Annals of Nuclear Medicine Vol. 19, No. 6, 461–468, 2005

Thallium-201 scintigraphy in bone and soft-tissue tumors: a comparison of dynamic, early and delayed scans

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Objective: It has been reported that delayed scan of thallium-201 (^{201}Tl) scintigraphy is useful for differentiating malignant tumors from benign lesions and for evaluating treatment response. However, physiological muscle uptake which usually increases in delayed scans, often makes it difficult to evaluate ^{201}Tl uptake and its washout in bone and soft-tissue tumors. The purpose of this study was to evaluate whether the delayed scan is necessary and whether a dynamic scan is useful in the evaluation of bone and soft-tissue tumors. ***Methods:*** We studied 175 cases of bone and soft-tissue tumors (malignant 45, benign 130). Dynamic scans were acquired every 5 seconds for 10 minutes after ^{201}Tl injection, and time activity curves (TACs) were generated by adaptive smoothing methods. Early and delayed scans were acquired at 10–15 minutes and 2 hours after injection. ^{201}Tl images were visually interpreted and the radioactivity count ratio (T/N) of tumors to normal tissues and washout rate [WR = (early T/N – delayed T/N)/early T/N] were defined. ***Results:*** When there were no ^{201}Tl uptake in dynamic (n = 67) and early scans (n = 68), no tumor uptake was also appreciated in delayed scans, and all but two cases of negative scans were benign. In 107 lesions, although there were significant differences in T/Ns between malignant and benign lesions both on early scans (2.84 ± 1.45 vs. 2.05 ± 1.13, $p < 0.05$) and delayed scans (2.17 ± 1.03 vs. 1.58 ± 0.64, $p < 0.05$), there was a substantial overlap. The T/Ns decreased in delayed scans (i.e., WR > 0) in 100 of 107 cases due to increase of surrounding muscle uptake, and there was no difference in WR between malignant tumors and benign lesions (0.21 ± 0.14 vs. 0.19 ± 0.14). ***Conclusions:*** For evaluating bone and soft-tissue tumors, delayed scan had little clinical usefulness and it may be time consuming. Dynamic scan would be useful for demonstrating the differences between tumor blood flow and ^{201}Tl uptake in tumors.

Key words: bone tumor, soft-tissue tumor, thallium-201, dynamic scan, delayed scan

INTRODUCTION

IT HAS BEEN REPORTED that thallium-201 (^{201}Tl) scintigraphy is useful for differentiating malignant from benign lesions and for evaluating therapeutic response in various tumors.[1–9] In general, both early and delayed scans of ^{201}Tl are acquired and the washout (or retention) of ^{201}Tl is evaluated. Delayed scan and washout rate (or retention index) are reportedly more useful than early scan for differentiating benign from malignant tumors and for evaluating therapeutic response in patients with brain, thyroid and lung tumors.[1,10–14]

However, the usefulness of delayed scans in bone and soft-tissue tumors has not been sufficiently evaluated and remains controversial.[4,6,7,15] ^{201}Tl uptake is not specific for malignant lesions; indeed some benign tumors and inflammatory lesions in bone and soft-tissues could show substantial ^{201}Tl uptake,[16–18] while some malignant tumors such as chondrosarcoma may show low or no ^{201}Tl uptake.[19] Physiological muscle uptake especially in the

Received March 2, 2005, revision accepted May 27, 2005.
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Table 1 Final diagnosis of 175 cases and Tl-201 uptake in dynamic scan

