Midcourse Thallium-201 Scintigraphy to Predict Tumor Response in Bone and Soft-Tissue Tumors

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The purpose of this study was to assess the predictive power of ^{201}Tl scintigraphy in the midcourse of chemotherapy for the final tumor response to chemotherapy in malignant bone and soft-tissue tumors. **Methods:** The 21 patients studied with ^{201}Tl scintigraphy were 14 males and 7 females (average age 39.8 ± 22.1 yr; age range 8–74 yr). Planar scintigraphy was performed 15 min after injection of 111 MBq ^{201}Tl before chemotherapy, after the third chemotherapy cycle (midcourse) in all 21 patients and after the final chemotherapy cycle but before surgery in 11 patients. The ^{201}Tl uptake ratio was calculated by dividing the count density of the lesion by that of the contralateral normal area. The percent reduction of the ^{201}Tl uptake ratio calculated by 100 × [(prechemotherapy ratio − postchemotherapy ratio)/prechemotherapy ratio] in the midcourse was compared with that after the final course of chemotherapy, and it also was compared with the histologic response. **Results:** In patients with histologically complete response [(CR), n = 6] and with partial response [(PR), n = 5], the percent reduction in ^{201}Tl uptake ratio after three cycles of chemotherapy was 64.1% ± 14.4% and 50.9% ± 10.5%, respectively. In patients with histologically no change [(NC), n = 10], the percent reduction was 0.40% ± 18.2% after the third cycle; −5.3% ± 20.9% in four patients with full courses of chemotherapy ($p < 0.0001$ and $p < 0.005$ compared with the CR and PR groups, respectively). After the final cycle of chemotherapy, the percent reduction in ^{201}Tl uptake ratio was 68.6% ± 14.7%, 56.2% ± 6.1% and −0.3% ± 17.2% in the CR, PR and NC groups, respectively (NC versus CR, $p < 0.0005$; NC versus PR, $p < 0.005$). **Conclusion:** Thallium-201 scintigraphy performed in the midcourse of chemotherapy is predictive of the final response to chemotherapy that can be demonstrated histologically. Serial ^{201}Tl scintigraphy in the midcourse of chemotherapy is useful in assessing final chemotherapeutic response in the early stage of chemotherapy, and it helps clinicians when choosing the most appropriate treatment strategies in patients with bone and soft-tissue tumors.

Key Words: thallium-201; bone tumor; soft-tissue tumor; chemotherapy

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Both the survival rate of patients with malignant bone and soft-tissue tumors and the success rate for limb-salvage surgery have improved markedly as a result of advances in chemotherapy and surgical technique (*1*). Preoperative chemotherapy reduces lesion size and makes limb-salvage surgery possible (*2,3*). Because the effects of preoperative chemotherapy are crucial to surgery, the early assessment of tumor response to chemotherapy is essential to treatment planning.

Thallium-201 has been widely used as a tumor imaging agent in various benign and malignant lesions because it accumulates in viable tumor cells through the potassium pathway with adenosinetriphosphatase-dependent Na^+/K^+ pump (*4*). In bone and soft-tissue tumors, ^{201}Tl scintigraphy is a valuable diagnostic method for evaluating tumor response to chemotherapy (*5*). However, there has not been a study of whether ^{201}Tl scintigraphy performed in the midcourse of chemotherapy provides information predictive of the final response to chemotherapy. In this study, the ^{201}Tl uptake ratio during chemotherapy was compared by quantitative analysis with that after the final cycle of chemotherapy and with histologic response.

