Annals of Nuclear Medicine Vol. 8, No. 1, 55–64, 1994

On clinical usefulness of Tl-201 scintigraphy for the management of malignant soft tissue tumors

Shoji TERUI, Takashi TERAUCHI, Hiroyuki ABE, Hisatoshi FUKUMA, Yasuo BEPPU, Koichi CHUMAN and Ryohei YOKOYAMA

Divisions of Nuclear Medicine and Orthopedics, National Cancer Center Hospital

The purpose of this study was to investigate Tl-201 as a tumor scanning agent in patients with malignant soft tissue sarcomas and to establish the sensitivity of this type of scintigraphy concerning local recurrences or metastases that may remain clinically suspected. Seventy-eight patients with malignant soft tissue sarcomas and 22 with benign soft tissue tumors were studied. Of these 78 malignant soft tissue sarcomas patients, the sensitivity of Tl-201(81.2%) was higher than that of Ga-67 (68.8%). Thirty-three out of 78 patients received a total of 95 consecutive scintigraphic follow-up examinations. Therapeutic effects was assessed by comparing the results of Tl-201 examinations with the clinical findings. Of these 33 patients, the therapeutic effects observed were as follows: complete remission 1, partial remission 8, progress of disease 1, and no remarkable change 23. Tl-201 scintigraphy has proved itself very useful not only in clinically detecting the malignant soft tissue sarcomas and in assessing therapeutic effects on these diseases, but also in assessing the follow-up patients with malignant soft tissue sarcomas.

Key words: neoplasm, soft tissue sarcomas, radionuclide diagnosis, Tl-201 scintigraphy, Ga-67 scintigraphy

INTRODUCTION

SOFT TISSUE SARCOMAS are relatively uncommon neoplasms. The poor prognosis of most patients with soft tissue sarcomas is due to its local recurrence (with or without hematogenous metastasis). However, a far greater problem is to diagnose a locally recurrent sarcoma, in contrast to a previously untreated one.[1] Such recurrences have often been identified as at an inoperable stage.

Radionuclide scans are not routinely used in the detection or management of soft tissue sarcomas. Radionuclide scanning with Tc-99m phosphate and Ga-67 demonstrates uptake in soft tissue tumors.[2–8] However, detection is hard to achieve and false-negative scans do occur.[4,5,9]

Some years ago, our team was able to present Tl-201 as an useful tumor seeking agent for malignant bone and soft tissue tumors.[10] The purpose of this study—a continuation of the former one—has been to investigate Tl-201 as a tumor scanning agent in patients with malignant soft tissue tumor, in order to establish this type of scintigraphy in its power to detect local recurrences that may not otherwise be clinically suspected. Such findings will be significant for patient management, since they may successfully alter the therapeutic procedure.

MATERIALS AND METHODS

From July, 1983 to August, 1989, 100 patients with soft tissue tumors were studied with Tl-201 chloride (Tl-201) scintigram at our National Cancer Center Hospital in Tokyo. There were 54 males and 46 females, averaging 44 years (from 3 to 84). Seventy-eight patients has malignant soft tissue sarcomas and 22 had benign soft tissue tumors (Tables 1 and 2). Of these 78 patients, there were 25 patients with liposarcoma, 17 patients with malignant fibrous histiocytoma (MFH), 10 patients with neurogenic sarcoma, 8 patients with leiomyosarcoma, 6 patients with synovial sarcoma, and the other 12 patients had malignant sarcomas. Diagnosis was determined histologically from the surgical and/or excisional specimens.

Of these 78 sarcoma patients, 28 were primary cases before treatment, 9 were distant metastatic cases (includ-

Received May 19, 1993, revision accepted November 19, 1993.

For reprint contact: Shoji Terui, M.D., Division of Nuclear Medicine, National Cancer Center Hospital, 5–1–1 Tsukiji, Chuo-ku, Tokyo 104, JAPAN.

Table 1 Patients with malignant soft tissue tumors

	No. of patients	Primary case	Recurrent case	Metastatic case	Rec. and Meta. case
Liposarcoma	25	6	16	3 (1)	
Malignant fibrous histiocytoma	17	8	8		1 (1)
Neurogenic sarcoma	10	5	4	1 (1)	
Leiomyosarcoma	8	2	1	2 (1)	3 (3)
Synovial sarcoma	6	1	3	1 (1)	1 (1)
Rhabdomyosarcoma	3	2	1		
Alveolar soft-part sarcoma	3	1		1 (1)	1 (1)
Clear cell sarcoma	2	1		1	
Angiosarcoma	2	1	1		
Fibrosarcoma	1	1			
Dermatofibrosarcoma protuberans	1	1			
Total	78	28	35	9 (5)	6 (6)

( ): Number of patients with lung metastasis

Table 2 Patients with benign soft tissue tumors

	No. of patients
Lipoma	5
Shwannoma	4
Giant cell tumor of tendon sheath	3
Hemangioma	1
Granular-cell tumor	1
Desmoid	4
Extraabdominal desmoid	1
Pigmented villonodullar synovitis	2
Ganglion	1
Total	22

ing 5 lung metastases), 6 were local recurrences together with lung metastases, and the other 35 were suspected cases of local recurrence after surgery. Of these 35 suspected cases, our clinical and/or surgical diagnosis has succeeded in proving 9 as having no local recurrence.