Diagnosis	No. of cases	Tl-201 uptake in dynamic scan			
		Negative	Positive		
			Decrease	Plateau	Increase
Malignant	45 (4)	2	6	33 (3)	4 (1)
Osteosarcoma	18	1	2	14	1
Liposarcoma	7		2	5	
Leiomyosarcoma	4			3	1
Angiosarcoma	2			2	
PNET*	2	1		1	
Chondrosarcoma	1			1	
Rhabdomyosarcoma	1			1	
Lymphoma	1			1	
MPNST**	1			1	
Ewing sarcoma	1		1	1	
Metastatic bone tumor	7 (4)		1	4 (3)	2 (1)
Benign	130 (75)	65 (52)	12 (4)	47 (19)	6
Post-therapeutic lesion	26 (24)	17 (17)		9 (7)	
Lipoma	15 (9)	12 (7)	2 (1)	1 (1)	
Inflammatory granuloma	13 (4)	3 (2)		8 (2)	2
Hemangioma	11 (5)	5 (3)	3 (1)	3 (1)	
Fibrous dysplasia	10 (7)	4 (4)		4 (3)	2
Giant cell tumor	8	1		6	1
Ganglion	7 (4)	2 (1)	2 (1)	2 (2)	1
Non-ossifying fibroma	4 (4)	3 (3)		1 (1)	
Neurofibroma	3 (1)	1 (1)		2	
Nodular fasciitis	2			2	
Desmoid tumor	2	1		1	
Neurinoma	1			1	
Schwannoma	1			1	
Aneurysmal bone cyst	1			1	
Lymphangioma	1	1			
Leiomyoma	1			1	
Osteochondroma	1		1		
Synovial osteochondromatosis	1		1		
Osteoid osteoma	1			1	
Benign mesenchymoma	1		1		
Myxoma	1		1		
Gauzeoma	1	1			
Pilomatricoma	1			1	
Not available #	17 (17)	14 (14)	1 (1)	2 (2)	

Numbers in parentheses are cases clinically diagnosed.
* primitive neuroectodermal tumor
** malignant peripheral nerve sheath tumor
# Final diagnosis is not available, but defined as benign on clinical follow-up of at least 6 months.

Table 2 Comparison of Tl-201 uptake among dynamic, early and delayed scans

Diagnosis	Tl-201 uptake					
	Dynamic		Early		Delayed	
	Positive	Negative	Positive	Negative	Positive	Negative
Malignant	43	2	43	2	43	2
Benign	65	65	64	66	60	70

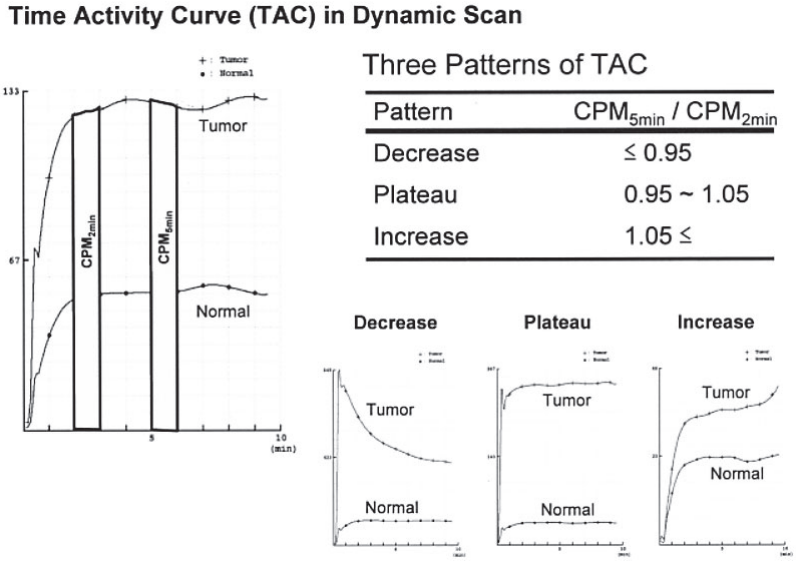


Fig. 1 Analysis of time activity curve (TAC) in dynamic scan. We classified the TACs in tumors into three patterns by the ratios of CPM_{5min} to CPM_{2min} (CPM: count per minute) in tumor: "decrease pattern" if $CPM_{5min}/CPM_{2min} \leq 0.95$, "plateau pattern" if $0.95 < CPM_{5min}/CPM_{2min} < 1.05$, and "increase pattern" if $1.05 \leq CPM_{5min}/CPM_{2min}$.