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MATERIALS AND METHODS

Patients

The study comprised 21 patients with various malignant bone and soft-tissue tumors confirmed pathologically in specimens obtained by biopsy and/or resection who were treated between September 1992 and February 1997. The 14 male and 7 female patients (age range 8–74 yr; average age 39.8 ± 22.1 yr) were studied with ^{201}Tl scintigraphy before and during preoperative chemotherapy, and 11 were studied after the completion of chemotherapy. There were 6 malignant fibrous histiocytomas; 5 osteosarcomas; 2 myxoid liposarcomas; and 1 each of synovial cell sarcoma, rhabdomyosarcoma, Ewing's sarcoma, malignant giant cell tumor, malignant schwannoma, bone metastatic adenocarcinoma, epithelioid sarcoma and myxoid chondrosarcoma. There were 10 bone tumors and 11 soft-tissue tumors. All patients were treated with preoperative intra-arterial chemotherapy according to the protocols as modified at our hospital (*6–8*). Five treatment cycles of cisplatin, doxorubicin and caffeine were given by catheterization at 2-wk intervals before surgery.

Thallium-201 Scintigraphy

Planar ^{201}Tl scintigraphy was performed 15 min after intravenous injection of 111 MBq of the radiopharmaceutical with a gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator. The ^{201}Tl scintigraphic study was performed before chemotherapy and after three cycles of chemotherapy in all 21 patients and after the final cycle of chemotherapy in 11 patients.

Image Analysis

The ^{201}Tl images were evaluated quantitatively. A region of interest (ROI) was set manually on the whole lesion and a symmetrical ROI was set on the contralateral normal area. If it was difficult to delineate the lesion on the scintigraphic image, we referred to a bone radiograph or MR image. The uptake ratio was then calculated by dividing the count density of the lesion by that of the contralateral normal area. In 1 patient with malignant fibrous histiocytoma adjacent to the spinal process (Patient 14), the reference ROI was set on the caudal side of the lesion.

Evaluation of Chemotherapy Effect

For the evaluation of tumor response to chemotherapy, the percent reduction of uptake ratio (Δ%) was calculated by using the following formula:

$$\Delta\% = [(\text{pre} - \text{post})/\text{pre}] \times 100, \qquad \text{Eq. 1}$$

in which pre = prechemotherapy uptake ratio and post = postchemotherapy uptake ratio. The histologic grading of the response to chemotherapy was based on the degree of necrosis in the largest

TABLE 1
Scintigraphic Results in All Patients

Patient no.	Age (yr)	Sex	Diagnosis	Tumor site	% ^{201}Tl uptake reduction		Cycles of chemotherapy completed
					3 cycles	5 cycles	
Complete response (100% necrosis)							
1	17	M	Osteosarcoma	Left femur	47.6	47.6	5
2	16	M	Osteosarcoma	Left femur	79.5	80.1	5
3	67	F	MFH	Right femur	61.7	NO	3
4	49	M	Myxoid liposarcoma	Left thigh	64.6	76.9	5
5	35	F	Synovial cell sarcoma	Left planta	81.7	69.9	5
6	9	M	Rhabdomyosarcoma	Right femur	49.5	NO	3
Partial response (>90% but <100% necrosis)							
7	38	M	Osteosarcoma	Left femur	62.9	62.1	5
8	9	F	Osteosarcoma	Left femur	42.2	56.6	5
9	50	M	MFH	Right thigh	37.8	NO	4
10	8	M	Ewing's sarcoma	Right calcaneus	56.7	50.0	5
11	56	F	Malignant giant cell tumor	Right tibia	55.1	NO	4
No change (≤90% necrosis)							
12	14	M	Osteosarcoma	Right femur	6.0	16.7	5
13	64	M	MFH	Right inguen	–9.6	–8.8	5
14	39	M	MFH	Lumbar subcutaneum	–20.1	NO	3
15	66	F	MFH	Left buttock	17.5	NO	3
16	74	M	MFH	Right upper arm	–11.4	NO	3
17	32	F	Myxoid liposarcoma	Left thigh	15.2	11.0	5
18	23	F	Malignant schwannoma	Right axilla	7.9	NO	3
19	67	M	Metastatic adenocarcinoma	Right pelvis	25.0	NO	4
20	58	M	Epithelioid sarcoma	Right thigh	6.1	NO	3
21	44	M	Myxoid chondrosarcoma	Left upper arm	–32.6	–20.2	5

MFH = malignant fibrous histiocytoma; NO = not obtained.