Thirty-three out of 78 patients received consecutive scintigraphic follow-up examinations with Tl-201. A total of 95 examinations were carried out, from a minimum of twice to maximum of 8 times per patient owing to the clinical characteristics of the cases in question. The therapeutic effects was assessed by comparing the results of Tl-201 examinations with the clinical findings. Scintigraphically, we followed up the patients and drew the following conclusions; 1. if there was no Tl-201 uptake by the tumor after treatments, complete remission (CR); 2. if there was decreased uptake of Tl-201 in the tumor or only a marginal uptake, partial remission (PR); 3. if there was no remarkable change in uptake on the Tl-201 scintigram, no change (NC); 4. if there was an increase in size and uptake of Tl-201 in the tumor, the tumor indicated progress of the disease (PD).

Our patients were given scintigrams in the following way: A dose of 3 mCi (111 MBq) of Tl-201 was administered intravenously and the scintigraphic images were taken 2 times; the first scintigram (early scintigram) was performed 5–10 minutes after the injection. The second (delayed scintigram) was taken 2–3 hours later, the purpose being evaluation of the influence of tumor vascularity. The collimator used is of the low-energy, parallel-hole type, and it gives at least 400,000 counts per image in the case of both the early and the delayed scintigram. With only the delayed scintigram, a whole body scintigram was obtained, while spot images were obtained with both the early and delayed scintigrams.

The uptake of Tl-201 in the tumor was compared in the early and delayed scintigram. For a final judgment on the Tl-201 uptake in a tumor, we always rely on the delayed scintigram.

For quantitative evaluation, counts of the image data of the spot image in a 64×64 matrix of the early and the delayed scintigram are stored for 5 minutes per image in a data analysis computer. In this case, Tl-201 accumulates in the tumor and can be recognized on the scintigram, and two regions of interest (ROI) are assigned to each image: first, over the tumor area, and second, over the background (BG). It is difficult to obtain an appropriate BG of a patient with a displaced location of the tumor, for example, on the leg, in the abdomen, or on the chest wall. And it is even harder to assign a correct BG to the muscle tissues because of increasing accumulation of Tl-201 there. What we do in our hospital is to assign BG circumstantially; if the tumor is localized in the leg, apparently the healthy leg is taken as the BG; there is always the possibility of muscle tissue having been affected. If the tumor is localized on the chest wall or near it—for example, in the upper arm or in the cervical region—the BG is assigned to the lung tissue. If the tumor is located in the abdominal region, the BG focuses on the abdominal wall excluding kidney and bowels. Of course, ROI of the BG for both the early and the delayed scintigram remains the same. For each ROI, the average count per pixel is determined by means of the computer.

The tumor-to-count ratio was determined by dividing the average per pixel count for the tumor by counts of the

