignant tumor · Chemotherapy

Introduction

Malignant bone and soft tissue tumors are relatively uncommon neoplasms. Most of them behave aggressively and rapidly progress in the absence of treatment. Delineation of the local extent of malignant tumors and their early detection are important for disease management.

Radionuclide scanning with technetium-99m methylene diphosphonate (^{99m}Tc-MDP) and gallium-67 (^{67}Ga) were previously used in the detection or management of bone and soft tissue tumors.[6,9,10] However, detection was hard to achieve, and false-negative scans did occur.[1,3,6,9,10,13,18] Because thallium-201 chloride (^{201}Tl) has an affinity for a variety of neoplasms, there has been growing interest in using ^{201}Tl for management of bone and soft tissue tumors since the early 1990s.[1–3,5,7,8,11,14–18] Terui et al.[18] showed that the sensitivity of detection with ^{201}Tl was higher than that with ^{67}Ga. Ramanna et al.[13] reported that ^{201}Tl scintigraphy was superior to ^{67}Ga and ^{99m}Tc-MDP scans in assessing the response of bone sarcomas to preoperative chemotherapy. However, this opinion was not long accepted because a series of studies then showed that ^{201}Tl scintigraphy alone is not helpful in differentiating malignant tumors from benign lesions.[1,3,14,16]

With these considerations in mind, we investigated the performance of ^{201}Tl scintigraphy for differentiating between malignant and benign lesions and for assessing the effectiveness of preoperative chemotherapy.

Materials and methods

Patient characteristics

A total of 62 patients (38 males and 24 females, aged 1–82 years) with various bone and soft tissue abnormalities were studied. There were 26 bone lesions (12 malignant tumors, 4 benign tumors, and 10 osteomyelitic lesions) and 36 soft tissue lesions (24 malignant tumors, 9 benign tumors, and 3 granulomatous lesions). Low-grade soft tissue sarcomas [American Joint Committee on Cancer (AJCC) G1/G2] were found in 8 patients (35%) and high-grade sarcomas (AJCC

Offprint requests to: Y. Goto
Received: September 21, 2001 / Accepted: January 11, 2002

G3/G4) were found in 15 patients (65%).[4] All lesions ranged from 1 to 24 cm in diameter, with a median size of 9 cm. Lesions size was <5 cm in 11 patients (18%) and ≤5 cm in 51 patients (82%). Lesions were located on an extremity in 42 patients (68%) and the trunk in 20 patients (32%). A total of 46 patients (74%) had high cellularity, and 16 (26%) had low cellularity. Preoperative chemotherapy was undergone by 8 patients with malignant bone tumors (5 with osteosarcoma, 1 malignant fibrous histiocytoma, 1 primitive neuroectodermal tumor, and 1 multiple myeloma) and 5 patients with malignant soft tissue tumors (2 with synovial sarcoma, 1 malignant fibrous histiocytoma, 1 leiomyosarcoma, and 1 alveolar soft part sarcoma). These patients were evaluated both before and after chemotherapy. The preoperative chemotherapy was multidrug combination therapy: doxorubicin (60–90 m/gm^2) and ifosfamide (12–16 mg/m^2) with or without high-dose methotrexate (8–12 g/m^2) and cisplatin (120 mg/m^2). All drugs were administered intravenously.

Thallium scintigraphy

Radioisotope imaging sequences included whole-body scans and static scans of selected regions of interest (ROI) starting 5 min (early) and 2–3 h (delayed) after intravenous administration. Both early and delayed scintigraphic images were taken of all patients. The ^{201}Tl dose was 0.185 MBq/kg for a maximum dose of 111 MBq and a minimum dose of 50 MBq. A scanning Anger camera (GCA901A/W2; Toshiba, Tokyo, Japan) at a speed of 20 cm/min was used for imaging. A large field-of-view rectilinear camera with a 3/8-in. sodium iodine crystal was used to obtain static views. Low-energy high-resolution collimators (Lehr model RDC-901HA; Toshiba, Tokyo, Japan) were used.

Image analysis

The amount of ^{201}Tl uptake in the lesions was visually graded on a scale of 0 to 4 as defined by Menendez et al.[11] Two observers (Y.G. and R.O.) without previous knowledge of the patient's outcome independently evaluated the extent of ^{201}Tl uptake in each lesion. A grade of 0 indicated background activity; a grade of 1, equivocal activity; a grade of 2, definite activity but less than that of myocardium; a grade of 3, definite activity equal to that of myocardium; and a grade of 4, activity greater than that of myocardium. Uptake was considered positive if the scintigram demonstrated grade 2 or more on visual inspection and negative if the scintigram demonstrated grade 1 or less. The diagnostic sensitivity, specificity, and accuracy were calculated based on the grades obtained from visually assessing early and delayed images of all 62 patients. For quantitative evaluation, image data from the spot images were stored in the computer (GMS550U; Toshiba). On each image, one ROI was placed inside the outer border of the lesion and a second ROI of equal size was placed contralateral or adjacent to the lesion in a normal area. For each ROI, the average counts per pixel were calculated by the computer. The average counts in the ROI of the lesion divided by that from the contralateral or adjacent normal tissue area yielded a lesion-to-normal tissue (L/N) ratio. L/N ratio was obtained for both early and delayed images. Retention index (RI) was calculated using early and delayed ratio, as follows: RI (%) = (delayed ratio − early ratio)/early ratio × 100. We compared the prechemotherapy L/N ratio with the post-chemotherapy L/N ratio, and the percent change was defined as an alteration ratio, as follows: alteration ratio (%) = (prechemotherapy L/N ratio − postchemotherapy L/N ratio)/prechemotherapy L/N ratio × 100.