slice of the resected tumor. Grade IV (100% necrosis) was considered complete response (CR), and Grade III (>90% but <100% necrosis) was considered partial response (PR). Tumors showing Grade II and I responses (≤90% but >50% and ≤50% necrosis, respectively) were considered to show no change (NC). There were 6 patients with CR, 5 with PR and 10 with NC. In 2 patients with CR, chemotherapy was abandoned after three cycles because of renal dysfunction caused by chemotherapy in 1 patient (Patient 3) and because of pneumonia in the other (Patient 6). In 2 patients with PR (Patients 9 and 11), chemotherapy was abandoned after four cycles because of renal dysfunction. In 6 patients with NC, chemotherapy was terminated after three or four cycles because of severe renal dysfunction in 2 patients (Patients 15 and 19) and because the chemotherapy was clinically not effective in the other 4 patients (Patients 14, 16, 18 and 20). These 6 patients with NC were not included in statistical analysis for comparison with the other groups.

Statistics

Values are presented as mean ± s.d. Statistical comparisons were made using Scheffe's test for the comparisons among the CR, PR and NC groups. A two-tailed, nonpaired Student's t-test was used to compare the good response (CR plus PR) group with the NC group, and a two-tailed, paired Student's t-test was used to compare the values obtained after three cycles of chemotherapy with those obtained after completion of all five cycles. A $p < 0.05$ was considered significant.

RESULTS

The patient data are summarized in Tables 1 and 2. The percent reduction of ^{201}Tl uptake ratio in patients histologically classified after surgery as in CR (n = 6) and PR (n = 5) was 64.1% ± 14.4% and 50.9% ± 10.5%, respectively, after three cycles of chemotherapy. The percent reduction in the patients with CR was not significantly different from that in the PR

TABLE 2
Percent Thallium-201 Reduction in Uptake Ratio in Each Group

Chemotherapy	Histologic response			
	CR	PR	Good response CR + PR	NC
After 3 cycles	64.1 ± 14.4*	50.9 ± 10.5†	58.1 ± 14.0*	–5.3 ± 20.9
After 5 cycles	68.6 ± 14.7‡	56.2 ± 6.1†	63.3 ± 12.8*	–0.3 ± 17.2

Values are expressed as mean ± s.d.
*$p < 0.0001$, significantly different from NC group.
†$p < 0.005$.
‡$p < 0.0005$.
CR = complete response; NC = no change with completion of chemotherapy; PR = partial response.

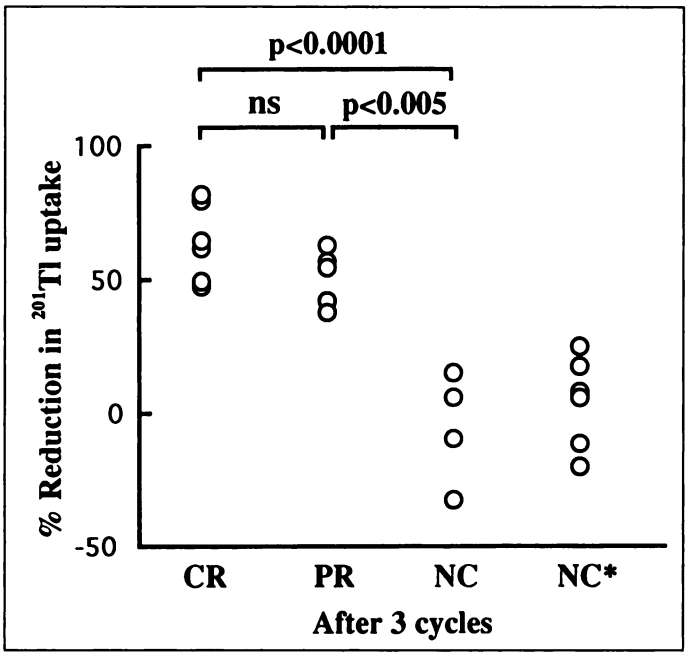

FIGURE 1. Percent reduction in ^{201}Tl uptake ratio after three cycles of chemotherapy in patient groups with complete response (CR), partial response (PR), no change with completion of chemotherapy (NC) and no change without completion of chemotherapy (NC*). Note that values in CR and PR groups do not overlap with those in NC or NC* groups.