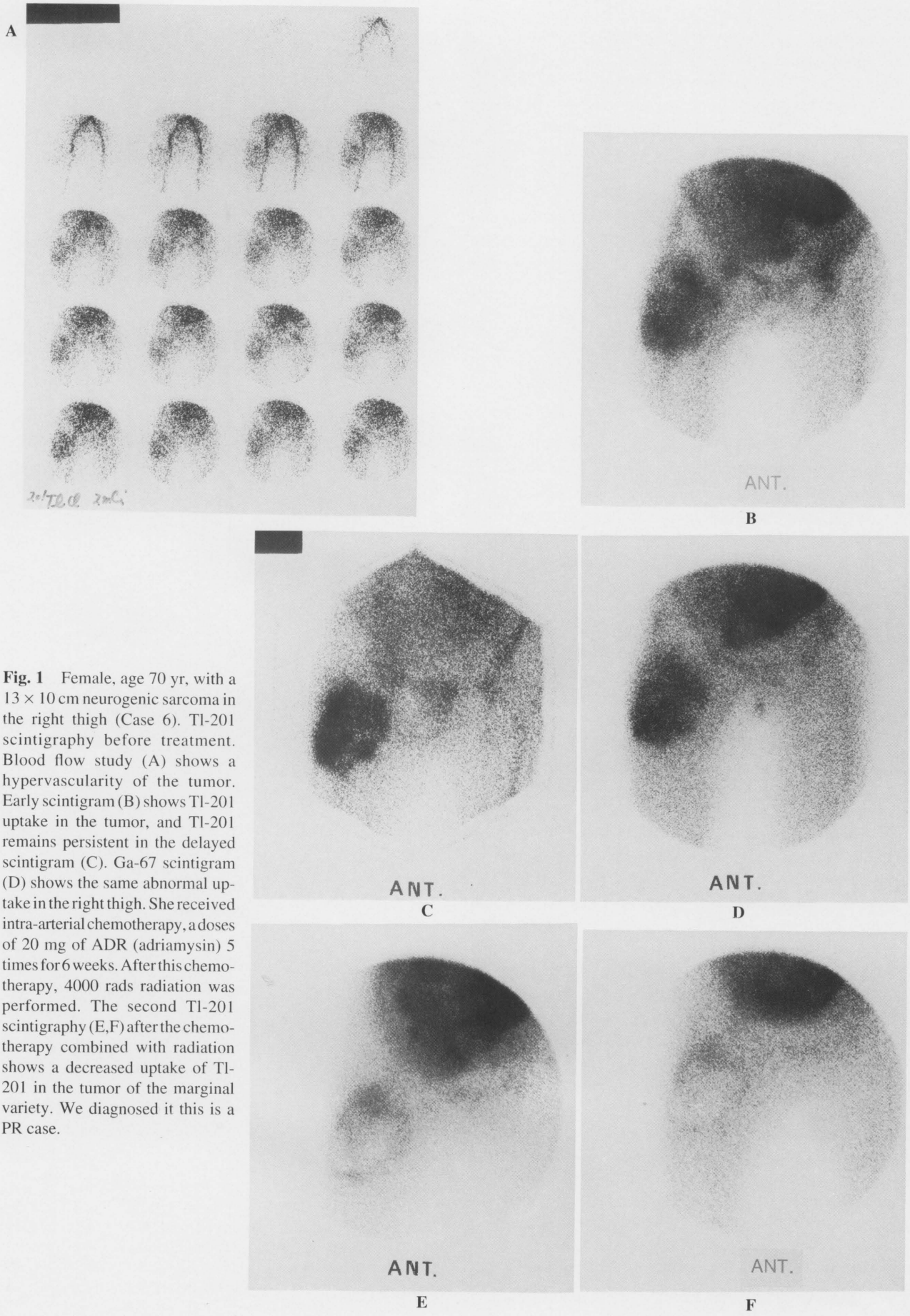


Fig. 1 Female, age 70 yr, with a 13 × 10 cm neurogenic sarcoma in the right thigh (Case 6). Tl-201 scintigraphy before treatment. Blood flow study (A) shows a hypervascularity of the tumor. Early scintigram (B) shows Tl-201 uptake in the tumor, and Tl-201 remains persistent in the delayed scintigram (C). Ga-67 scintigram (D) shows the same abnormal uptake in the right thigh. She received intra-arterial chemotherapy, a doses of 20 mg of ADR (adriamysin) 5 times for 6 weeks. After this chemotherapy, 4000 rads radiation was performed. The second Tl-201 scintigraphy (E,F) after the chemotherapy combined with radiation shows a decreased uptake of Tl-201 in the tumor of the marginal variety. We diagnosed it this is a PR case.

background. Finally to obtain statistical information, we compare the tumor-to-background count ratios (T/BG) of both the early and the delayed scintigram.

As stated at the beginning, our study comprised 6 years of research; but, unfortunately, due to unforeseen technical difficulties, such as preservation of the data-carrying magnetic tapes, we have been able to establish the uptake of Tl-201 in the tumor in only 44 patients out of 100. There were 31 patients with malignant soft tissue sarcomas and 13 with benign soft tissue tumors. We have acquired confidence in the usefulness of evaluating even such a limited number.

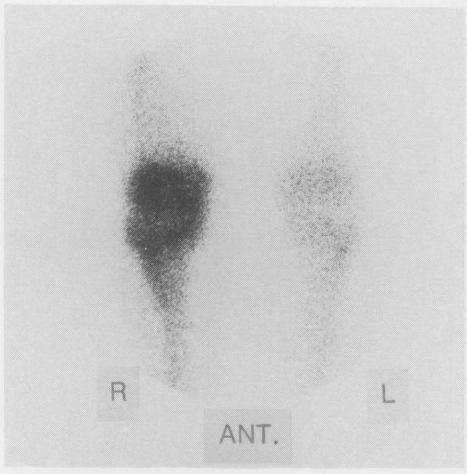
Thirty-five out of 100 patients were examined by Ga-67 citrate (Ga-67) scintigram within 2 weeks after the Tl-201 scintigram and the results were compared.

RESULTS

Tl-201 uptake in the tumor was stronger than the related background activity. Tl-201 uptake was registered in both the early and the delayed scintigram (Fig. 1 A,B,C). Concerning the malignant soft tissue sarcomas, there was one exception: a patient with MFH showed no uptake in the early scintigram but registered it in the delayed scintigram. On the other hand, 3 benign soft tissue tumor patients (one with extra-abdominal desmoid and the other 2 with pigmented villonodular synovitis) showed Tl-201 uptake in the early scintigram, while the delayed scintigram remained equivocal in 2 patients and no uptake was registered in a pigmented villonodullar synovitis patient (Fig. 2).

There was no significant difference in uptake compared with Ga-67 uptake in the tumors (Fig. 1D).

The clinical efficacy of Tl-201 and Ga-67 scintigram for detecting both primary tumors and the recurrent and metastatic tumors is shown in Tables 3 and 4. For each group, true-positive results predominated. The positive predictive value exceeded 90% in all 4 groups. The sensitivity exceeded 80% except in the recurrent and metastatic tumor of Ga-67 examinations (58.8%). No differences were observed among the primary tumors in Tl-201 scintigrams, the recurrent and metastatic tumors in Tl-201, or the primary tumors in the Ga-67 scintigram. Whereas the recurrent and metastatic tumors in Ga-67 scintigrams showed unsatisfactory results, its sensitivity and diagnostic accuracy were 58.8% and 60%, respectively (Table 4). False negatives occurred in each group. In the Tl-201 test for 28 primary tumors, 5 were false negative (2 liposarcoma, 2 neurogenic sarcoma, and 1 rhabdomyosarcoma). In the Ga-67 test for 15 primary tumors, 3 were false negative (1 liposarcoma, 1 neurogenic sarcoma, and 1 synovial sarcoma, respectively). In the Tl-201 test for 50 recurrent and metastatic tumors, 8 were false negative (5 lung metastasis, 1 liposarcoma, 1 synovial sarcoma, and 1 MFH, respectively). In the Ga-67 test for 20 recurrent and metastatic tumors, 7 were false