Histologic evaluation

The resected specimen was sliced coronally or axially to include the largest portion of the tumor. The slices were fixed in 10% neutral buffered formalin and embedded separately in paraffin. The sections were stained with hematoxylin and eosin and examined by an experienced pathologist (S.K.) who had no knowledge of the results of scintigraphic assessment. The lesions were investigated by macroscopic appearances and histological specimens. Cellularity was determined by the relations between the proportion of matrix component and of cellular component. Cellularity was considered high if the cellular component demonstrated 50% or more in the lesion and low if the matrix component demonstrated 50% or more.

Statistical analysis

The following baseline variables were considered for thallium uptake: histology (malignant or benign lesion), grade (high grade or low grade in soft tissue sarcomas), cellularity (high or low cellularity), size (≤5 cm or <5 cm), and site (extremity or trunk). Relationships between two variable quantities were analyzed by the Mann–Whitney *U* test. To establish a hierarchy among the variables of most important value, multivariate analysis using a logistic regression model was performed. A two-tailed P value <0.05 was considered significant.

The percentage of tumor necrosis was correlated with the percentage alteration ratio using Spearman's rank correlation. Statistical analyses were performed by

using Stat View 4.5 statistical software (Abacus Concepts, Berkeley, CA, USA).

Results

^{201}Tl accumulation in bone lesions

^{201}Tl uptake was observed in all 12 (100%) malignant bone tumors (MBT) on early and delayed images (Table 1). However, it was also observed in 7 of the 14 (50%) benign bone lesions (BBL) on early images (EI) and 4 of the 14 (29%) BBL on delayed images (DI). ^{201}Tl has been shown to have an affinity for osteomyelitis lesions; it was found in 6 of the 10 (60%) on EI and 3 of the 10 (30%) on DI. The median grade of visual uptake was 4 on EI and DI in MBT, whereas it was 1.5 on EI and 1.0 on DI in BBL. The median L/N ratio was 4.8 on EI and 3.4 on DI in MBT, whereas it was 1.8 on EI and 1.3 on DI in BBL. There were significant differences between MBT and BBL on early and delayed images. The percentage of RI was not significantly different between MBT and BBL. False-positive cases occurred in some cases of osteomyelitis and aneurysmal bone cyst (Fig. 1).

^{201}Tl accumulation in the soft tissue lesions

^{201}Tl uptake was observed in 22 of the 24 (95%) malignant soft tissue tumors (MST) on EI and DI (Table 2; Fig. 2). Uptake was observed in only 2 of the 12 benign soft tissue lesions (BSL) on EI and in none of the 12 BSL on DI. The median grade of visual uptake was 2.0 on EI and DI in MST; it was 0 on EI and DI in BSL. The median L/N ratio was 2.3 on EI and 1.9 on DI

Table 1. Summary of clinical and scintigraphic data of 26 patients with untreated bone lesions

No./age/sex	Diagnosis	Site	Size (cm)	Grade of visual uptake		L/N ratio		Retention index (%)
				Early	Delay	Early	Delayed	
A. Malignant bone tumors								
1/14/F	Osteosarcoma	Femur	16	3	3	4.5	3.2	−28.9
2/12/M	Osteosarcoma	Femur	15	4	4	6.2	4.2	−32.3
3/20/M	Osteosarcoma	Tibia	6	4	3	6.0	2.6	−56.7
4/20/F	Osteosarcoma	Femur	20	4	4	4.7	5.3	12.8
5/53/M	Osteosarcoma	Tibia	10	4	4	6.2	3.5	−43.5
6/48/M	Multiple myeloma	Sternum	6	4	4	4.5	4.8	6.7
7/67/M	Multiple myeloma	Sacrum	11	3	3	5.3	2.1	−60.4
8/14/M	MFH	Tibia	7	4	3	7.7	3.1	−59.7
9/68/M	PNET	Ilium	10	3	4	4.8	5.2	8.3
10/72/F	Angiosarcoma	Fibula	2	4	4	3.4	2.9	−14.7
11/60/M	Metastatic carcinoma	Femur	5	4	4	4.4	3.5	−20.5
12/67/F	Metastatic carcinoma	Ilium	10	2	2	1.5	1.4	−6.7
Range				2–4	2–4	1.5–7.7	1.4–5.3	−60.4–12.8
Median				4.0*	4.0**	4.8^{+}	3.4^{++}	−24.7^{+++}
B. Benign bone lesions								
13/7/F	Desmoplastic fibroma	Humerus	8	0	0	1.2	0.8	−33.3
14/18/F	ABC	Tibia	5	2	2	2.7	2.1	−22.2
15/21/M	Solitary bone cyst	Femur	7	0	0	1.2	1.1	−8.3
16/40/M	Fibrous dysplasia	Rib	8	0	0	0.9	1.1	22.2
17/22/F	Osteomyelitis	Humerus	2	1	1	1.1	1.4	27.3
18/39/M	Osteomyelitis	Femur	20	0	0	1.1	0.9	−18.2
19/45/M	Osteomyelitis	Calcaneus	7	2	1	3.1	1.3	−58.1
20/53/M	Osteomyelitis	Humerus	10	3	1	2.7	1.4	−48.1
21/55/M	Osteomyelitis	Femur	5	0	0	1.2	1.1	−8.3
22/57/M	Osteomyelitis	Tibia	15	4	3	9.5	5.9	−37.9
23/57/M	Osteomyelitis	Tibia	12	2	2	2.3	2.6	13.0
24/66/M	Osteomyelitis	Femur	10	2	1	2.8	1.3	−53.6
25/75/M	Osteomyelitis	Tibia	16	3	2	5.0	2.6	−48.0
26/76/M	Osteomyelitis	Ilium	6	0	0	1.0	1.1	10.0
Range			6	0–4	0–3	0.9–9.5	0.8–5.9	−58.1–27.3
Median				1.5*	1.0*	1.8^{+}	1.3^{++}	−20.2^{+++}