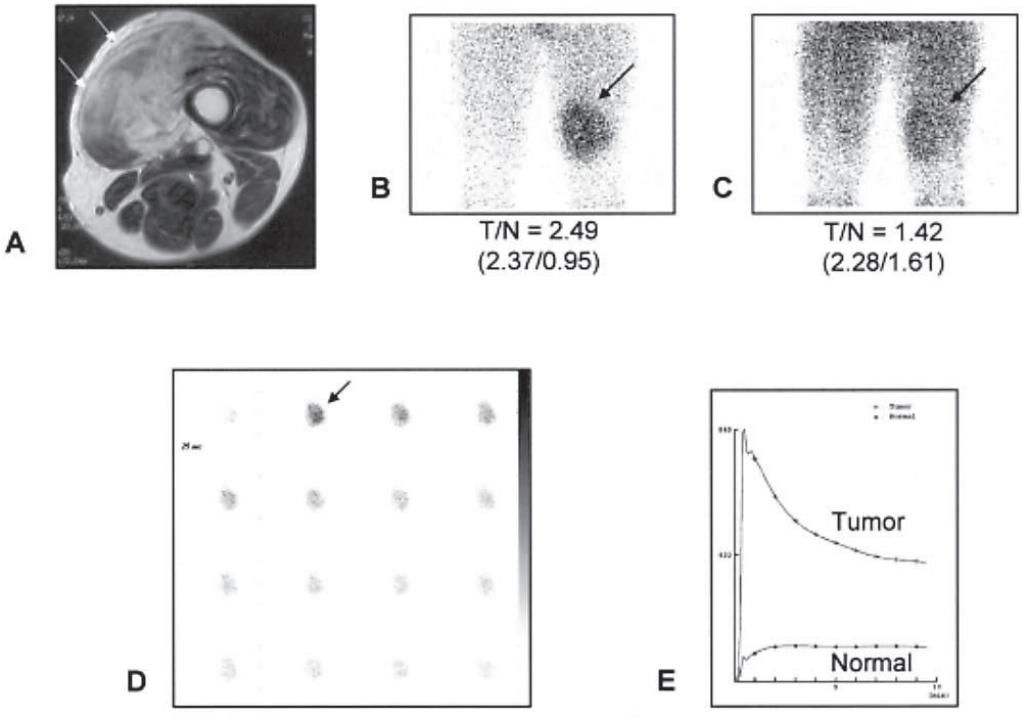


Fig. 2 Intramuscular hemangioma of left vastus medialis muscle in a 37-year-old man. (A) Malignant soft-tissue tumor is initially suspected by MRI (*arrows*, T2-weighted image). (B) Early scan of ^{201}Tl shows increased uptake in tumor (*arrow*). (C) In delayed scan, the tumor uptake (*arrow*) is obscured by increased surrounding normal muscle uptake. Dynamic scans (D) and time activity curve (E) clearly demonstrate "decrease pattern" in the tumor with relatively low uptake in surrounding normal muscle.

extremities, which usually increases in the delayed scan, often makes it difficult to evaluate the uptake and washout of ^{201}Tl in bone and soft-tissue tumors. In this study, we compared dynamic scans, early scans and delayed scans in bone and soft-tissue tumors, and evaluated whether the delayed scan is necessary and whether a dynamic scan is useful for evaluating bone and soft-tissue tumors.

MATERIALS AND METHODS

We evaluated 175 patients with diagnosed or suspected bone and soft-tissue tumors. There were 84 males and 91 females, and patients' ages ranged from 8 to 89 with a mean of 43 ± 21 years. Final diagnoses were malignant in 45 and benign in 130, which were obtained by