group ($p = 0.39$). In patients who were histologically classified as NC ($n = 10$), the percent reduction was 0.4% ± 18.2% after the third cycle; −5.3% ± 20.9% ($p < 0.0001$ and $p < 0.005$ compared with the CR and PR groups, respectively) in 4 patients who underwent all five chemotherapy cycles; and 4.2% ± 17.1% in 6 patients who did not complete chemotherapy. The values in the CR or PR group did not overlap at all with those in the NC group (Fig. 1). For the good response group, the percent reduction (58.1% ± 14.0%) was significantly higher ($p < 0.0001$) than that in the NC group (−5.3% ± 20.9%).

The percent reduction of ^{201}Tl uptake ratio after the completion of five cycles of chemotherapy was 68.6% ± 14.7%, 56.2% ± 6.1% and −0.3% ± 17.2% in the CR ($n = 4$), PR ($n = 3$) and NC ($n = 4$) groups, respectively. The percent reduction in the NC group was significantly smaller than that in the CR ($p < 0.0005$) or PR group ($p < 0.005$), whereas the latter two groups showed no significant difference ($p = 0.54$). The value for the good response group was significantly higher than that for the NC group ($p < 0.0001$). No significant difference was obtained between the percent reduction after three cycles of chemotherapy and that after five cycles in any of the CR, PR and NC patients who underwent all five cycles (CR: 68.4% ± 15.8% versus 68.6% ± 14.7%; PR: 53.9% ± 10.6% versus 56.2% ± 6.1%; and NC: −5.3% ± 20.9% versus −0.3% ± 17.2%).

Representative patients are shown. Figure 2 shows a 49-yr-old man (Patient 4) with myxoid liposarcoma in the left thigh. A large mass was seen on the gadolinium-enhanced MR image and markedly increased ^{201}Tl uptake was observed in the lesion before chemotherapy. After three cycles of chemotherapy, the size of the mass decreased but an enhanced lesion was still seen on the MR image. Thallium-201 uptake was markedly reduced. After the final chemotherapy cycle, the activity in the mass was almost the same as the background activity. The surgical specimen pathologically confirmed CR. In this patient, the ^{201}Tl

