dual-headed gamma camera to our department, we aim to extend SPECT imaging to include regions other than the pelvis for future patients.

CONCLUSION

These findings suggest that RIS using ^{99m}Tc CYT-351 may have a useful place in staging prostate cancer and monitoring its response to treatment. With further refinement in the data analysis technique, it may be capable of defining the extent of the primary tumor and prove to be a useful adjunct in the staging of primary malignancy when evaluating patients for radical treatment. This ability to image prostatic malignancy in soft tissues and lymph nodes provides a new and clinically useful method for evaluating prostate cancer in the patient with rising PSA levels and a negative bone scan and other negative imaging test results.

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Comparison of Technetium-99m-MIBI and Technetium-99m-Tetrofosmin Uptake by Musculoskeletal Sarcomas

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Technetium-99m-MIBI was initially developed for heart studies but it can also be used to depict tumors, predict multidrug resistance and evaluate chemotherapy. Recently, ^{99m}Tc-tetrofosmin, which exhibits similar physical properties, has been launched for heart studies. Tumor uptake and prediction of multidrug resistance have also been reported regarding the latter tracer. A comparison of these two tracers regarding the detectability of musculoskeletal sarcoma has been made. **Methods:** Twenty patients with musculoskeletal sarcoma of the extremities or pelvis underwent planar examination after the administration of ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin with an interval of 2–7 days. The tumor activity was compared with one ipsilateral and one contralateral background region. **Results:** There was a small, but not significant, difference in favor of ^{99m}Tc-MIBI with regard to both background regions. **Conclusion:** Technetium-99m-MIBI and ^{99m}Tc-tetrofosmin can both be used to visualize musculoskeletal sarcomas. The choice may depend on which agent is used routinely for myocardial studies in the laboratory.

Key Words: musculoskeletal sarcoma; technetium-99m-MIBI; technetium-99m-tetrofosmin; tumor imaging

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Various radiopharmaceuticals have been explored for use in tumor detection and characterization. Technetium-99m-hexakis-2-methoxyisobutyl isonitrile (^{99m}Tc-MIBI, ^{99m}Tc-sestamibi, RP-30, Cardiolite®) was developed for myocardial studies (*1,2*). After the incidental detection of a lung metastasis at cardiac imaging (*3*), several case reports describing tracer uptake in various tumors appeared (*4–8*) and several articles reporting uptake in series of tumors have recently been published (*9–13*). In addition, it has been suggested that ^{99m}Tc-MIBI may be used for the prediction of multidrug resistance (MDR) as well as for response evaluation after chemotherapy (*14,15*). Consequently, ^{99m}Tc-MIBI must be considered to be an established agent for nuclear oncology as well.

Recently, ^{99m}Tc-1,2-bis[bis(2-ethoxyethyl)phosphino]ethane (^{99m}Tc-tetrofosmin, P53, PPN0.1011, Myoview®) has been launched for myocardial studies (*16,17*). The functional characteristics of this agent are similar to those of ^{99m}Tc-MIBI. Uptake in malignant lesions have been described, and a potential as a predictor of MDR in breast cancer has been suggested (*18–22*).

TABLE 1
Clinical Data and Tumor-to-Background Activity for Technetium-99m and Technetium-99m-Tetrofosmin*

Patient no.	Gender (M/F)	Age (yr)	Diagnosis	Tumor grade†	Size (cm)	Localization	^{99m}Tc-MIBI Tumor/ contralateral background	^{99m}Tc-MIBI Tumor/ ipsilateral background	^{99m}Tc-Tetrofosmin Tumor/ contralateral background	^{99m}Tc-Tetrofosmin Tumor/ ipsilateral background
Primary bone tumors										
1	M	14	Small cell osteosarcoma	III-IV	5 × 2 × 2	Distal radius	3.54	2.49	2.64	2.23
2	M	15	Ewing's sarcoma	—	10 × 4 × 3	Pelvis	2.13	2.16	1.95	2.25
3	M	16	Osteosarcoma	IV	8 × 7 × 3	Proximal tibia	2.24	2.97	1.88	2.06
4	F	16	Osteosarcoma	III	3 × 3 × 2	Proximal radius	5.85	5.02	4.78	2.72
5	M	17	Osteosarcoma	IV	10 × 7 × 4	Distal femur	1.99	1.53	2.86	2.10
6	M	17	Osteosarcoma	IV	10 × 8 × 5	Distal femur	2.95	2.02	1.66	1.12
7	F	19	Periosteal osteosarcoma	III	7 × 3 × 2	Middle tibia	2.13	1.98	2.12	2.13
8	M	25	Osteosarcoma	III	9 × 4 × 4	Distal femur	1.99	1.66	2.14	1.33
9	M	37	Osteosarcoma	III-IV	4 × 3 × 2	Proximal radius	2.57	3.08	2.84	3.70
10	F	54	Osteosarcoma	IV	12 × 8 × 7	Proximal femur	1.81	2.35	2.02	2.94
11	M	68	Chondrosarcoma	III	4 × 3 × 3	Proximal femur	1.30	1.37	1.18	1.20
12	M	67	Chondrosarcoma	III	10 × 8 × 7	Pelvis	1.07	1.63	1.72	2.75
Soft-tissue tumors										
13	M	40	Liposarcoma	III	5 × 3 × 2	Quadriceps	1.76	1.81	1.76	1.67
14	F	51	Malignant fibrous histiocytoma	III	10 × 9 × 4	Proximal brachium	3.58	4.12	3.85	3.17
15	M	54	Malignant fibrous histiocytoma	III	5 × 4 × 4	Tensor fasciae latae	1.81	1.55	1.37	1.46
16	F	58	Hemangiopericytoma	IV	16 × 6 × 5	Calf	8.20	6.03	5.38	4.74
17	F	61	Malignant fibrous histiocytoma	III	12 × 10 × 10	Quadriceps	1.11	1.08	1.17	1.17
18	F	71	Myxoid chondrosarcoma‡	II	4 × 4 × 3	Knee	4.71	2.68	3.84	2.37
19	F	77	Malignant fibrous histiocytoma	III-IV	6 × 5 × 4	Vastus lateralis	2.54	1.98	2.88	2.65
20	M	78	Leiomyosarcoma	III	5 × 3 × 3	Thigh, intermuscular	2.58	2.64	2.20	2.20