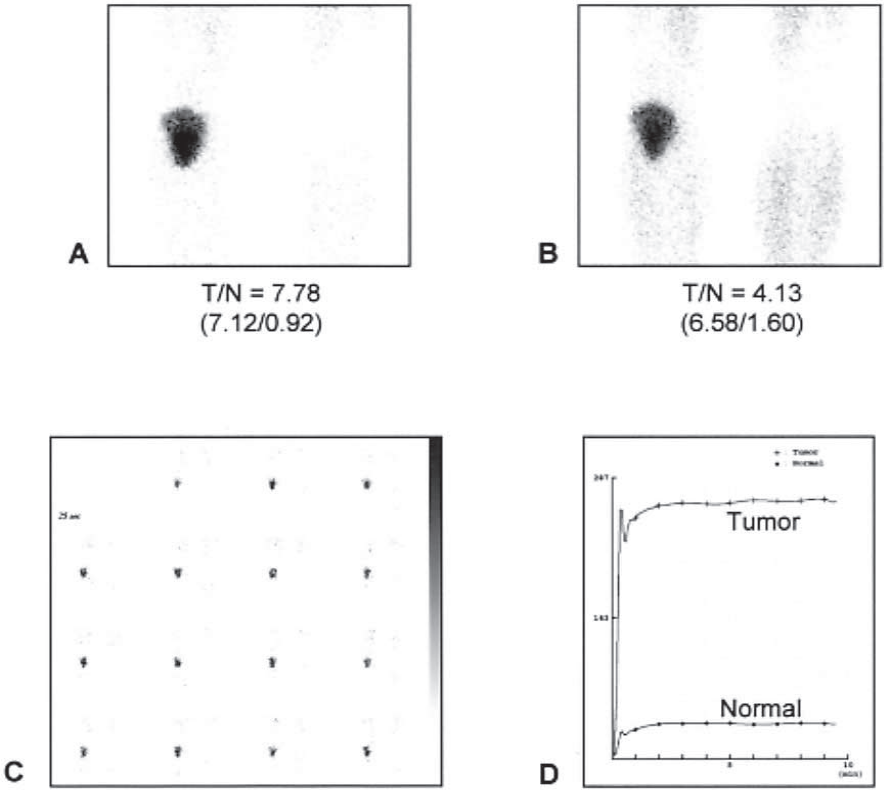


Fig. 3 Giant cell tumor of right proximal tibia in a 56-year-old woman. (A) Early scan shows intense uptake in the tumor. (B) In delayed scan, the uptake ratio (T/N) of tumor (T) to normal tissue (N) decreases mainly due to increase of normal muscle uptake. Dynamic scans (C) and time activity curve (D) clearly demonstrate that ^{201}Tl is delivered by blood flow and rapidly taken up in tumor, and the uptake remains constant.

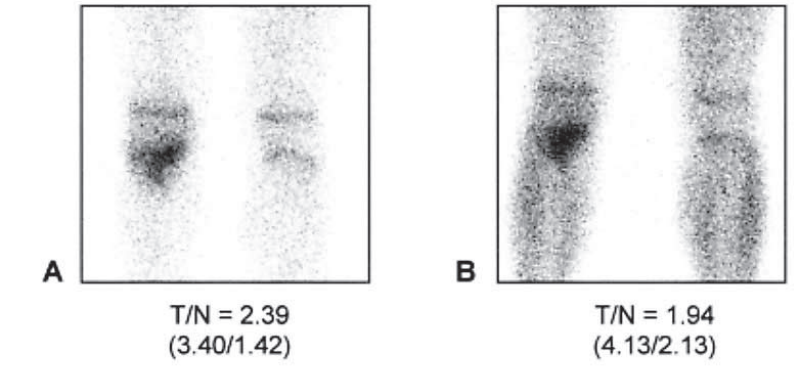
histopathological examination (n = 96: malignant 41, benign 55) or clinical follow-up of at least 6 months (n = 79: malignant 4, benign 75) (Table 1). A total of 37 post-therapeutic lesions were included, in which ^{201}Tl scintigraphy was performed to evaluate treatment response and to differentiate tumor recurrence/remnant from post-therapeutic changes. Informed consent was obtained from all patients or/and their relatives after detailed explanation of the examinations.

Dynamic scans were acquired every 5 seconds for 10 minutes after 74 MBq of ^{201}Tl injection using a gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator in a 128 × 128 matrix. Early scans were acquired after the completion of dynamic scans (at 10–15 minutes after injection) and the delayed scans were acquired at 2 hours after injection. Both the static scans (early and delayed scans) were acquired with a gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator in a 512 × 512 matrix for 7 minutes.

^{201}Tl images were interpreted by two nuclear medicine physicians and the uptake in tumors was defined as positive (increased uptake rather than contralateral or adjacent normal tissues) or negative (decreased uptake or not detectable) by the consensus reading, with reference to other radiological images (such as CT and MRI) if available. When ^{201}Tl uptake in tumor was appreciated, a region of interest (ROI) was drawn manually on the whole lesion of tumor and a copy of the same ROI was placed on the contralateral or adjacent normal tissue. On the dynamic images, time activity curves (TACs) in tumors and those in normal tissues were generated by adaptive smoothing methods.[20] We classified the TACs in tumors into three patterns by the ratios of CPM_{5min} to CPM_{2min} ($CPM_{5\,min}$ = count per minute during 5 and 6 minutes after injection): "decrease pattern" if $CPM_{5min}/CPM_{2min} \leq 0.95$, "plateau pattern" if $0.95 < CPM_{5min}/CPM_{2min} < 1.05$, and "increase pattern" if $1.05 \leq CPM_{5min}/CPM_{2min}$ (Fig. 1). Radioactivity count ratios (T/N) of tumors to normal tissues were obtained both in the early scans (ER: early ratio) and in the delayed scans (DR: delayed ratio), and the washout rate (WR) was determined as follows: WR = (ER – DR)/ER.

