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

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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. 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. Whole-body bone scintigraphy that includes a three-phase study for the involved
region helps to outline the vascularity of the lesion and to evaluate involvement of soft and bony tissue and other bones.\textsuperscript{10–15}

The purpose of this study was to evaluate the usefulness of \textsuperscript{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.

\section*{MATERIALS AND METHODS}

\subsection*{Patients}
Between April 1994 and January 2003, thirty-five \textsuperscript{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

\begin{table}[h]
\centering
\caption{Patient clinical and radionuclide data}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
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 \\
\hline
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 & 2 \\
13 & 81/F & MFH & 48 & shoulder & 15 & Recurrence & & 2 & 2 & 2 & 2 & 2 \\
14 & 84/F & MFH & 36 & shoulder & 10 & Recurrence & & 2 & 2 & 2 & 2 & 2 \\
15 & 67/M & MFH & 19 & limb & 10 & Recurrence & & 2 & 2 & 2 & 2 & 2 \\
16 & 36/M & MFH & 108 & limb & 8 & Recurrence & & 2 & 2 & 2 & 2 & 2 \\
17 & 42/M & MFH & 36 & limb & 5 & Recurrence & & 2 & 2 & 2 & 2 & 2 \\
18 & 61/F & liposarcoma & 14 & limb & / & No recurrence & & 2 & 2 & 2 & 2 & 2 \\
19 & 64/F & liposarcoma & 12 & limb & 2 & Recurrence & & 2 & 2 & 0 & 0 & 0 \\
20 & 64/F & liposarcoma & 24 & limb & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
21 & 46/M & liposarcoma & 17 & limb & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
22 & 64/M & liposarcoma & 96 & limb & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
23 & 54/M & synovial sarcoma & 55 & limb & 10 & Recurrence & & 2 & 2 & 2 & 2 & 2 \\
24 & 32/M & synovial sarcoma & 60 & limb & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
25 & 54/F & synovial sarcoma & 30 & limb & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
26 & 22/M & synovial sarcoma & 8 & limb & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
27 & 68/F & leiomyosarcoma & 36 & back & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
28 & 50/M & leiomyosarcoma & 108 & limb & / & No recurrence & & 0 & 0 & 0 & 0 & 0 \\
29 & 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 \\
30 & 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 \\
\hline
\end{tabular}
\end{table}

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

**201Tl and three-phase bone scintigraphy**

For 201Tl scintigraphy, 111 MBq 201Tl 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 99mTc-HMDP at the same lesion site as for 201Tl 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. 201Tl 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 201Tl 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 201Tl 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 201Tl 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 201Tl 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. 201Tl early and delayed images and 99mTc-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 201Tl 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 201Tl 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 201Tl scans and all three parts of the three-phase bone scans were negative in all cases.
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.
tumor cells. Sato et al. reported that none of six liposarcomas, a positive scintigraphic finding represents viable formation about tumor metabolism in such cases, thereby procedure and the heterogeneity of the treated tumor. Biopsy studies are limited by the invasiveness of the imaging artifacts from metallic limb salvage prostheses. Of the 12 cases with residual or recurrent soft-tissue tumor, the early and delayed 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 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 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 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. 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.

In the present study, 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 Tl is to be expected in malignant bone tumors. 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. 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. Because Tl does not accumulate in necrotic tumors, a positive scintigraphic finding represents viable tumor cells. Sato et al. reported that none of six liposarcoma (four well-differentiated type and two myxoid type) was visualized by 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 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. The bone phase images of the bone scan reflect the bone repair processes in the lesion and the adjacent margins. Caluser et al. reported that the three-phase bone scan has a high sensitivity, but a lower specificity for detecting sarcoma. However, their study was designed to assess the differentiation of malignant and benign lesions using the three-phase bone scan. 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 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 Tl scan in differentiating malignant from benign tumors in various organs, because Tl activity in malignant tumors shows a delayed washout compared with benign tumors. From this point of view, delayed Tl image may be more suitable for tumor evaluation. However, on visual analysis in the present study, results from early Tl image were the same as those from delayed images. We suggest that early 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 Tl scintigraphy had already been performed previously. Comparisons of 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 Tl scintigraphy in patients with soft tissue tumors.

Semiquantitative evaluation has been used in the evaluation of the chemotherapeutic response using Tl scintigraphy. In these reports, 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 Tl accumulation such as chondrosarcoma, low-grade osteosarcoma and well-differentiated or myxoid...
liposarcoma.9,18

Although positron emission tomography with 18F-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, 201Tl 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 201Tl uptake after treatment does not always indicate recurrence, 201Tl 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, 201Tl scintigraphy for studying patients with residual or recurrent soft tissue tumor is the method of choice.

REFERENCES