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A comparative study of ^{201}Tl scintigraphy and three-phase bone scintigraphy following therapy in patients with bone and soft-tissue tumors

Yoshihiro NISHIYAMA,* Yuka YAMAMOTO,* Koiku YOKOE,* Yoji KAWAGUCHI,**
Yoshihiro TOYAMA,* Katashi SATOH* and Motoomi OHKAWA*

*Departments of *Radiology and **Orthopedics, Faculty of Medicine, Kagawa University*

Objective: The purpose of this study was to evaluate the usefulness of ^{201}Tl scintigraphy in comparison with three-phase bone scintigraphy in the differentiation of residual/recurrent tumors from post-therapeutic changes, in patients previously treated for bone and soft-tissue tumors. ***Methods:*** Thirty-five ^{201}Tl and three-phase bone scintigraphy scans were obtained for 30 patients with a history of bone or soft-tissue tumor who had undergone chemotherapy, radiation therapy, tumor resection, or a combination of these treatments. The planar ^{201}Tl images were acquired 10 mins (early) and 2 hrs (delayed) after the intravenous injection of 111 MBq ^{201}Tl-chloride. Three-phase bone scintigraphy was performed using 740 MBq ^{99m}Tc-HMDP at the same lesion site as for ^{201}Tl imaging. The blood flow images were obtained every 10 sec for 2 mins and were immediately followed by the blood pool image after 5 mins. Three to 4 hrs later, bone images were obtained. ^{201}Tl and three-phase bone scintigraphies were correlated with the histopathologic findings and/or clinical follow-up of more than 3 months. ***Results:*** Of the 35 cases, 15 were free of disease and 20 had residual or recurrent tumors. Of the 20 residual or recurrent cases, all had true-positive ^{201}Tl early and delayed scans, while bone scintigraphy was true-positive on the blood flow, blood pool and bone images in 16, 18 and 12 cases, respectively. ^{201}Tl early and delayed images and ^{99m}Tc-HMDP blood flow and blood pool images were false-positive in one patient. The histology of this false-positive case showed the presence of lymph proliferative tissue. ***Conclusions:*** Although ^{201}Tl uptake after treatment does not always indicate recurrence, ^{201}Tl scintigraphy may still be more useful than three-phase bone scintigraphy in the follow-up of patients with bone and soft-tissue tumors following therapy.

Key words: bone and soft-tissue tumor, recurrence, ^{201}Tl, scintigraphy

INTRODUCTION

THE CURRENT DIAGNOSTIC TOOLS for the detection or exclusion of recurrences for bone and soft-tissue tumors are clinical examination, magnetic resonance imaging (MRI), computed tomography (CT), X-ray of the primary tumor site and bone scintigraphy.[1,2] There are diagnostic difficulties in the detection of residual or recurrent tumors in post-surgical and post-radiotherapy fields because of distortion of the normal architecture. The post-treatment imaging appearance immediately following surgical treatment or radiotherapy is often non-specific. To overcome these limitations, various nuclear medicine procedures aimed at imaging the metabolic aspects of tumor have been tested. Because imaging is dependent on the metabolic activity of the constituent cellular tissue and not just on size or anatomical distortion, radionuclide imaging can enable detection of occult carcinoma and monitoring of the therapeutic response. ^{201}Tl-chloride (^{201}Tl) is useful for imaging malignant lesions, differentiating malignant from benign lesions, and evaluating the response to preoperative chemotherapy.[3–9] Whole-body bone scintigraphy that includes a three-phase study for the involved

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For reprint contact: Yoshihiro Nishiyama, M.D., Department of Radiology, Faculty of Medicine, Kagawa University, 1750–1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761–0793, JAPAN.
E-mail: nisiyosi@kms.ac.jp