M, male; F, female; L/N, lesion to normal ratio; PNET, primitive neuroectodermal tumor; MFH, malignant fibrous histiocytoma; ABC, aneurysmal bone cyst.
* $P = 0.0002$; ** $P < 0.0001$; $^{+}$ $P = 0.002$; $^{++}$ $P = 0.0009$; $^{+++}$ $P = 0.57$ (Mann–Whitney U test)

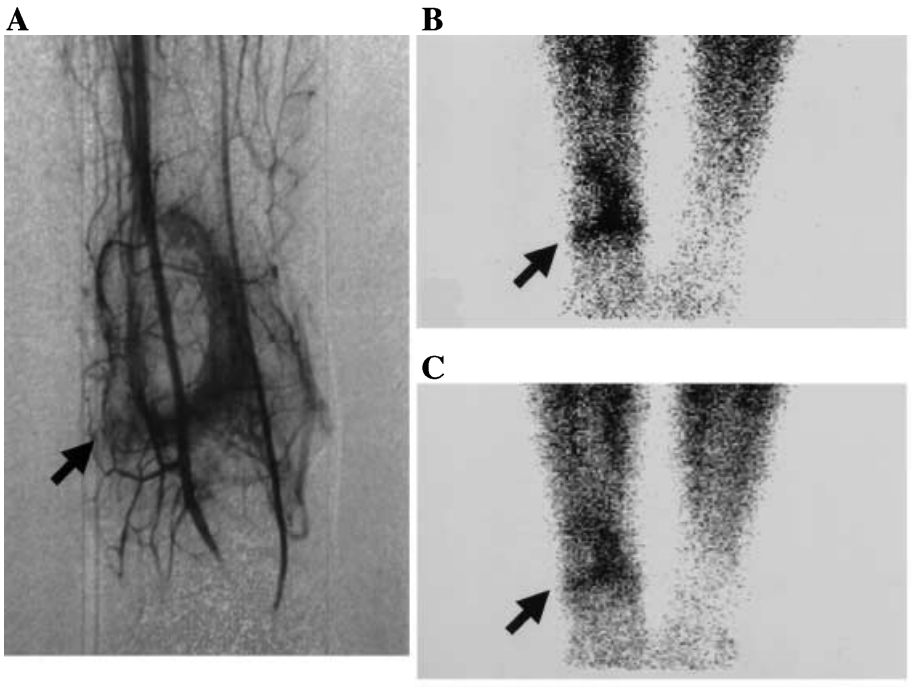

Fig. 1A–C. An 18-year-old woman (case 14, Table 1) with a history of aneurysmal bone cyst in the distal right tibia. Angiography demonstrates a hypervascular area in the inside of the outer border of the tumor (*arrow*) (**A**). ^{201}Tl scintigraphy reveals ringlike accumulation in the hypervascular area (*arrows*) (**B**, early image; **C**, delayed image)