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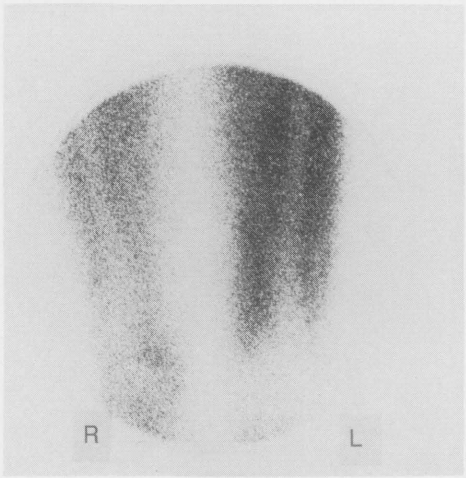

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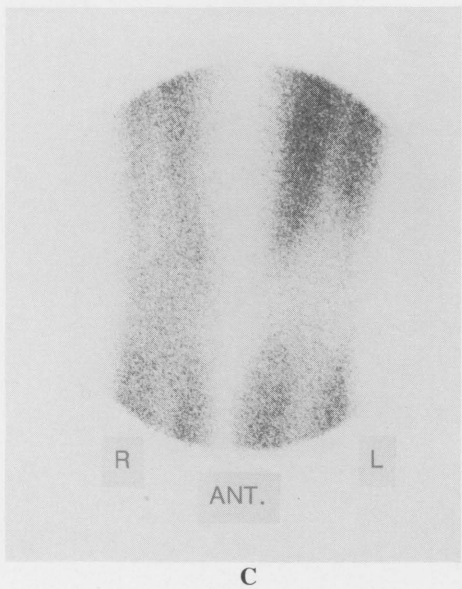

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Fig. 2 Female, 34 yr, with pigmented villonodullar synovitis of the right knee. Bone scintigram with Tc-99m HMDP (A) shows abnormal accumulation in the right knee. Early scintigram (B) shows a spotty uptake of Tl-201 in the lower right knee. It is rather obscure on the delayed sicntigram (C). T/M ratio of the early scintigram is 1.2 and 0.9 of the delayed scintigram.

Table 3 Clinical efficacy of Tl-201 for malignant soft tissue tumors

	Total	Primary tumors	Recurrent and Metastatic tumors
Number of Tests	78	28	50
Case of correct test: true positive (n)	56	23	33
true negative (n)	9	0	9
Case of test error: false positive (n)	0	0	0
false negative (n)	13	5	8
Positive predictive value (%)	100	100	100
Negative predictive value (%)	40.9	0	52.9
Sensitivity (%)	81.2	80	80.5
Specificity (%)	100	—	100
Diagnostic accuracy (%)	83.3	82.1	84

Table 4 Clinical efficacy of Ga-67 for malignant soft tissue tumors

	Total	Primary tumors	Recurrent and Metastatic tumors
Number of Tests	35	15	20
Case of correct test: true positive (n)	22	12	10
true negative (n)	2	0	2
Case of test error: false positive (n)	1	0	1
false negative (n)	10	3	7
Positive predictive value (%)	95.7	100	90.9
Negative predictive value (%)	16.7	0	22.2
Sensitivity (%)	68.8	80	58.8
Specificity (%)	66.7	—	66.7
Diagnostic accuracy (%)	68.6	82	60

Table 5 Sensitivity of Tl-201 for the malignant soft tissue tumors

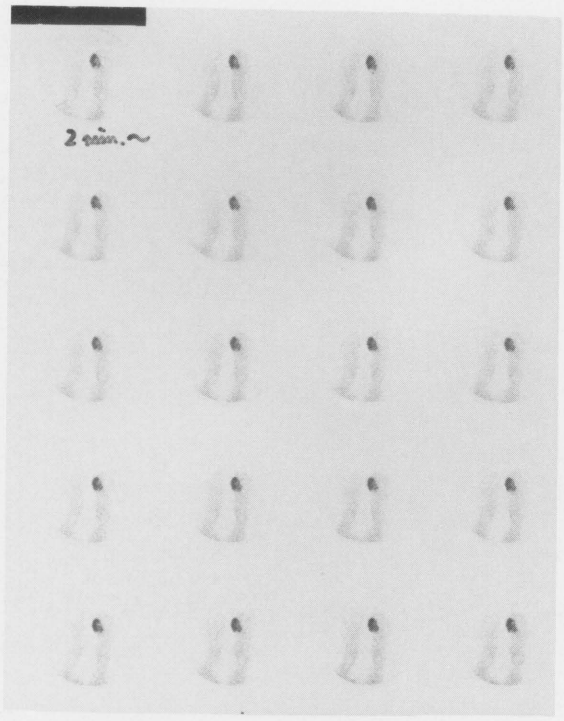
Disease	Tl-201 (%)	Ga-67 (%)
Liposarcoma	78.9 (15/19)	40 (4/10)
Malignant fibrous histioccytoma	94.1 (16/17)	100 (6/6)
Neurogenic sarcoma	55.6 (5/9)	66.7 (4/6)
Leiomyosarcoma	100 (8/8)	100 (5/5)
Synovial sarcoma	50 (2/4)	0 (0/3)
Rhabdomyosarcoma	66.7 (2/3)	100 (2/2)
Alveolar soft-part sarcoma	66.7 (2/3)	100 (1/1)
Clear cell sarcoma	100 (2/2)	100 (1/1)
Angiosarcoma	100 (2/2)	NT
Fibrosarcoma	100 (1/1)	100 (1/1)
Dermatofibrosarcoma protuberans	100 (1/1)	NT
Average	81.2 (56/69)	68.6 (24/35)