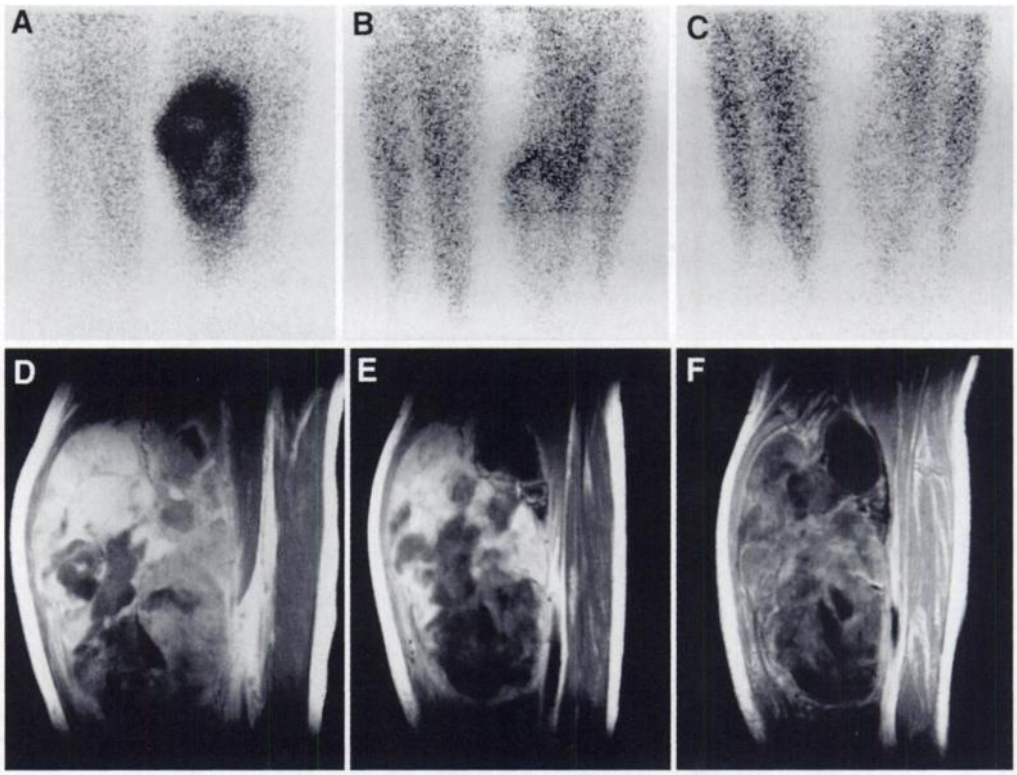

FIGURE 2. A 49-yr-old man (Patient 4) with myxoid liposarcoma in left thigh. (A) Prechemotherapeutic ^{201}Tl scintigraphy demonstrates increased uptake in left thigh. (B) Thallium-201 scintigraphy after three cycles of chemotherapy reveals markedly decreased uptake in the lesion. (C) After five cycles of chemotherapy, ^{201}Tl scintigraphy does not demonstrate any substantial uptake in left thigh, although mass lesion was still visible. Thallium-201 uptake ratios were 3.08, 1.09 and 0.71, respectively, and percent reduction was 64.6% and 76.9% for second and third studies, respectively. Complete tumor necrosis was verified after resection of tumor. (D) Prechemotherapeutic gadolinium-enhanced T1-weighted MR image demonstrates heterogeneously enhanced large mass in left thigh. (E) After third cycle of chemotherapy, mass size is decreased but enhanced lesion is still seen. (F) After final cycle of chemotherapy, no enhanced lesion is seen.