*Data for the 20 patients with musculoskeletal sarcomas.
†Histologic malignancy Grades I-IV.
‡Recurrency.

The choice of an adequate tumor-depicting radiopharmaceutical in the clinical situation is not always obvious in the expanding field of nuclear oncology. Agents like ^{123}I-MIBG, ^{111}In-octreotide and radiolabeled monoclonal antibodies, with a specific uptake mechanism, have a clear indication. In contrast to such agents, the use of unspecific agents like ^{99m}Tc-MIBI is

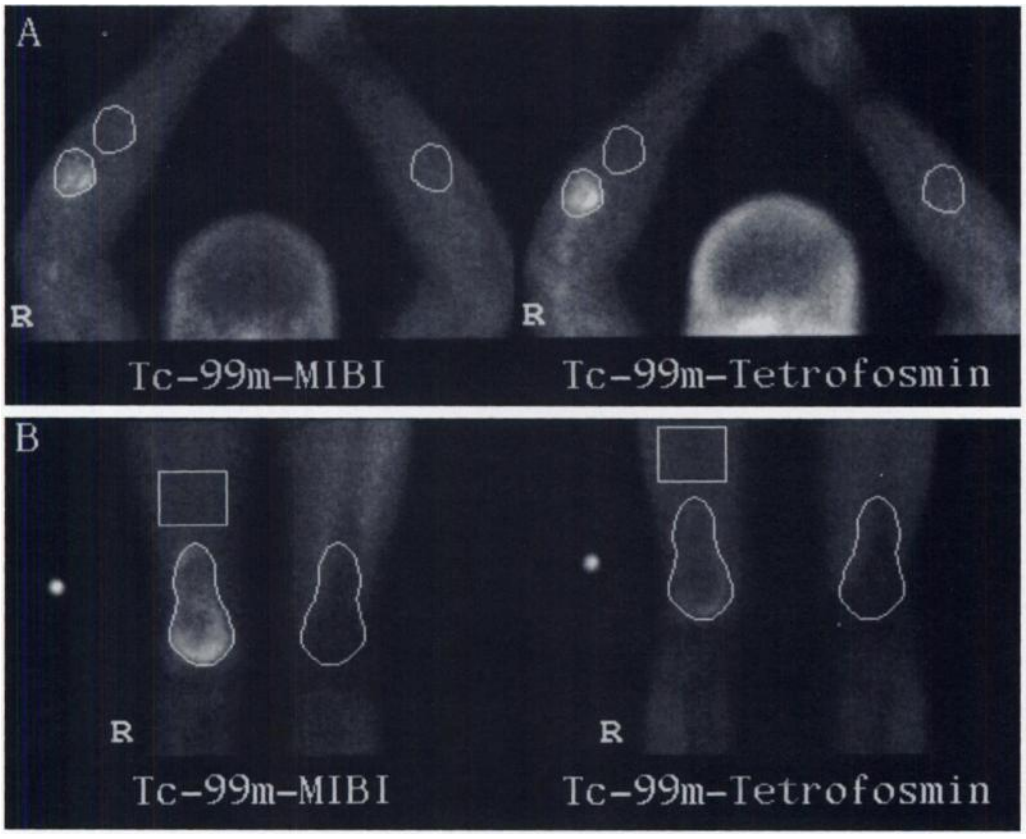

FIGURE 1. (A) Anterior acquisitions from the arms of Patient 9 with an osteosarcoma of right radius 10 min after the administration of ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin. One ROI covers the tumor. An identical mirrored ROI at the corresponding position in the left arm represents contralateral background activity and a ROI representing the ipsilateral background is positioned close to the tumor. There is a higher uptake of ^{99m}Tc-tetrofosmin than of ^{99m}Tc-MIBI. (B) Similar acquistions from Patient 6 with an osteosarcoma of the right distal femur. This tumor shows a higher accumulation of ^{99m}Tc-MIBI than of ^{99m}Tc-tetrofosmin.