NT: Not Tested

negative (5 liposarcoma and 2 synovial sarcoma). Overall sensitivity of the very first examination by the Tl-201 as well as the Ga-67 scintigrams was 81.2% and 68.8%, respectively. However, the overall specificity of this first examination was 100% and 66.7%, respectively.

The difference in sensitivity seems to related to the kind of sarcoma (Table 5). There was 100% sensitivity both with Tl-201 and Ga-67 in patients with clear cell sarcoma, leiomyosarcoma, and fibrosarcoma. There was also 100% sensitivity with Ga-67 in 6 patients with MFH, 2 with rhabdomyosarcoma, and 1 with alveolar soft part sarcoma. Liposarcoma showed a higher sensitivity for Tl-201 (78.9%) than for Ga-67 (40%), and synovial sarcoma showed 50% sensitivity with Tl-201 as against 0% with Ga-67.

Concerning the benign soft tissue tumors, 7 patients showed Tl-201 uptake in the tumor (Table 6). Of this 7, 3 patients were suffering from desmoid (3/4) and the other 4 from giant cell tumor of the tendon sheath (2/3), shwannoma (1/4), and granular cell tumor (1/1), respectively (Fig. 3). No uptake was found in lipoma or hemangioma. Equivocal uptake was noticed in 1 patient



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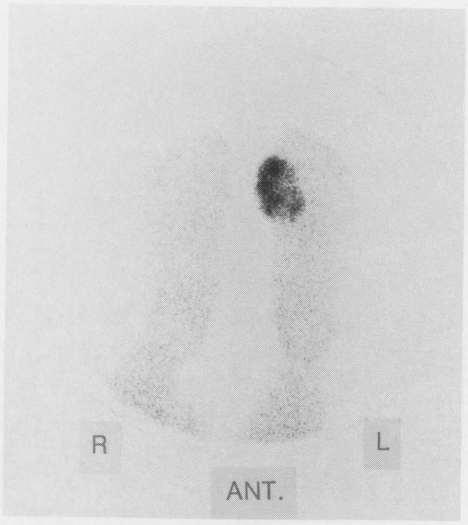

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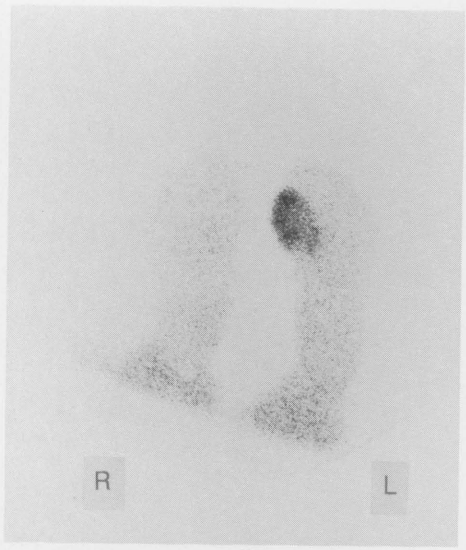

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Fig. 3 Female, 43 yr, with giant cell tumor of tendon sheath of the left toe. Blood flow study (A) and the early (B) and the delayed scintigram (C) shows Tl-201 uptake in the tumor.

Table 6 Results of Tl-201 uptake in the benign soft tissue tumors

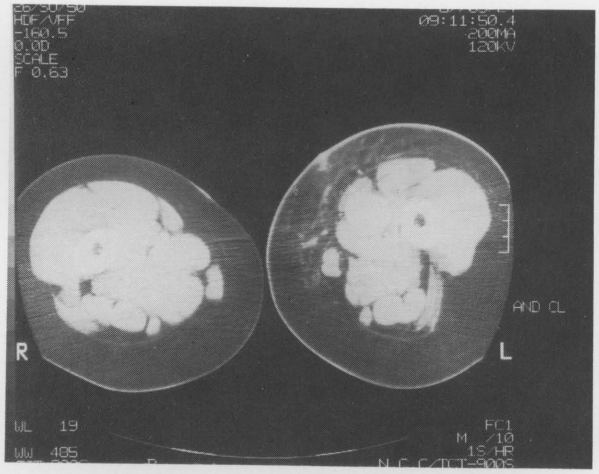
	No. of Pt.	Positive	Negative	Equivocal
Lipoma	5	0	5	
Shwannoma	4	1	3	
Giant cell tumor of tendon sheath	3	2	1	
Hemangioma	1	0	1	
Granular-cell tumor	1	1	0	
Desmoid	4	3	1	
Extraabdominal desmoid	1	0	0	1
Pigmented villonodullar synovitis	2	0	1	1
Ganglion	1	0	1	
Total	22	7	13	2

with extraabdominal desmoid tumor and 1 with pigmented villonodullar synovitis. Positive uptake of Tl-201 in the benign soft tissue tumors was 31.8% (7/22). There is a significant difference from those of malignant soft tissue sarcomas ($p < 0.01$).