Table 1 Patient clinical and radionuclide data

Patient	Age (years)/ Sex	Initial histology	Time between therapy and scintigraphy (month)	Site	Size (cm)	Diagnosis	Scintigraphic evaluation				
							Tl (E)	Tl (D)	Blood flow	Blood pool	Bone
1	24/F	osteosarcoma	2	limb	3	Recurrence	2	2	2	2	2
2	65/F	osteosarcoma	60	limb	10	Recurrence	2	2	2	2	2
3	67/M	chondrosarcoma	30	limb	10	Recurrence	2	2	2	2	2
4	12/M	osteosarcoma	4	limb	5	Recurrence	2	2	2	2	2
5	20/F	osteosarcoma	27	pelvis	8	Recurrence	2	2	0	2	1
	21/F	osteosarcoma	10	pelvis	/	No recurrence	0	0	0	0	0
6	21/M	osteosarcoma	48	shoulder	/	No recurrence	0	0	0	0	0
7	51/M	osteosarcoma	36	limb	/	No recurrence	1	0	0	0	0
8	46/F	osteosarcoma	24	limb	/	No recurrence	0	0	0	0	0
9	20/M	osteosarcoma	24	limb	/	No recurrence	1	0	0	1	0
10	78/F	meta	24	pelvis	4	Recurrence	2	2	2	2	2
11	68/F	meta	12	limb	5	Recurrence	2	2	2	2	2
12	84/F	chordoma	24	pelvis	8	Recurrence	2	2	2	2	0
13	81/F	MFH	48	shoulder	15	Recurrence	2	2	2	2	2
	84/F	MFH	36	shoulder	10	Recurrence	2	2	2	2	2
14	67/M	MFH	19	limb	10	Recurrence	2	2	2	2	2
15	36/M	MFH	108	limb	8	Recurrence	2	2	2	2	2
16	42/M	MFH	36	limb	5	Recurrence	2	2	2	2	0
17	61/F	liposarcoma	14	limb	/	No recurrence	2	2	2	2	0
	62/F	liposarcoma	12	limb	2	Recurrence	2	2	0	0	0
	64/F	liposarcoma	24	limb	/	No recurrence	0	0	0	0	0
18	46/M	liposarcoma	17	limb	/	No recurrence	0	0	0	0	0
19	64/M	liposarcoma	96	limb	/	No recurrence	0	0	0	0	0
20	54/M	synovial sarcoma	55	limb	10	Recurrence	2	2	2	2	2
21	32/M	synovial sarcoma	60	limb	/	No recurrence	0	0	0	0	0
22	54/F	synovial sarcoma	30	limb	/	No recurrence	0	0	0	0	0
23	22/M	synovial sarcoma	8	limb	/	No recurrence	0	0	0	0	0
24	68/F	leiomyosarcoma	36	back	/	No recurrence	0	0	0	0	0
25	50/M	leiomyosarcoma	108	limb	/	No recurrence	0	0	0	0	0
26	47/F	desmoid	14	shoulder	6	Recurrence	2	2	2	2	1
27	39/M	desmoid	12	limb	3	Recurrence	2	2	2	2	0
	40/M	desmoid	12	limb	2	Recurrence	2	2	2	2	0
28	28/F	desmoid	24	limb	5	Recurrence	2	2	0	2	2
29	29/F	malignant schwannoma	30	limb	2	Recurrence	2	2	0	0	0
30	25/M	peripheral nerve sheath tumor	4	limb	/	No recurrence	0	0	0	0	0

MFH, malignant fibrous histiocytoma; meta, bone metastasis; Tl (E), ^{201}Tl early image; Tl (D), ^{201}Tl delayed image; Blood flow, blood flow image; Blood pool, blood pool image; Bone, bone image

region helps to outline the vascularity of the lesion and to evaluate involvement of soft and bony tissue and other bones.[10–15]

The purpose of this study was to evaluate the usefulness of ^{201}Tl scintigraphy in comparison with three-phase bone scintigraphy in differentiating residual or recurrent tumors from post-therapeutic changes, in patients previously treated for bone and soft-tissue tumors.

MATERIALS AND METHODS

Patients

Between April 1994 and January 2003, thirty-five ^{201}Tl and three-phase bone scintigraphy scans were obtained for 30 patients with a history of bone or soft-tissue tumor who had undergone chemotherapy, radiation therapy, tumor resection, or a combination of these treatments. We undertook a retrospective review of the 35 scintigraphic scans. Four patients had 2 or more scintigraphic scans. All patients had presented with clinically suspected recurrent or residual tumor 4 months-9 years after the last therapy (average 22.8 months). Informed consent was obtained from each patient at the time of scintigraphy.