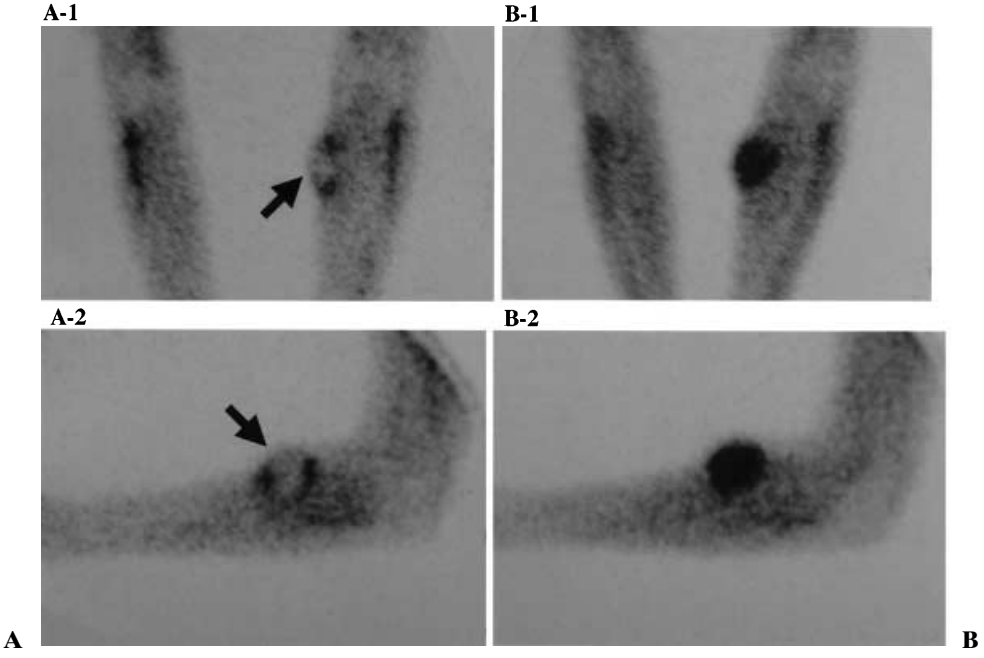

Fig. 2A,B. A 65-year-old woman (case 6, Table 2) with a history of malignant fibrous histiocytoma in the left proximal forearm. Early (*arrows*) (**A-1**, **A-2**) and delayed (**B-1**, **B-2**) images demonstrate increased ^{201}Tl accumulation

in MST, and 1.2 on EI and 1.1 on DI in BSL. There were significant differences between MST and BSL on early and delayed images. The median percentage of RI was not significantly different MST and BSL. False-positive cases included 1 neurofibroma and 1 granuloma on EI. False-negative cases included 1 myxoid malignant fibrous histiocytoma on EI, 1 myxoid liposarcoma on DI (Fig. 3), and 1 well-differentiated liposarcoma on EI and DI.

In the 23 cases of primary soft tissue sarcomas, the median L/N ratio of 15 high-grade sarcomas was 2.6 on EI and 2.2 on DI. However, an L/N ratio of 1.8 on EI and 1.5 on DI was observed in 8 low-grade sarcomas. The L/N ratio was significantly higher in high-grade sarcomas than low-grade sarcomas on early and delayed images (EI, $P = 0.009$; DI, $P = 0.01$). The RI was not significantly different between high-grade and low-grade sarcomas.

Table 2. Summary of clinical and scintigraphic data of 36 patients with untreated soft tissue lesions

No./age/sex	Diagnosis	Histological subtype	Grade	Site	Size (cm)	Grade of visual uptake		Ratio		Retention index (%)
						Early	Delay	Early	Delayed	
A. Malignant soft tissue tumors										
1/22/M	MFH	Ordinary	High	Axilla	12	2	2	2.8	2.0	−28.6
2/58/M	MFH	Myxoid	Low	Thigh	10	2	2	2.5	2.2	−12.0
3/59/F	MFH	Myxoid	Low	Elbow	2	1	2	1.2	1.5	25.0
4/60/M	MFH	Ordinary	High	Knee	10	4	3	4.0	2.8	−30.0
5/63/F	MFH	Ordinary	High	Buttock	8	3	2	3.2	1.7	−46.9
6/65/F	MFH	Ordinary	High	Forearm	5	2	4	2.4	3.5	45.8
7/82/M	MFH	Ordinary	High	Back	10	2	2	1.8	1.6	−11.1
8/40/F	Liposarcoma	Myxoid	Low	Thigh	9	2	0	1.6	0.7	−56.3
9/57/F	Liposarcoma	Myxoid	Low	Back	9	2	2	2.2	1.9	−13.6
10/60/F	Liposarcoma	Well differentiated	Low	Thigh	8	0	0	1.0	0.8	−20.0
11/65/M	Liposarcoma	Well differentiated	Low	Thigh	24	2	2	1.8	1.3	−27.8
12/67/M	Liposarcoma	Pleomorphic	High	Axilla	18	2	2	2.2	1.5	−31.8
13/77/F	Liposarcoma	Myxoid	Low	Thigh	6	2	2	1.8	1.6	−11.1
14/82/M	Liposarcoma	Myxoid	Low	Back	10	2	2	1.8	1.5	−16.7
15/26/M	Synovial sarcoma	Monophasic	High	Neck	12	3	3	2.6	2.4	−7.7
16/32/M	Synovial sarcoma	Monophasic	High	Abdominal wall	5	3	3	2.5	2.2	−12.0
17/36/M	Synovial sarcoma	Biphasic	High	Thigh	5	3	3	3.5	2.2	−37.1
18/47/M	Synovial sarcoma	Monophasic	High	Knee	4	2	2	1.6	1.3	−18.8
19/31/F	MPNST		High	Thigh	18	3	2	3.2	2.5	−21.9
20/46/F	MPNST		High	Axilla	16	2	2	1.5	1.6	6.7
21/65/F	Leiomyosarcoma		High	Thigh	6	3	2	2.8	1.9	−32.1
22/65/F	Leiomyosarcoma		High	Inguen	11	4	4	3.2	3.4	6.3
23/20/F	Alveolar soft part sarcoma		High	Chest wall	8	2	3	2.2	2.6	18.2
24/66/M	Metastasic carcinoma			Forearm	5	3	3	3.9	3.2	−17.9
Range						0–4	0–4	1.0–4.0	0.7–3.5	−56.3–45.8
Median						2.0*	2.0**	2.3^{+}	1.9^{++}	−17.3^{+++}
B. Benign soft tissue lesions										
25/52/F	Lipoma			Thigh	16	0	0	1.2	1.1	−8.3
26/56/F	Lipoma			Chest wall	6	0	0	0.8	0.9	12.5
27/57/M	Lipoma			Upper arm	10	0	0	1.1	1.0	−9.1
28/1/M	Hemangioma			Back	1	0	0	1.0	1.1	10.0
29/70/F	Hemangioma			Forearm	4	1	1	1.2	1.3	8.3
30/31/M	Neurofibroma			Thigh	10	2	1	1.7	1.5	−11.8
31/43/M	Neurilemoma			Retroperitoneum	3	0	0	1.2	1.2	0
32/54/M	Epidermal cyst			Thigh	1	1	0	1.1	0.8	−27.3
33/70/M	Epidermal cyst			Hand	3	1	0	1.3	1.0	−23.1
34/1/M	Granuloma			Abdominal wall	1	0	0	1.1	0.9	−18.2
35/26/M	Granuloma			Buttock	5	0	0	1.0	0.9	−10.0
36/57/F	Granuloma			Planta	4	3	1	3.7	1.5	−59.5
Range						0–3	0–1	0.8–3.7	0.8–1.5	−59.5–12.5
Median						0*	0**	1.2^{+}	1.1^{++}	−9.6^{+++}