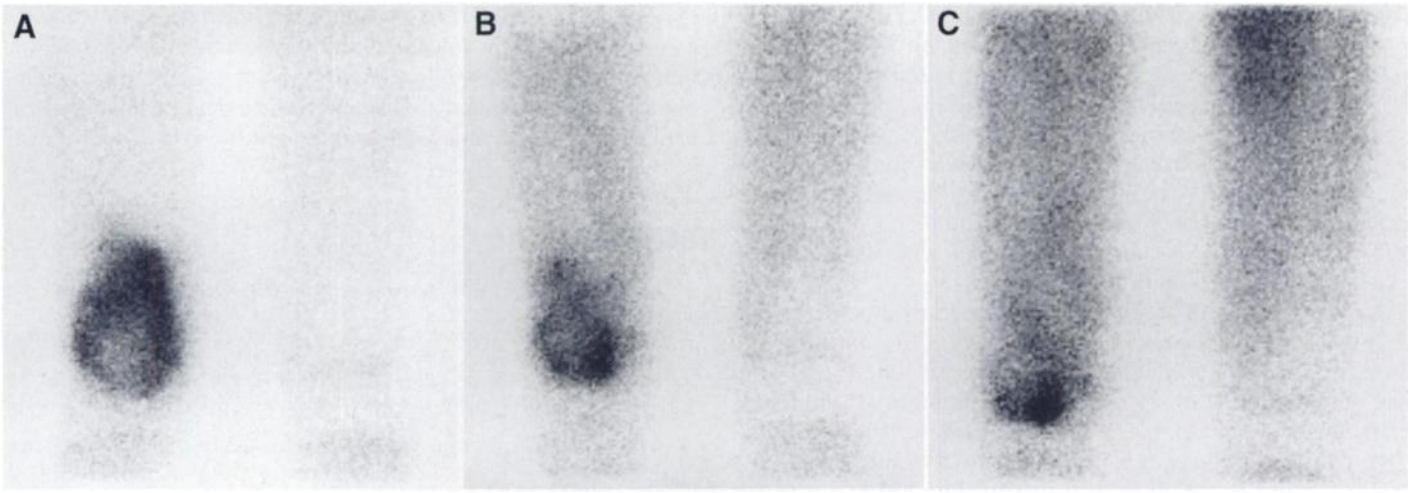

FIGURE 3. A 14-yr-old boy (Patient 12) with osteosarcoma in right distal femur. (A) Markedly increased uptake is seen in lesion before chemotherapy. (B) After third cycle of chemotherapy, no significant change in tumor uptake is apparent. (C) After final cycle of chemotherapy, uptake is decreased but intense activity is still seen in lower portion of tumor. Thallium-201 uptake ratios were 3.83, 3.60 and 3.19, respectively, and percent reduction was 6.0% and 16.7% for second and third studies, respectively.

scintigraphic study after three cycles of chemotherapy provided predictive information as to the scintigraphic result after the final cycle of chemotherapy and as to the histologic response obtained after surgery, even though the lesion still showed enhancement on MRI after three cycles of chemotherapy.

Figure 3 shows a 14-yr-old boy (Patient 12) with osteosarcoma in the right distal femur. Markedly increased uptake was seen in the lesion before chemotherapy. After three cycles of chemotherapy, no significant change was seen in tumor uptake. After five cycles of chemotherapy, the uptake decreased but intense activity was still seen in the lower portion of the tumor. The surgical specimen, especially the distal portion, contained viable tumor cells, and the histologic response was NC. Also in this patient, the ^{201}Tl scintigraphic study after three cycles of chemotherapy provided predictive information as to the result after the final cycle of chemotherapy and the histologic outcome.

DISCUSSION

Preoperative chemotherapy is essential in increasing the likelihood of success in limb-salvage surgery in patients with malignant bone and soft-tissue tumors (*2,3*). In the evaluation of tumor response to chemotherapy, several modalities are used, including CT, MRI, angiography and radionuclide imaging. Although tumor size can be well evaluated with CT and MRI, estimating residual tumor cell viability is somewhat difficult. In their study of radionuclide imaging, Ramanna et al. (*5*) found that ^{201}Tl scintigraphy was superior to bone scintigraphy and to ^{67}Ga imaging in assessing tumor response to chemotherapy of bone and soft-tissue lesions. Several reports suggest that ^{201}Tl scintigraphy is a valuable tool for evaluating tumor response to chemotherapy (*5,9–15*). Quantitative analysis, which is easy to perform with radionuclide imaging, is superior to visual analysis (*13*).

In this study, good and poor responses, as assessed by histologic examination after surgery, were predicted well with the percent reduction of ^{201}Tl uptake ratio after the third cycle of chemotherapy. In the 11 patients with CR and PR, the ranges did not overlap with that of NC, indicating that we could determine which patients would show good and poor responses using the percent reduction of uptake ratio without exception, even in this small sample of patients. In addition, the percent reduction values after the third cycle of chemotherapy were similar to those after the final cycle, with the result that the study after the third cycle was predictive of the results after the final cycle. The CR and PR groups did not show a significant difference in percent reduction, and we cannot separate them into two groups on the basis of the uptake ratio. However, the difference between CR and PR in percent necrosis is small (100% versus >90% but <100%) and it may not be necessary to separate these patients into two groups. It may be more practical to combine the CR and PR groups into a good response group and compare it with the NC group, since more than 90% necrosis is an indicator of good prognosis in osteosarcoma (*16–18*).

Because no significant difference was obtained between the percent reduction after three cycles of chemotherapy and that after five cycles in the NC group, patients with small percent reduction of ^{201}Tl uptake ratio after three cycles of chemotherapy will probably not benefit from continuing the same chemotherapy. If some reduction of the ^{201}Tl uptake ratio is apparent after the third cycle, the chemotherapy should be continued, but if it is not apparent, the chemotherapy should be abandoned and other treatments, including other drugs, additional radiation and prompt surgery, should be considered (Fig. 4).