The patient population comprised 16 males and 14 females who ranged in age from 12 to 84 years, with a mean age of 46.7 years. The suspicious recurrent site was

Table 2 Sensitivity, specificity and accuracy of ^{201}Tl and three-phase bone scintigraphies in detecting residual/recurrent tumors in patients with bone and soft-tissue tumors

	^{201}Tl scintigraphy		Bone scintigraphy		
	Early	Delayed	Blood flow	Blood pool	Bone
Total					
Sensitivity	100% (20/20)	100% (20/20)	80% (16/20)	90% (18/20)	60% (12/20)
Specificity	93.3% (14/15)	93.3% (14/15)	93.3% (14/15)	93.3% (14/15)	100% (15/15)
Accuracy	97.1% (34/35)	97.1% (34/35)	85.7% (30/35)	91.4% (32/35)	77.1% (27/35)
Bone tumor					
Sensitivity	100% (8/8)	100% (8/8)	87.5% (7/8)	100% (8/8)	75% (6/8)
Specificity	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)	100% (5/5)
Accuracy	100% (13/13)	100% (13/13)	92.3% (12/13)	100% (13/13)	84.6% (11/13)
Soft-tissue tumor					
Sensitivity	100% (12/12)	100% (12/12)	75% (9/12)	83.3% (10/12)	50% (6/12)
Specificity	90% (9/10)	90% (9/10)	90% (9/10)	90% (9/10)	100% (10/10)
Accuracy	95.5% (21/22)	95.5% (21/22)	81.8% (18/22)	86.4% (19/22)	72.7% (16/22)

limb in 26, pelvis in 4, shoulder in 4 and back in 1. The recurrent tumor size range from 3.0 cm to 15.0 cm. There were 13 bone tumors (osteosarcoma, chondrosarcoma, chordoma, and bone metastasis) and 22 soft-tissue tumors (leiomyosarcoma, liposarcoma, desmoid, malignant fibrous histiocytoma, malignant schwannoma, synovial sarcoma and peripheral nerve sheath tumor). Histopathologic diagnoses in recurrent lesions were made at biopsy or surgery. The lesion was considered not to be recurrent if the biopsy result was negative or if the lesion did not change during a period of at least 3 months as demonstrated clinically and by other imaging modalities including radiography, CT, or MRI.

^{201}Tl and three-phase bone scintigraphy

For ^{201}Tl scintigraphy, 111 MBq ^{201}Tl was administered intravenously, and images were obtained after 10 minutes (early) and 2 hours (delayed). Within 14 days, three-phase bone scintigraphy was performed using 740 MBq ^{99m}Tc-HMDP at the same lesion site as for ^{201}Tl scintigraphy. Blood flow images were obtained every 10 seconds according to the location of the lesion for a total of 2 minutes and were followed immediately by blood pool imaging after 5 minutes (approximately 1500 K counts). Bone imaging was performed 3 to 4 hours later. ^{201}Tl scintigraphic images were obtained using a Prism 2000 gamma camera (Picker International, Cleveland, OH), and three-phase bone scintigraphy was performed using a RC 2600I camera (Hitachi, Tokyo, Japan). Both cameras were equipped with a low-energy all-purpose collimator.