MPNST, malignant peripheral nerve sheath tumor; MFH, malignant fibrous histiocytoma

* $P = 0.0001$; ** $P < 0.0001$; $^{+}$ $P = 0.0003$; $^{++}P = 0.0002$; $^{+++}P = 0.24$ (Mann–Whitney U test)

Efficacy of ^{201}Tl scan

The sensitivity, specificity, and accuracy of ^{201}Tl scintigraphy in detecting malignant tumors are shown in Table 3.

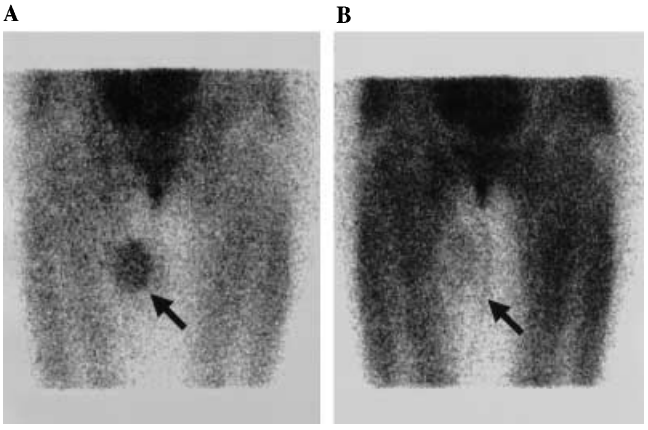

Fig. 3A,B. A 40-year-old woman (case 8, Table 2) with a history of myxoid liposarcoma in the right medial thigh. Early image demonstrates ^{201}Tl accumulation; the lesion-to-normal tissue (L/N) ratio is 1.6 (*arrow*) (**A**). Delayed image demonstrates decrease of ^{201}Tl accumulation; the L/N ratio is 0.7 (*arrow*) (**B**)

Multivariate analysis of ^{201}Tl accumulation

The clinically important variables associated with thallium uptake (as determined using a logistic regression model) are given in Table 4. According to this model, histology and cellularity were independent factors affecting thallium uptake on EI. Histology was the only independent factor on DI.

Evaluation of histological response to preoperative chemotherapy

Scintigraphic assessments in the 13 patients with bone and soft tissue tumors evaluated before and after chemotherapy by ^{201}Tl scintigraphy are shown in Table 5. ^{201}Tl uptake decreased in patients with good response after chemotherapy (Fig. 4). Figure 5 shows the relationship between the alteration ratio and percent necrosis of the resected tumor on the early and delayed images. There were significant correlations between the decrease in L/N ratio and percent necrosis of the resected tumor (EI: $r = 0.801$, $P = 0.0055$; DI: $r = 0.664$, $P = 0.036$).

Discussion

Malignant bone and soft tissue tumors are usually aggressive tumors. For that reason, the detection of

Table 3. Percentage sensitivity, specificity, and accuracy of ^{201}Tl scan

	Bone lesions		Soft tissue lesions		All lesions	
	Early	Delayed	Early	Delayed	Early	Delayed
Sensitivity (%)	100	100	92	92	94	94
Specificity(%)	50	71	83	100	65	85
Accuracy (%)	65	77	89	94	82	90

Table 4. Factors associated with ^{201}Tl accumulation

	Early images			Delayed images		
Variable	Score *P*	RR	95% CI	Score *P*	RR	95% CI
History						
Malignant lesion ($n = 36$)	0.0002	45.5	5.9–333	<0.0001	142.9	13.7–1000
Benign lesion ($n = 26$)						
Cellularity						
Low ($n = 16$)						
High ($n = 46$)	0.039	8.0	1.1–59	0.074	10.5	0.8–143
Size (cm)						
<5 ($n = 11$)						
≥5 ($n = 51$)	0.054	14.0	0.9–205	0.28	5.5	0.2–123
Site						
Extremity ($n = 42$)	0.13	4.6	0.6–33	0.66	1.6	0.2–13
Trunk ($n = 20$)						