RESULTS

On the visual analysis of dynamic scans, there were positive ^{201}Tl uptake in 108 cases (malignant 43, benign



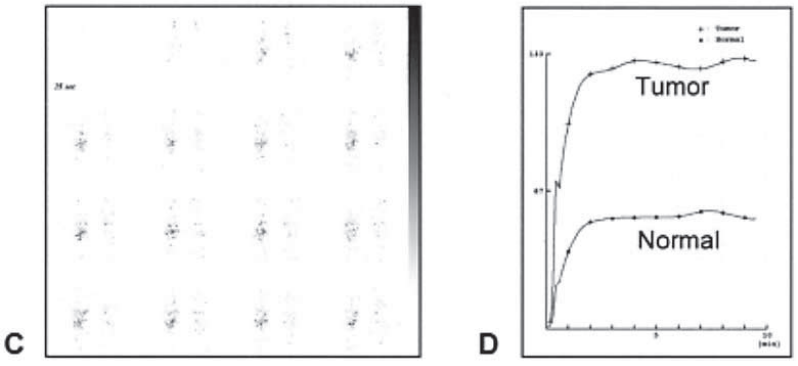
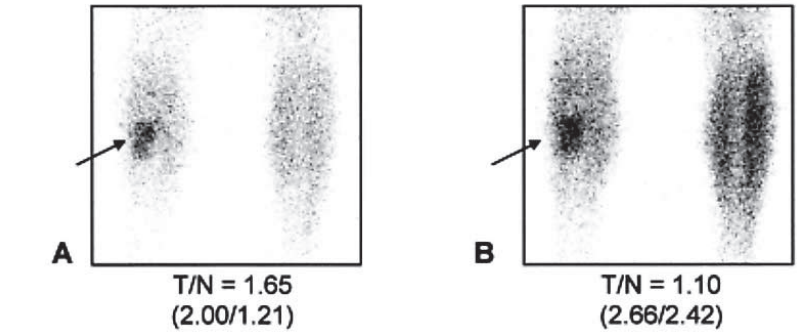


Fig. 4 Osteosarcoma of right proximal tibia in a 14-year-old boy. (A) Early scan shows intense uptake in the tumor. (B) In delayed scan, the uptake ratio (T/N) of tumor (T) to normal tissue (N) decreases mainly due to increase of surrounding normal muscle uptake. Dynamic scans (C) and time activity curve (D) demonstrate rapid uptake in the tumor and no change ("plateau pattern") until the early scan.



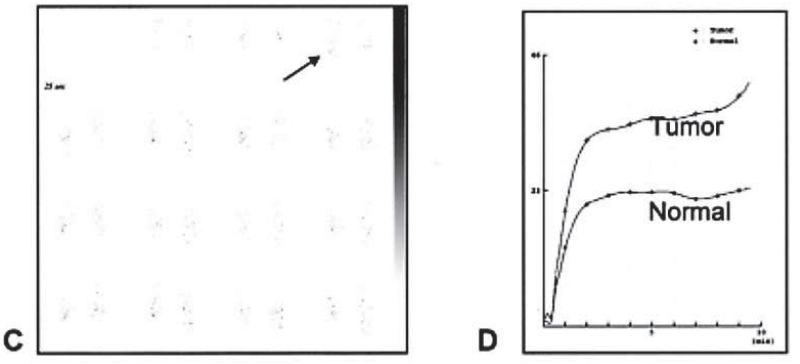


Fig. 5 Fibrous dysplasia of right proximal tibia in a 56-year-old woman. (A) Early scan and (B) delayed scan show increased uptake in the tumor, while the uptake ratio (T/N) of tumor (T) to normal tissue (N) decreases in the delayed scan due to substantial increase of surrounding normal muscle uptake. Dynamic scans (C) and time activity curve (D) show "increase pattern" in the tumor.