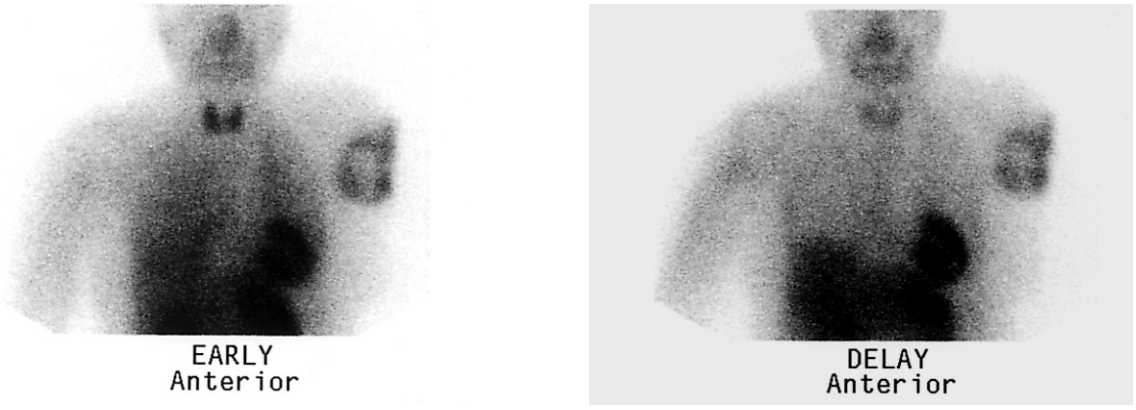
Scintigraphic evaluation

Two nuclear medicine physicians evaluated both ^{201}Tl and three-phase bone scintigraphies visually. A 3-point scoring system was used to judge the degree of activity (0 = background activity, 1 = slightly increased uptake less than the normal contralateral side or adjacent normal tissue, and 2 = equal or greater uptake than the normal contralateral side or adjacent normal tissue). Score 2 is defined as pathological. In the case of disagreement, the final decision was made by consensus. Sensitivity, specificity, and accuracy rates for ^{201}Tl early and delayed images and for each phase of bone scan were calculated.

RESULTS

The clinical and radionuclide data of the 30 patients are shown in Table 1. Table 2 shows the sensitivity, specificity and accuracy of ^{201}Tl and three-phase bone scintigraphies in detecting residual/recurrent tumors in patients with bone and soft-tissue tumors. Of the 35 cases, 15 were free of disease and 20 had residual or recurrent tumor. Of the 20 cases with residual or recurrent bone and soft-tissue tumor, the early and delayed ^{201}Tl scans were positive in all cases (100%), while bone scintigraphy was true-positive on the blood flow, blood pool and bone images in 16, 18 and 12 cases, respectively. ^{201}Tl early and delayed images and ^{99m}Tc-HMDP blood flow and blood pool images were false-positive in one case. The histology of this false-positive case showed the presence of lymph proliferative tissue. The sensitivity of ^{201}Tl early and delayed image for evaluation of residual or recurrent tumor was 100%, specificity 93.3% and accuracy 97.1%. The corresponding values using blood flow images were 80%, 93.3% and 85.7%, respectively, using blood pool images 90%, 93.3% and 91.4%, respectively, and using bone images 60%, 100% and 77.1%, respectively.

Of the 8 cases with residual or recurrent bone tumor, the early and delayed ^{201}Tl scans were positive in all cases (100%), while the blood flow, blood pool and bone images were positive in 7 (87.5%), 8 (100%) and 6 (75%) cases, respectively. Of the 5 cases with no recurrent bone tumor, the early and delayed ^{201}Tl scans and all three parts of the three-phase bone scans were negative in all cases



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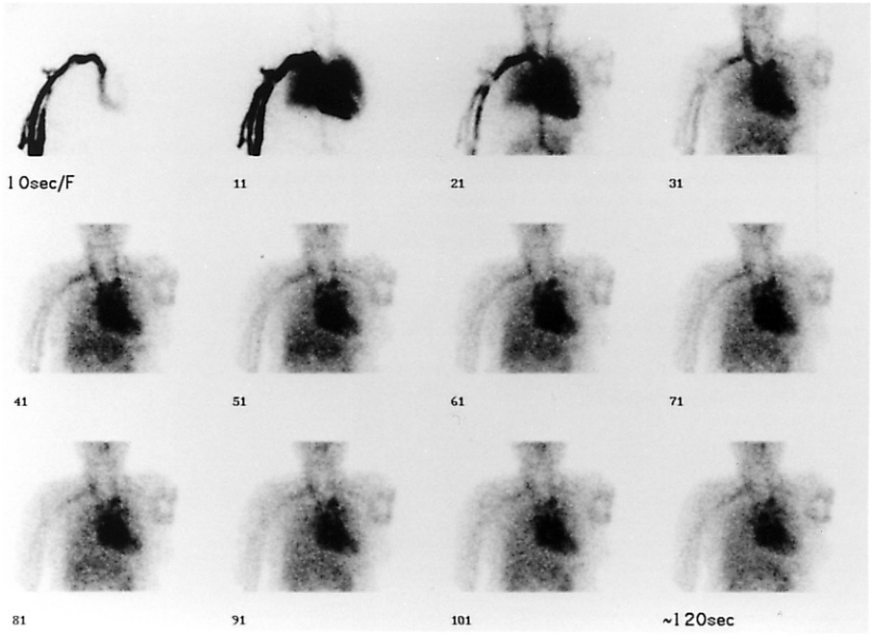