The T/BG ratio was calculated from the visualized tumors on the Tl-201 scintigram. The average background count per pixel was 106 with the early scintigram and 130 with the delayed scintigram. Comparing the average count per pixel for the early and the delayed scintigram, the average count was increased in all regions except for pulmonary ones. Malignant soft tissue sarcomas showed a higher ratio than benign soft tissue tumors. The average ratio of malignant soft tissue sarcomas was 2.51 with the early scintigram and 1.89 with the delayed one. It was 1.5 and 1.3, respectively, in the case of benign soft tissue tumors. There was no difference in the T/BG ratio related to the histologic type of the sarcoma.

There were 11 patients whose lung metastases were detected by radiographs and/or CT scanning. Three of them were solitary metastatic cases and the other 8 were multiple ones. Of the 11, 6 patients had local recurrences and 5 had none. All the recurrent lesions in these 6 patients showed Tl-201 uptake and were diagnosed. But in the case of lung metastasis none of the 11 patients showed signs of Tl-201 uptake in the lung tumors (Fig. 4).

Thirty-three out of 78 patients received a total of 95 consecutive scintigraphic follow-up examinations. In these



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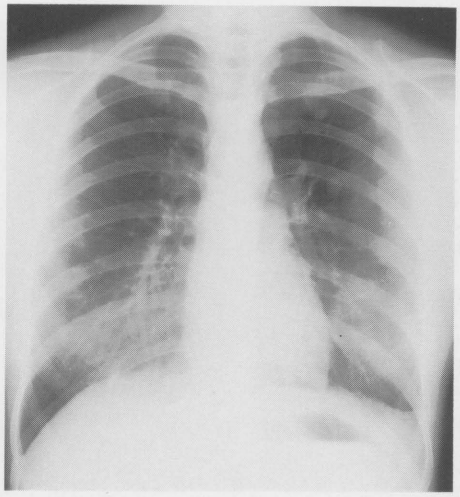

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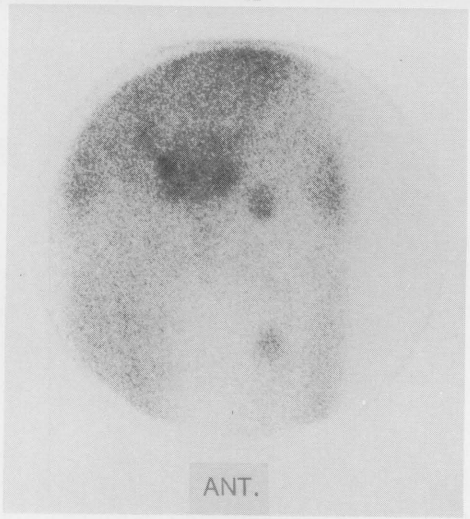

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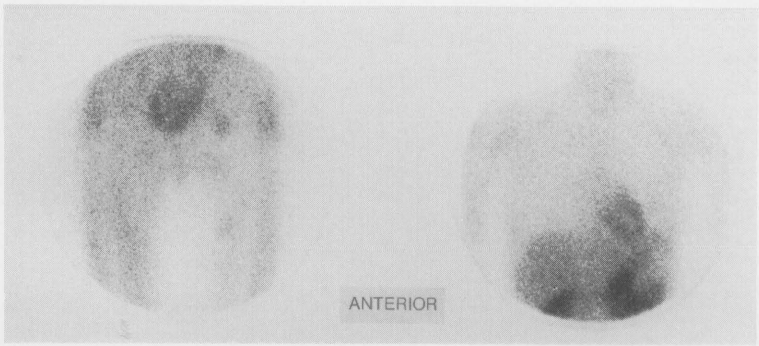

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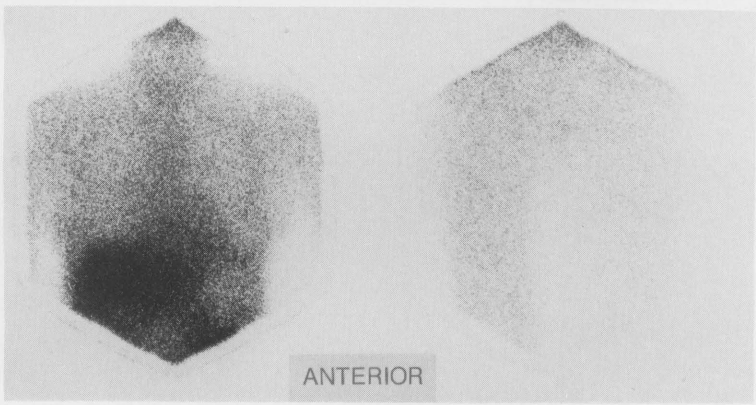

Fig. 4 Female, 24 yr, with a local recurrence of synovial sarcoma and lung metastases. CT scan (A) abnormal mass in the left thigh and chest X-ray (B) shows multiple lung metastases. Early scintigram (C) shows 2 abnormal accumulations in the left thigh. Delayed scintigram (D) shows the same accumulations (left) but shows no abnormal uptake in the lung (right). Ga-67 scintigram (E), a week after the Tl-201 examination, shows no uptake in both the tumors and the lung metastases. T/BG ratio of the early and the delayed scintigram is 1.29 and 1.09, respectively.