65) and negative uptake in 67 cases (malignant 2, benign 65) (Table 1). When there was no ^{201}Tl uptake in dynamic scans and early scans, no tumor uptake was also appreciated in delayed scans (Table 2). All but two cases of negative scans were benign: a case of primitive neuroectodermal tumor in the buttock with massive necrosis and a case of osteosarcoma after chemotherapy (extensive tumor necrosis but some viable tumor remnant) showed

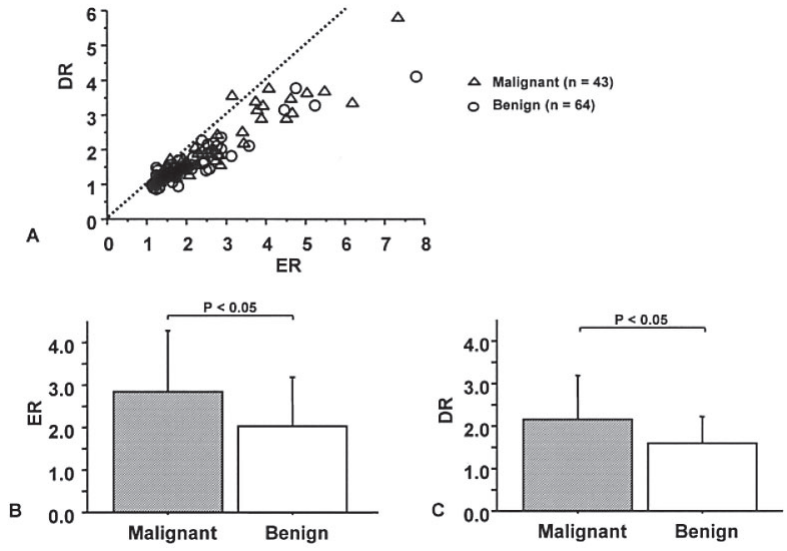


Fig. 6 Scattergram (A) and comparisons of ERs (B) and DRs (C) between malignant and benign bone and soft-tissue lesions. DRs are lower than ERs in most of cases (A), and there are significant differences both in the ERs (2.84 ± 1.45 vs. 2.05 ± 1.13, $p < 0.05$) and DRs (2.17 ± 1.03 vs. 1.58 ± 0.64, $p < 0.05$) between malignant tumors and benign lesions (B, C). However, it seems to be difficult to differentiate malignant tumor from benign lesions, since there are substantial overlaps between the two groups.

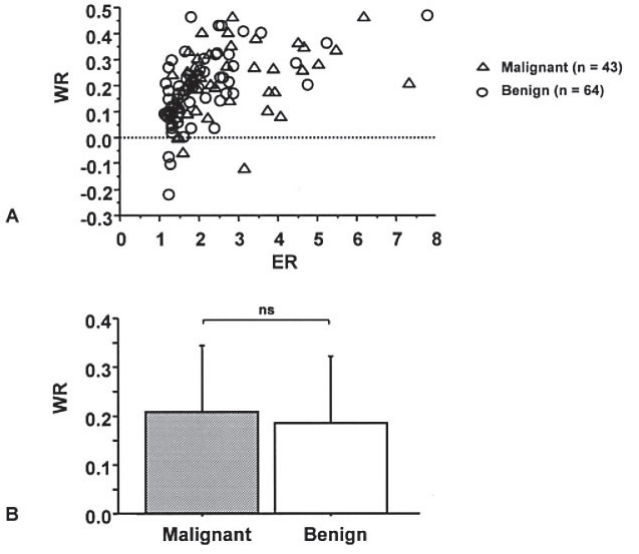


Fig. 7 Scattergram (A) and comparison of WRs (B) between malignant and benign bone and soft-tissue lesions. (A) In most cases (except 7 cases), WRs are positive (WR > 0, i.e., DRs are lower than ERs as shown in Fig. 6A), mainly due to increase of surrounding normal muscle uptake. (B) There is no difference in WRs between malignant tumors and benign lesions (0.21 ± 0.14 vs. 0.19 ± 0.14).