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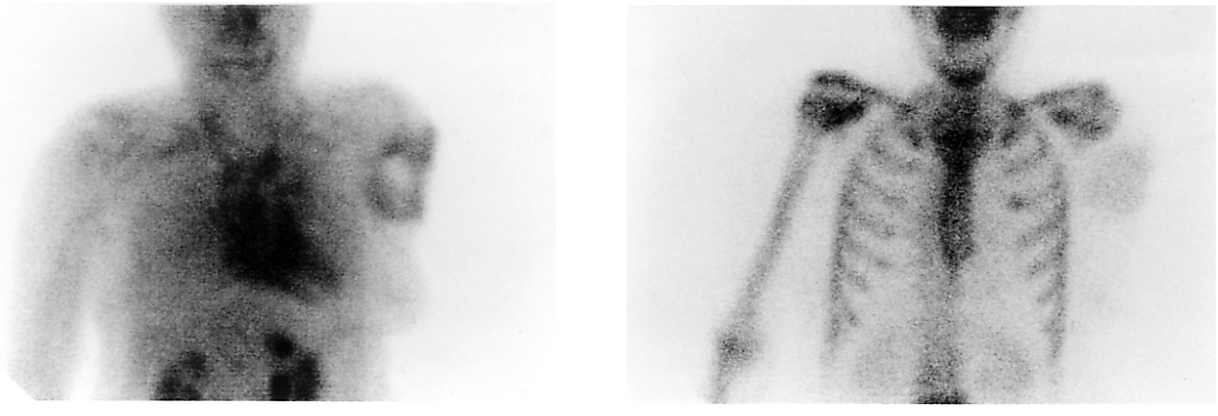

D E

Fig. 1 ^{201}Tl early and delayed scans and three phase bone scans in an 82-year-old female with local recurrence after surgical resection for malignant fibrous histiocytoma of the left arm. ^{201}Tl early (A) and delayed (B) anterior images demonstrate abnormal accumulation in the left stump. The blood flow (C), blood pool (D) and bone (E) anterior images also demonstrate abnormal accumulation in the left stump.