RR, relative risk; CI, confidence interval

Table 5. Results of ^{201}Tl scan for malignant tumor

No./age/sex	Diagnosis	Site	Alteration ratio (%)		Necrosis (%)
			Early	Delayed	
A. Malignant bone tumors					
1/12/M	Osteosarcoma	Femur	−19.4	−10	30
2/14/F	Osteosarcoma	Femur	−40	−12.5	10
3/20/F	Osteosarcoma	Femur	74.5		85
4/20/M	Osteosarcoma	Tibia	56.7	15.4	66
5/53/M	Osteosarcoma	Tibia	43.5	37.1	70
6/14/M	MFH	Tibia	83.1	61.3	99
7/68/M	PNET	Illium	35.5	26.3	10
8/67/M	Multiple myeloma	Sacrum	66	38.1	60
B. Malignant soft tissue tumors					
9/26/M	Synovial sarcoma	Neck	0	20.8	15
10/32/M	Synovial sarcoma	Abdominal wall	40		30
11/22/M	MFH	Axilla	17.9	−10	15
12/65/F	Leiomyosarcoma	Thigh	3.6	26.3	33
13/20/F	Alveolar soft part sarcoma	Chest wall	31.8	50	50

^{201}Tl, thallium-201; PNET, primitive neuroectodermal tumor; MFH, malignant fibrous histiocytoma

malignant tumors and evaluation of the chemotherapeutic response are important in the management of patients with these tumors. Scintigraphy has been used to differentiate malignant from benign lesions and to evaluate the response of chemotherapy.

Radionuclide bone scintigraphy with ^{99m}Tc-MDP has proved to be very sensitive in the detection of primary and metastatic lesions of bone; however, this modality is not accurate in the assessment of response to therapy because osseous uptake mostly reflects healing response.[1,3,9,10,13] The gallium scintigram can be useful in differentiating between sarcoma and benign noninflammatory conditions.[18] Successful chemotherapy has also been shown to decrease the tumor-to-nontumor ratio on ^{67}Ga scan.[13] However, ^{67}Ga uptake involves complex mechanisms such as inflammation and bone remodeling, not all of which are related to tumor viability.[13,18] It may not be consistently accurate in defining the extent of bone and soft tissue lesions and in assessing treatment response.

In bone and soft tissue tumors, ^{99m}Tc-hexakis-2-methoxyisobutylisonitrile (MIBI)[2,17] and ^{201}Tl[1–3,5,7,8,11-18] scintigraphy were proven to be valuable diagnostic methods during the current decade. ^{99m}Tc-MIBI has lipophilic cationic properties, accumulating largely in mitochondria by its negative transmembrane potential.[2,17] ^{201}Tl is a potassium analogue that accumulates in tumor cells.[1–3,5,7,8,11–18] Changes in blood flow, capillary permeability, cell membrane ATPase activity, and the number of viable tumor cells have been proposed as the main reasons for the preferential concentration of ^{201}Tl in neoplasms.[1–3,5,7,8,11–18] Despite these suggested differences in uptake mechanisms, accumulation of ^{99m}Tc-MIBI and ^{201}Tl in various tumors was broadly similar to that reported in previous studies.[2,17]

So far as know, however, little has been reported regarding clinical detection of malignancy and chemotherapeutic response using the quantitative analysis of both EI and DI concerning ^{201}Tl scintigraphy. In addition, the important factors that influence ^{201}Tl accumulation have not been identified by the multivariate technique in clinical studies. With respect to the evaluation of ^{201}Tl uptake, many studies have been reported using only EI[2,3,5,7,8,11,13,14,15,17] or DI[1,12,18] but never both. Therefore, we investigated EI and DI of ^{201}Tl scintigraphy in 62 patients with various bone and soft tissue lesions and scintigraphically assessed the effect of preoperative chemotherapy.

Concerning bone lesions, the uptake of thallium was observed in all patients with malignant bone tumors, and its sensitivity was 100%. Its specificity, however, was only 55% on EI and 72% on DI, because accumulation can occur in aneurysmal bone cysts (ABC) and osteomyelitis. Although ABC and osteomyelitis are not malignant, ABC is characterized by hypervascularity. Similarly, osteomyelitis is characterized by inflammatory changes including proliferated capillary vessels and increased permeability as well. These histological features may contribute to the consistent ^{201}Tl uptake in these lesions.

In contrast, ^{201}Tl scintigraphy provides invaluable information for discriminating between soft tissue lesions. In primary soft tissue sarcomas, ^{201}Tl uptake was significantly different between high-grade sarcomas and low-grade sarcomas (EI, $P = 0.009$; DI, $P = 0.01$). Sato et al.[14] reported that none of six liposarcomas (four well-differentiated type and two myxoid type) were