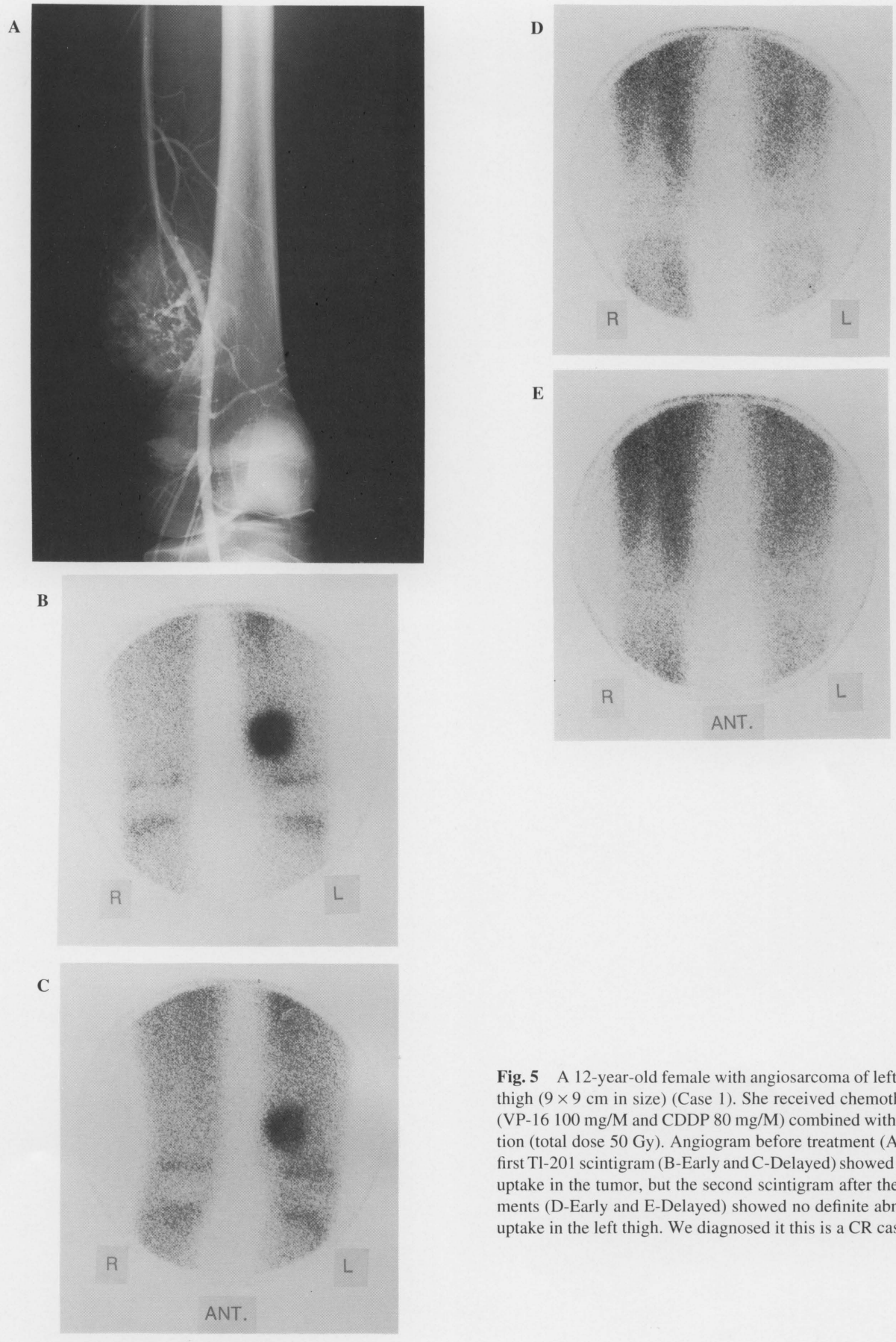

Fig. 5 A 12-year-old female with angiosarcoma of left lower thigh (9 × 9 cm in size) (Case 1). She received chemotherapy (VP-16 100 mg/M and CDDP 80 mg/M) combined with radiation (total dose 50 Gy). Angiogram before treatment (A). The first Tl-201 scintigram (B-Early and C-Delayed) showed strong uptake in the tumor, but the second scintigram after the treatments (D-Early and E-Delayed) showed no definite abnormal uptake in the left thigh. We diagnosed it this is a CR case.