Because the histologic grade of tumor response to chemotherapy was evaluated using the largest slice from the resected tumor, some discrepancies might have arisen if viable cells were situated diffusely in the tumor. Diagnosis based on

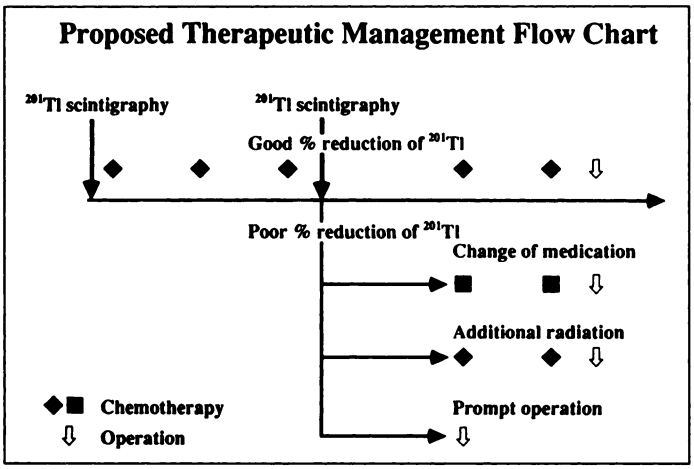

FIGURE 4. Proposed therapeutic management flow chart for use in patients with bone and soft-tissue tumors.

pathologic findings is not always definite, and radionuclide imaging provides supplementary information to a diagnosis made in this manner, perhaps compensating for deficiencies in the histologic evaluation. It may be more appropriate to compare the scintigraphic findings with the clinical outcome (e.g., prognosis, recurrence rate or survival rate) rather than with the histologic findings. However, for the purpose of evaluating the tumor response to chemotherapy, we think comparing the ^{201}Tl scintigraphic finding with the histologic response is the most appropriate method.

In this study, ^{201}Tl scintigraphy was performed before and in the midcourse of chemotherapy. Lin et al. (*13*) indicated the necessity for early prediction of chemotherapeutic response in osteosarcoma, leading to earlier consideration of alternative chemotherapeutic regimens or salvage surgery. Hoekstra et al. (*19*) reported that they predicted chemotherapeutic effect with few exceptions by visual analysis of ^{18}F-fluorodeoxyglucose or ^{67}Ga uptake during chemotherapy in 26 lymphoma patients. We cannot compare their results with ours because their analytical method, the patients they studied and the radionuclides they used all differed from those in this study. Yeh et al. (*20*) reported that in 36 osteosarcoma patients the percentage differences from the initial ^{67}Ga uptake ratio calculated at the time of last study before resection were almost the same as those approximately 1 mo after the initiation of chemotherapy. However, the uptake ratios in their good and poor response groups overlapped with each other. We think that the completely separate ranges in our patient groups were due to the different radionuclide we used, because ^{67}Ga uptake reflects healing response similar to the bone-seeking agent (*5*) and ^{201}Tl uptake does not. Their chemotherapy periods, ranging from 1.5 to 4.5 mo, might have been another reason.

Our method of early evaluation of the likely chemotherapeutic response might be applied to other tumors, such as lymphoma or brain tumors, needing several cycles of chemotherapy. However, more studies are needed to determine the appropriate thresholds of percent reduction of ^{201}Tl uptake, delineating groups with good and poor response among patients with various tumors, because the threshold could change with the tumor characteristics. It would also be worthwhile exploring whether final tumor response can be predicted using ^{201}Tl scintigraphy after only two cycles or even after one cycle of chemotherapy. More studies are needed to answer this question.

CONCLUSION

This study revealed that ^{201}Tl scintigraphy performed in the midcourse of chemotherapy provided a predictive indicator of the final bone and soft-tissue tumor response to chemotherapy, as demonstrated histologically. This is a useful method of predicting final chemotherapeutic response, and it will help clinicians in choosing the most appropriate treatment strategy in patients with bone and soft-tissue tumors.

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