negative ^{201}Tl uptake on all images of dynamic, early and delayed scans. In 108 cases of positive uptake in dynamic scans, the TAC showed "decrease pattern," i.e. early peak and washout in 18 cases (malignant 6, benign 12) (Fig. 2) (Table 1). In most cases (80 cases: malignant 33, benign 47), the TAC demonstrated "plateau pattern," i.e. the early peak within initial 2–3 minutes and no remarkable change until the early scans (Figs. 3, 4) (Table 1). In the remaining 10 cases (malignant 4, benign 6), the TAC showed "increase pattern," i.e. gradual increase and no peak during the dynamic scans (Fig. 5) (Table 1).

The T/Ns both in the early and delayed scans were compared in 107 cases (malignant 43, benign 64). There were significant differences in the T/Ns between malignant tumors and benign lesions both in the ERs (2.84 ± 1.45 vs. 2.05 ± 1.13, $p < 0.05$) and in the DRs (2.17 ± 1.03 vs. 1.58 ± 0.64, $p < 0.05$). However, substantial overlaps were observed (Fig. 6). In most cases (except for 7 cases), the T/Ns decreased in the delayed scans (i.e., WR > 0) mainly due to the increase in surrounding normal muscle uptake. The ^{201}Tl uptake in surrounding normal muscles increased in the delayed scans with a mean percentage of 43 ± 23% (the range of 0% to 111%). The WRs below zero (i.e., T/Ns increased in delayed scans) were seen in 4 malignant tumors of metastatic bone tumor, leiomyosarcoma, osteosarcoma and Ewing sarcoma, and in 3 benign lesions of lipoma, ganglion and neurofibroma. There was no difference in the WR between malignant tumors and benign lesions (0.21 ± 0.14 vs. 0.19 ± 0.14) (Fig. 7).

DISCUSSION

In patients with brain, thyroid and lung tumors, delayed scan and washout rate (or retention index) of ^{201}Tl are reportedly more useful than early scan for differentiating malignant tumors from benign lesions and for evaluating therapeutic response.[1,10–14] Since the background ^{201}Tl uptake in normal tissue is relatively low or ^{201}Tl washout from normal tissues is relatively prompt in these organs, the delayed scan is preferably evaluated and the washout rate from tumor is reliably calculated. It is considered that tumor uptake in delayed scans and washout rate (or retention index) better reflect tumor viability, while the uptake in early scans is affected by tumor vascularity. However, physiological muscle uptake usually increases in the delayed scan, making it difficult to evaluate the uptake and washout of ^{201}Tl in bone and soft-tissue tumors. The utility of delayed scans in bone and soft-

tissue tumors has not been sufficiently evaluated.

In bone and soft-tissue tumors, the utility of ^{201}Tl scintigraphy has been reported.[2,4,6–8,12,15,19,21] ^{201}Tl scintigraphy offers high negative predictive value in the assessment of malignant bone tumors and it can eliminate the need for more expensive and invasive tests.[4] ^{201}Tl scintigraphy is also more accurate than other imaging modalities in differentiating residual/recurrent bone and soft-tissue sarcomas from post-therapy changes.[8,21] Although early scans of ^{201}Tl scintigraphy have been generally used for analysis,[4,8,21] Caluser et al.[6] and Nishiyama et al.[15] similarly reported that persistent ^{201}Tl uptake in tumors in delayed scans with ratios higher than those of blood pool ratios was highly indicative of malignancy. Thus, the usefulness and necessity of delayed scans in bone and soft-tissue tumors remains controversial.

In this study, we compared the uptake ratio (T/N) of tumor to normal tissue both in early and delayed scans and we calculated the washout rate. Although there were significant differences in the T/Ns both in early scans (ER) and delayed scans (DR) between malignant tumors and benign lesions and high negative predictive value in assessment of malignant tumors was observed, there were substantial overlaps and it seemed impossible to perfectly differentiate malignant tumors from benign lesions. Moreover, the T/Ns in bone and soft-tissue lesions decreased in delayed scans, mainly due to the increase in surrounding normal muscle uptake, and thus the washout rate was substantially affected by the change of normal muscle uptake (rather than the change of tumor uptake). Moreover, overlying muscle uptake might be misinterpreted as tumor uptake. There was no difference in washout rate between malignant and benign bone and soft-tissue lesions (Fig. 7).