Table 7 Results of Tl-201 scintigraphy during radiation combined with or without chemotherapy

Case	Sex Age	Extent of Diagnosis	Disease	Treatments	Tl-201 scintigram		Therapeutic effects
					Before	After	
1.	M/12	Angiosarcoma	Lt. knee	VP-16, CDDP Radiation	(+)	No uptake	CR
2.	F/53	Liposarcoma	Lt. thigh	SM 5887	(+) Central defect	Marginal uptake	PR
3.	M/34	MFH	Lt. hip	VCR, ADR DTIC	(+)	Decreased uptake	PR
4.	M/80	MFH	Lt. thigh	Radiation	(+)	Marginal uptake	PR
5.	F/75	MFH	Lt. thigh	SM 5887 Radiation	(+) Irregular	Marginal uptake	PR
6.	F/70	Neurogenic sarcoma	Rt. thigh	ADR Radiation	(+)	Marginal uptake	PR
7.	M/26	Leiomyosarcoma recurrent	Lt. chest wall	EX, VCR, ADR, DTIC Radiation	(+)	Decreased uptake	PR
8.	M/36	Leiomyosarcoma	Lt. leg	EX, ADR, VCR, DTIC Radiation	(+)	Marginal uptake	PR
9.	F /19	Rhabdomyosarcoma	Rt. buttock	VCR, EX, ADR Radiation	(+)	Marginal uptake	PR
10.	M/83	Liposarcoma	Lt. thigh	Radiation	(+)	Increased uptake	PD

VP-16 = Etoposide; CDDP = Cisplatin; SM 5887 = Derivative of Adriamysin; VCR = Vincristine; ADR = Adriamysin; DTIC = Dacarbazine; EX = Cyclophosphamide; (+); Tl-201 uptake in the tumor

33 patients, the following therapeutic effects were observed: complete remission (CR) in 1 (Fig. 5), partial remission (PR) in 8 (Fig. 1 D, E), progress of disease in 1, and no remarkable change (NC) in 23 (Table 7).

DISCUSSIONS

Tl-201 scintigraphy has been used on many malignant neoplasms such as thyroid cancer, ovarian cancer, lung cancer, and soft tissue sarcomas.[11-17] Unlike Ga-67, Tl-201 scintigram needs no premedication and images can be easily obtained on the day of the injection. Of course, a Ga-67 scintigram can be useful in differentiating between sarcoma and benign non-inflammatory conditions, but it is a far more difficult to diagnose a locally recurrent sarcoma, in contrast to a previously untreated one,[1] because soft tissue sarcomas and inflammatory lesions will show increased uptake of Ga-67. A Ga-67 scintigram will not provide a clear diagnosis as to possible recurrence. Tl-201, in contrast with Ga-67, does not accumulate in the inflammatory lesions caused by such treatments as surgery and/or radiation. Our follow-up cases revealed Tl-201 uptake by the tumor itself. Tl-201 scintigrams showed no false positive at all and there was 100% specificity (Table 3). Concerning the tumor lesion itself, especially in recurrent and metastatic cases, the sensitivity of Tl-201 (80.5%) was higher than that of Ga-67 (58.8%) (Tables 3 and 4).

Tl-201 scintigraphy has proved very useful in assessing therapeutic effects in these malignant soft tissue sarcomas. To assess the therapeutic effects, pathological findings for the tumor are essential. However, it is very difficult to perform a biopsy especially in recurrent cases of malignant soft tissue tumors. So we observed the therapeutic effects in the results of Tl-201 examinations and the clinical findings (Table 7). By means of Tl-201 scintigraphy, we were able to follow up the patients with the malignant soft tissue tumors and to assess the effects of the treatments (Figs. 1, 5, and Table 7). In this respect, we think Tl-201 scintigram is clinically very useful and a rather handy examination tool for follow-up patients with malignant soft tissue tumors.

There is a difference in sensitivity among the histological types of malignant soft tissue sarcomas (Table 5). There was 100% sensitivity in patients with leiomyosarcoma. MFH showed a higher sensitivity (94. 1%) than liposarcoma (78.9%). Both neurogenic sarcoma and synovial sarcoma showed a lower sensitivity than the other malignant soft tissue sarcomas. As yet, we do not know the reason for the difference in sensitivity of Tl-201.

Concerning the visualization itself, we were not able to find a significant difference between the early and delayed scintigrams. However, we noted exception: 3 benign soft tissue tumor patients showed Tl-201 uptake in the early scintigram, while the delayed scintigram remained equivocal (Fig. 2). On the other hand, a MFH patient showed no uptake in the early scintigram but registered it in his delayed scintigram. There seems to be a different uptake

pattern in the malignant soft tissue sarcomas and benign soft tissue tumors. In this respect, malignant soft tissue sarcomas can be distinguished from benign soft tissue tumors.

While practically every other metastatic lesion could be seen, those of lung metastases could not be seen on Tl-201 scintigraphy. As yet we do not know the reason for this. Tonami et al. stated that a Tl-201 planar scintigram is inadequate for imaging lung tumors[18] and they suggested that we should rather take SPECT images.

The mechanism of Tl-201 uptake by the tumor is probably dependent on both blood flow and the permeability of Tl-201 through the cell membranes. We think that the higher T/BG ratio in the early scintigram than in the delayed T/BG represents rich blood flow in the tumor. On the other hand, the T/BG ratio of the delayed scintigram is higher than 1; in fact it is 1.89, which seems to suggest that there exists an uptake mechanism in the malignant soft tissue sarcoma cells revealed by increased Tl-201 permeability of the cell membranes as well as the another mechanism binding to cytoplasm.

Although there is as yet not a relatively limited number of examined patients to allow us to conclude more generally, Tl-201 scintigram has proved its value in the detection of malignant primary or recurrent/metastatic soft tissue sarcomas. It is also of marked value in the assessment of therapeutic effects (chemotherapy combined with radiation) in these cases.

ACKNOWLEDGMENT

This research was supported by Nihon Medi-Physics Co., Ltd., Japan.

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