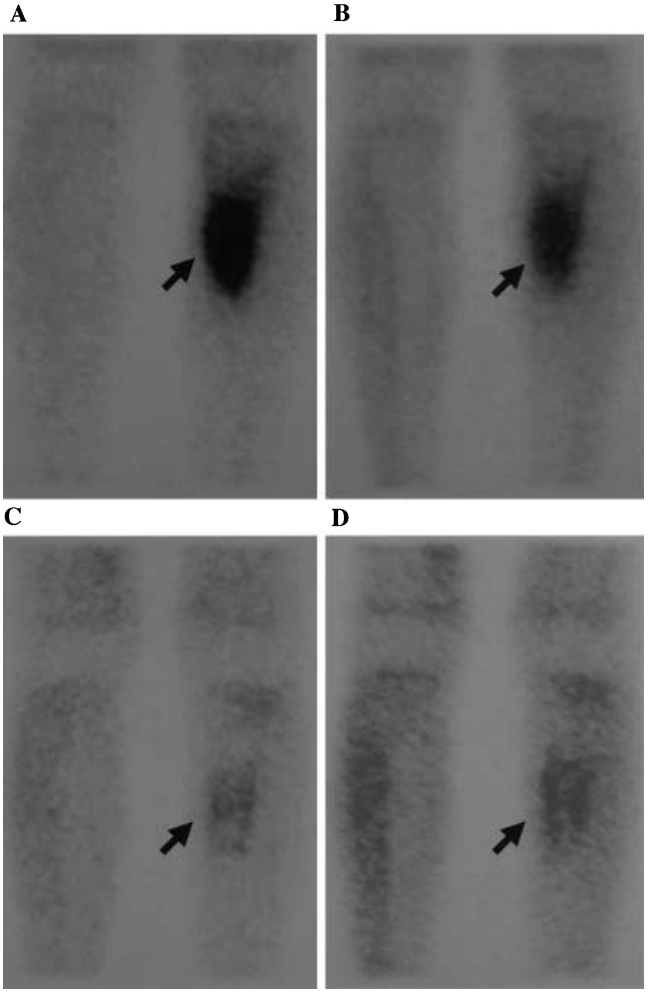

Fig. 4A–D. A 14-year-old boy (case 6, Table 5) with a history of malignant fibrous histiocytoma in the left proximal tibial bone. The ^{201}Tl scan obtained before chemotherapy shows an accumulation on the early (**A**) and delayed (**B**) images (*arrows*). The ^{201}Tl scan obtained after completion of chemotherapy shows a considerable reduction on the early (**C**) and delayed (**D**) images (*arrows*). Histologically, the percent tumor necrosis is 99%

visualized by ^{201}Tl scintigraphy. Low-grade liposarcoma (well-differentiated type, myxoid type) and malignant fibrous histiocytoma (myxoid type) demonstrated only minimal or no increased uptake, unlike other sarcomas among our cases. This behavior could be the result of the hypocelllularity and intercellular matrix of the lesions.

According to our multivariate analysis, we found that malignancy with a high metabolic rate was the most important variable determining early and delayed ^{201}Tl accumulation. Cellularity was also the independent factor on EI. However, ^{201}Tl uptake showed no differences between large (≥5 cm) and small (<5 cm) size. Because ^{201}Tl accumulation depends on cell viability and metabolic condition,[1–3,5,7,8,11,14–18] we believe that uptake of ^{201}Tl tended to be higher in the viable parenchymal tumor cell component of the stromal tissue than in large cystic lesions that consist of nonviable cells.

Preoperative chemotherapy is now a common treatment for malignant bone and soft tissue tumors. The effect of preoperative chemotherapy influences subsequent surgical procedures and postoperative chemotherapeutic regimens. ^{201}Tl[5,7,8,11–16] and ^{99m}Tc-MIBI scintigraphies[17] have been reported to be very useful in assessing chemotherapeutic effects in bone and soft tissue sarcomas. Because ^{99m}Tc-MIBI is a technetium-labeled radiopharmaceutical, administration of a sufficient dose for radionuclide angiography is possible.[2,17] Furthermore, in addition to tumor uptake, changes of blood flow can be assessed.[2,7] However, when the lesion is located in the pelvic or abdominal area, ^{99m}Tc-MIBI uptake might be significantly affected by bladder or gastrointestinal uptake.[2,17] Therefore, ^{201}Tl scintigraphy has an advantage concerning the assessment of patients with hypogastric and pelvic lesions.

Lin et al.[8] reported the necessity for early prediction of chemotherapeutic response in osteosarcoma using the ^{201}Tl scintigram on EI, leading to earlier con-

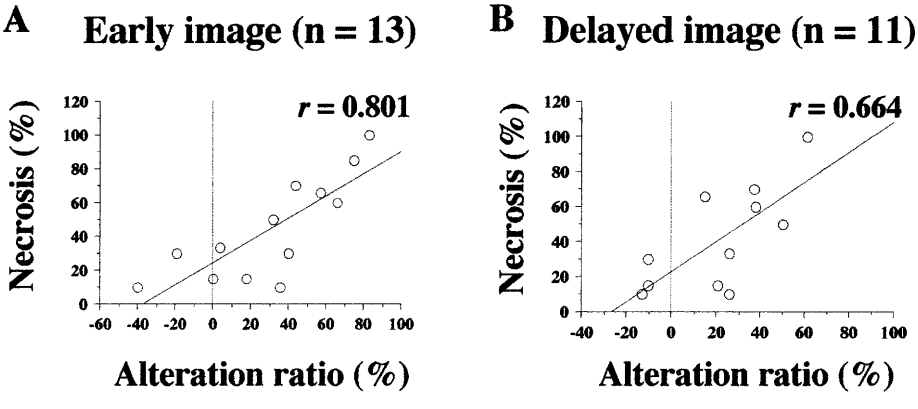

Fig. 5A,B. Correlation between percentage of tumour necrosis and alteration ratio on early (**A**) and delayed (**B**) images

sideration of alternative chemotherapeutic regimens or salvage surgery. Sumiya et al.[16] indicated that a ^{201}Tl scintigram on EI in the midcourse of chemotherapy was useful in assessing final chemotherapeutic response in the early stage of chemotherapy. In the current study, both EI and DI were obtained before and after chemotherapy. There was a statistically significant correlation between alteration ratio and percent necrosis of the resected specimen, and EI ($r = 0.801$) demonstrated a higher significant correlation coefficient than DI ($r = 0.664$).