Since the washout rate between early and delayed scans was substantially affected by the change (i.e., substantial increase) of surrounding muscle uptake and thus seems not directly reflect the ^{201}Tl washout from tumors, we paid attention to the dynamic phase of ^{201}Tl uptake in tumors after bolus injection. Dynamic scans would be expected to reflect tumor vascularity and cell ability to pick up ^{201}Tl in tumors with relatively low uptake in surrounding normal muscle. In general, early scans of ^{201}Tl scintigraphy are acquired at 10 to 20 minutes after injection and not much change can be expected during recirculation.[1] Indeed, in this study ^{201}Tl uptake in most malignant tumors [33/43 (77%) cases of positive uptake] and benign lesions [47/65 (72%) cases of positive uptake] increased within initial 2 to 3 minutes and there was no remarkable change until the early scans (plateau pattern) (Figs. 3, 4). However, we found different patterns in some cases (18 cases of decrease patterns and 10 cases of increase patterns) (Figs. 2, 5). And if there was no tumor uptake in dynamic scans and early scans, no tumor uptake was also appreciated in delayed scans in all cases. This suggested that the delayed scan can be omitted in bone and soft-tissue tumors if there is no uptake in tumor uptake in dynamic and early scans, although there are some exceptional cases previously reported in the literature.[22,23]

A few studies have been reported about the dynamic scanning of ^{201}Tl.[24] Kanegawa[24] reported the usefulness of dynamic scan for differentiating benign from malignant thyroid lesions: all the cases (5/5) of decrease pattern in the dynamic curve were benign, while most of the cases (18/20) of increase pattern were malignant. In contrast, in the current study of bone and soft-tissue tumors, both malignant and benign lesions showed decrease patterns and increase patterns. It was still difficult to differentiate malignant tumors from benign lesions; however the dynamic scans clearly demonstrated the differences between tumor blood flow and tumor uptake in some tumors such as hemangioma (Fig. 2).

There were some limitations in this study. We evaluated only planar images of ^{201}Tl scintigraphy. Some cases of false positive and false negative seem to be misinterpreted due to overlying physiological muscle uptake. The uptake ratio of tumor to normal tissue was also substantially affected by surrounding background uptake. Indeed, the ^{201}Tl uptake in surrounding muscle uptake substantially increased in the delayed scans (mean 43%, up to 111%). These limitations might be partly reduced by SPECT.[19] In this study, patients were free between the early and delayed scans (i.e., not prohibited from walking). Since the uptake and washout of ^{201}Tl (in both the tumors and surrounding muscles) could be changed by exercise between the scans, the value of DR and WR may have been different if the patients had been kept at rest (i.e., prohibited from walking). Next, the current study included a variety of lesions and a relatively small number of malignant tumors (larger numbers of benign lesions). Not all the cases were confirmed by histopathological examinations, i.e., especially many of the benign lesions (75 of 130 lesions) were defined as benign on clinical follow-up. However, the incidence of malignant bone and soft-tissue tumors is much lower than that of benign lesions,[25,26] and indeed the high negative predictive value [66/68 (97%) in this study] of ^{201}Tl scans in bone and soft-tissue lesions seemed to be quite worthwhile in clinical practice to avoid more expensive and invasive surgery, as previously reported.[4]

In the evaluation of bone and soft-tissue tumors, ^{201}Tl uptake in delayed scans is substantially affected by increased surrounding muscle uptake. As a result, the ^{201}Tl uptake ratios of tumors to normal tissues decrease on delayed scans, mainly due to the increase of surrounding normal muscle uptake, and thus the washout from tumor is complicated. Dynamic scan clearly demonstrates that ^{201}Tl is delivered by blood flow and rapidly taken up in tumor with relatively low uptake in surrounding normal muscle uptake. If there is no ^{201}Tl uptake in dynamic and early scans, the delayed scan could be omitted. In evaluation of bone and soft-tissue tumors, delayed scan of ^{201}Tl

has little clinical utility and it may be time consuming, while dynamic scan would be able to demonstrate the differences between tumor blood flow and ^{201}Tl uptake in tumors and would be useful for evaluating bone and soft-tissue tumors.

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