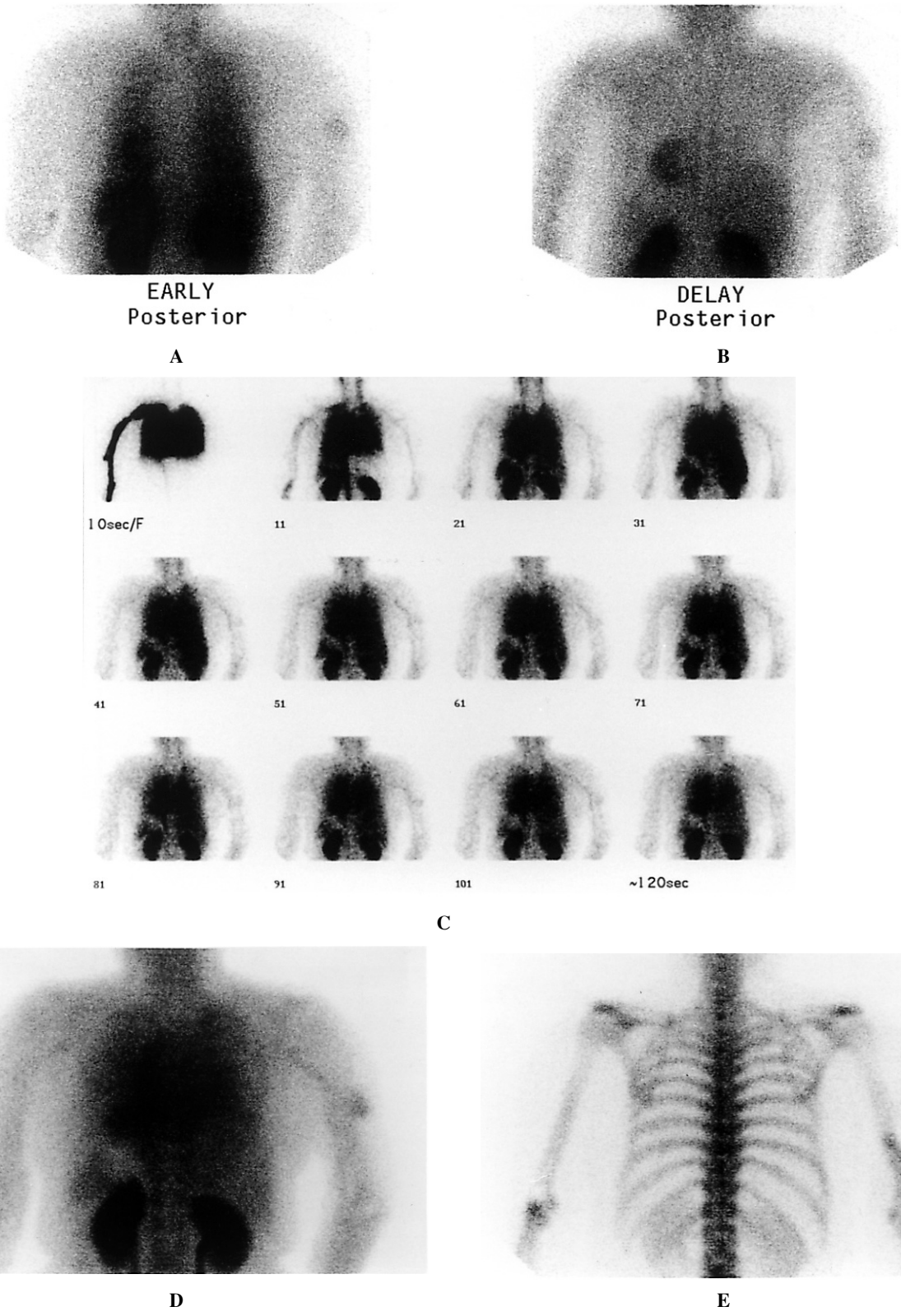

Fig. 2 ^{201}Tl early and delayed scans and three phase bone scans in a 61-year-old female with inflammation after surgical resection for liposarcoma of the right arm. ^{201}Tl early (A) and delayed (B) posterior images demonstrate slight abnormal accumulation in the right upper arm. The blood flow (C) and blood pool (D) posterior images demonstrate abnormal accumulation in the right upper arm. The bone (E) posterior image shows no abnormal accumulation. The histology showed the presence of lymph proliferative tissue, and recurrence was not evident.

(100%). Accuracies of ^{201}Tl early and delayed scans and the three parts of the three-phase bone scans were 100%, 100%, 92.3%, 100% and 84.6%, respectively.

Of the 12 cases with residual or recurrent soft-tissue tumor, the early and delayed ^{201}Tl scans were positive in all cases (100%), while the blood flow, blood pool and bone images were positive in 9 (75%), 10 (83.3%) and 6 (50%) cases, respectively. Of the 10 cases with no recurrent soft-tissue tumor, the early and delayed ^{201}Tl scans were negative in 9 cases (90%), while the blood flow and blood pool images were negative in 9 (90%), and bone images were negative in all cases (100%). Accuracies of ^{201}Tl early and delayed scans and the three parts of the three-phase bone scans were 95.5%, 95.5%, 81.8%, 86.4% and 72.7%, respectively.

Figure 1 shows ^{201}Tl and three-phase bone scintigraphic scans of a true positive case of recurrent malignant fibrous histiocytoma of the left arm. Figure 2 shows similar scans of a false positive case of liposarcoma of the right arm.

DISCUSSION

The development of new limb-salvaging surgical techniques combined with chemotherapy and radiation therapy in the treatment of musculoskeletal sarcoma has resulted in the need for a way to accurately evaluate patients after they have undergone therapy.[16,17] However, current imaging methods have limitations in distinguishing viable tumors from post-therapeutic changes because of alterations in normal anatomy, distortion of tissue planes, lack of distinction between tumor and post-operative tissue, or imaging artifacts from metallic limb salvage prostheses. Biopsy studies are limited by the invasiveness of the procedure and the heterogeneity of the treated tumor. Nuclear medicine procedures can provide additional information about tumor metabolism in such cases, thereby reducing the need for invasive procedures.[9]