The DI (2–4 h after injection) reflect mostly cellular uptake kinetics.[16] However, most studies reported that the evaluation of chemotherapeutic response on EI reflected disease activity after chemotherapy, and none reported on DI.[5,7,8,11,13–15] Sumiya et al.[16] indicated that DI are not necessarily indicated in evaluation of chemotherapy effect because ^{201}Tl washout from a tumor is complicated. We also think that the evaluation of chemotherapeutic response on DI has a disadvantage compared with EI. The reason is as follows: (1) spatial resolution is compromised by the fact that a relatively low activity leads to poor counting statistics with increasing times; and (2) the signal provided by mercury X-rays is resolved poorly by currently available gamma cameras. For that reason, ^{201}Tl scintigram on EI is clinically very useful and a rather handy examination tool for assessing chemotherapeutic effects.

In conclusion, ^{201}Tl scintigraphy is a simple, easy, and reliable tool to differentiate malignant tumors from benign lesions. Although ^{201}Tl scintigraphy is useful, it should be noted that there are some false-positive and false-negative findings, reflecting the confounding effects of a combination of local blood flow and cellularity. ^{201}Tl scintigraphy, especially on EI, is also of marked value in assessing the chemotherapeutic response of malignant bone and soft tissue tumors.

Acknowledgment. The authors thank Dr. K. Suga, Department of Radiology, Yamaguchi University School of Medicine, for his great assistance for preparing the manuscript.

References

1. Abe H, Terui S, Terauti T, et al. Comparison of Tc-99m pertechnetate wit Tl-201 and Ga-67 scintigraphy of malignant soft-tissue tumors. Clin Nucl Med 1997;22:38–41.
2. Adalet I, Ozger H, Cantez S, et al. Comparison of Tc-99m MIBI and Tl-201 uptake in musculoskeletal lesions. Clin Nucl Med 1996;21:118–21.
3. Caluser CI, Abdel-Dayem HM, Macapinlac HA, et al. The value of thallium and three-phase bone scans in the evaluation of bone and soft tissue sarcomas. Eur J Nucl Med 1994;21:1198–205.
4. Cheng EY, Thompson RC. New developments in the staging and imaging of soft-tissue sarcomas. J Bone Joint Surg Am 1999;81:882–92.
5. Imbriaco M, Yeh SDJ, Yeung H, et al. Thallium-201 scintigraphy for the evaluation of tumor response to preoperative chemotherapy in patients with osteosarcoma. Cancer 1997;80:1507–12.
6. Kaufman JH, Cedermark BJ, Parthasarathy KL, et al. The values of ^{67}Ga scintigraphy in soft-tissue sarcoma and chondrosarcoma. Radiology 1977;123:131–4.
7. Kunisada T, Ozaki T, Kawai A, et al. Imaging assessment of the responses of osteosarcoma patients to preoperative chemotherapy: angiography compared with thallium-201 scintigraphy. Cancer 1999;86:949–56.
8. Lin J, Leung W, Ho SKW, et al. Quantitative evaluation of thallium-201 uptake in predicting chemotherapeutic response of osteosarcoma. Eur J Nucl Med 1995;22:553–5.
9. McKillop JH, Etcubanas E, Goris ML. The indications for and limitations of bone scintigraphy in osteogenic sarcoma: a review of 55 patients. Cancer 1981;48:1133–8.
10. McNeil BJ. Rationale for the use of bone scans in selected metastatic and primary bone tumors. Semin Nucl Med 1978;8:336–45.
11. Menendez LR, Fideler BM, Mirra J. Thallium-201 scanning for the evaluation of osteosarcoma and soft-tissue sarcoma. J Bone Joint Surg Am 1993;75:526–31.
12. Ohtomo K, Terui S, Yokoyama R, et al. Thallium-201 scintigraphy to assess effect of chemotherapy in osteosarcoma. J Nucl Med 1996;37:1444–8.
13. 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;31:567–72.
14. Sato O, Kawai A, Ozaki T, et al. Value of thallium-201 scintigraphy in bone and soft tissue tumors. J Orthop Sci 1998;3:297–303.
15. Sumiya H, Taki J, Tsuchiya H, et al. Midcourse thallium scintigraphy to predict tumor response in bone and soft-tissue tumors. J Nucl Med 1998;39:1600–4.
16. Sumiya H, Taki J, Higuchi T, et al. Nuclear imaging of bone tumors: thallium-201 scintigraphy. Semin Musculoskelet Radiol 2001;5:177–82.
17. Taki J, Sumiya H, Tsuchiya H, et al. Evaluating benign and malignant bone and soft tissue lesions with technetium-99m-MIBI scintigraphy. J Nucl Med 1997;38:501–6.
18. Terui S, Terauchi T, Abe H, et al. On clinical usefulness of Tl-201 scintigraphy for the management of malignant soft tissue tumors. Ann Nucl Med 1994;8:55–64.