In the present study, ^{201}Tl accumulation was observed in all cases with residual or recurrent tumor on both early and delayed images. The result confirms previous findings that preferential uptake of ^{201}Tl is to be expected in malignant bone tumors.[18] ^{201}Tl scintigraphy was more helpful in distinguishing post-therapeutic changes from tumor recurrence than three-phase bone scintigraphy in patients with bone and soft-tissue tumors. ^{201}Tl accumulation is dependent on blood flow and several metabolic processes, particularly Na-K-ATPase activity and indicates viability and metabolic activity of the diseased cells.[10] Because ^{201}Tl does not accumulate in necrotic tumors, a positive scintigraphic finding represents viable tumor cells. Sato et al.[18] reported that none of six liposarcoma (four well-differentiated type and two myxoid type) was visualized by ^{201}Tl scintigraphy. This could be due to hypocellularity and intercellular matrix of the lesion. However, one liposarcoma with recurrence in the present study was visualized by ^{201}Tl scintigraphy. The histological type of this case was dedifferentiated type.

The blood flow image of the bone scan shows the arterial supply to the lesion, whereas the blood pool image represents the extracellular and extravascular distribution of radionuclide determined by local vascularity and vascular permeability.[19] The bone phase images of the bone scan reflect the bone repair processes in the lesion and the adjacent margins.[19] Caluser et al. reported that the three-phase bone scan has a high sensitivity, but a lower specificity for detecting sarcoma.[11] However, their study was designed to assess the differentiation of malignant and benign lesions using the three-phase bone scan.[11] In the present study, three-phase bone scan was performed to evaluate the differentiation between residual or recurrent tumor and post-therapeutic change. The results showed a high specificity for detecting bone and soft-tissue tumor recurrence and almost the same specificity for three-phase bone scintigraphy compared with ^{201}Tl scintigraphy.

One false-positive case of soft-tissue tumor was detected, in the present study, and pathologically showed the presence of lymph proliferative tissue. The reason for this may be the hypercellularity of inflammatory cells.

Many published reports have emphasized the usefulness of the delayed ^{201}Tl scan in differentiating malignant from benign tumors in various organs, because ^{201}Tl activity in malignant tumors shows a delayed washout compared with benign tumors.[20] From this point of view, delayed ^{201}Tl image may be more suitable for tumor evaluation. However, on visual analysis in the present study, results from early ^{201}Tl image were the same as those from delayed images. We suggest that early ^{201}Tl image alone may be sufficient for the evaluation of bone and soft-tissue tumors recurrence, and has the advantages of yielding a quick result and saving time in a busy clinical setting. Furthermore, three-phase bone scintigraphies add no additional clinical information in detecting bone and soft-tissue local recurrences if ^{201}Tl scintigraphy had already been performed previously. Comparisons of ^{201}Tl scintigraphy and three-phase bone scintigraphies in bone tumor patients have demonstrated no significant difference between the two methods, whereas there is a significant advantage for ^{201}Tl scintigraphy in patients with soft tissue tumors.

Semiquantitative evaluation has been used in the evaluation of the chemotherapeutic response using ^{201}Tl scintigraphy.[7,8] In these reports,[7,8] the degree of accumulation in the tumor lesion was compared with that in the background. In the present study, on the other hand, the degree of accumulation was evaluated by visual examination and almost all recurrent tumors were visualized easily. These results indicate that semiquantitative evaluation is not needed for the detection of tumor recurrence. However, it must be remembered that there are tumors which may have a low ^{201}Tl accumulation such as chondrosarcoma, low-grade osteosarcoma and well-differentiated or myxoid

liposarcoma.[9,18]

Although positron emission tomography with ^{18}F-fluorodeoxyglucose has been shown to be effective in evaluating bone and soft-tissue tumor recurrence,[21] this technique is not widely available because of its high cost and the need for multiple technicians to operate it. The technique is especially restricted in Japan because it is not covered by the national health insurance system, with this hampering its routine use for evaluation of bone and soft-tissue tumors. In contrast, ^{201}Tl scintigraphy can be performed in any hospital with a nuclear medicine department. Further well-designed studies are required to determine the appropriate role for this and other imaging modalities in the proper management of patients with possible bone and soft-tissue tumor recurrence.

CONCLUSION

Although ^{201}Tl uptake after treatment does not always indicate recurrence, ^{201}Tl scintigraphy may still be more useful than three-phase bone scintigraphy in the follow-up of patients with bone and soft-tissue tumors following therapy. Especially, ^{201}Tl scintigraphy for studying patients with residual or recurrent soft tissue tumor is the method of choice.

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