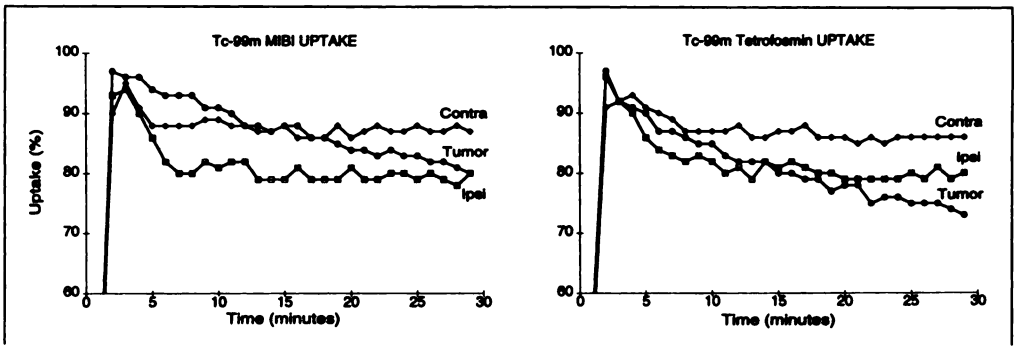

FIGURE 2. Time-activity curves show average tumor, contralateral background and ipsilateral background activity of ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin with time after normalization to the highest value for the first 10 patients included in the study.

more empirical. Due to the similarities between ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin, the choice, in practice, is between one of these agents. The aim of this study was to compare the tumor detectability of these two agents. This has been done in the form of a paired comparison in patients with musculoskeletal sarcomas.

MATERIALS AND METHODS

Patients

Twenty consecutive patients with recently discovered musculoskeletal sarcoma of the extremities or the pelvis were included. Clinical data are presented in Table 1. Each patient was examined using both agents with an interval of 2–7 days. The order of examination with the tracers varied. Most patients had a fine-needle biopsy for diagnostic purposes, but no other invasive diagnostic or therapeutic measures were taken before or between the examinations. The diagnoses were later verified by histologic examination of the excised specimen. All patients also underwent an MRI examination at which the size of the tumor was estimated. The additional examination with ^{99m}Tc-tetrofosmin was approved by the local Ethical and Isotope Committees. The subjects received written information about the procedure before the examinations.

Radiopharmaceuticals

Technetium-99m-MIBI and ^{99m}Tc-tetrofosmin were reconstituted with pertechnetate according to the instructions. The adults received 250 MBq (6.8 mCi) of each agent intravenously. This activity was reduced in the children.

Examination

Identical examinations were performed on both occasions using a gamma camera equipped with low-energy, high-resolution, parallel-hole collimators. The limbs in question were examined with one camera at the most adequate projection in each patient. In the first 10 patients, a dynamic acquisition in a 256 × 256 matrix with 1-min frames during 30 min was initiated at injection of the radiopharmaceutical. In the remaining 10 patients, a 5-min acquisition with the same parameters was effectuated 10 min after injection of the agent. Whole-body images were not obtained in addition to this series of recordings. The radiopharmaceutical was never injected into the affected limb.

Evaluation

The evaluation procedure was identical for both examinations and performed on the same occasion. A region of interest (ROI) was drawn around the tumor area in the image. An identical mirrored ROI representing contralateral background activity was placed at the corresponding position in the contralateral limb/structure. A third ROI representing ipsilateral background activity was placed close to the tumor (Fig. 1). For anatomical reasons, this ROI could not always have the configuration of the tumor, but the shape was identical and the position was similar at both examinations. The number of recorded events was sufficient to give a maximal statistical uncertainty of 3%, indicated as one s.d., at each observation.

The values from both dynamic acqusitions in the 10 patients were normalized to the highest value registered (100%). The appearance of this peak varied between 2 and 5 min after injection. Thereafter, the arithmetic means of the 10% age values at each point of time were calculated, and time-activity curves were plotted. Time-activity curves representing tumor-to-contralateral background and tumor-to-ipsilateral background activity ratios were also calculated.

The final evaluation was made by calculating tumor-to-contralateral and tumor-to-ipsilateral background activity ratios for both agents.

Statistical Analysis

Comparisons between the different types of quotients were made by means of the standard double-sided paired t-test. $P < 0.05$ was considered significant.

RESULTS

Dynamic Analysis

To establish the optimal time for examination, a dynamic acquisition during 30 min was made after injection with both radiopharmaceuticals in the first 10 patients. Figure 2 shows the average tumor, contralateral background and ipsilateral background activity with the time after normalization to the highest value. The findings were similar for both agents. After a stabilization period of 5–10 min, there was a slowly decreasing

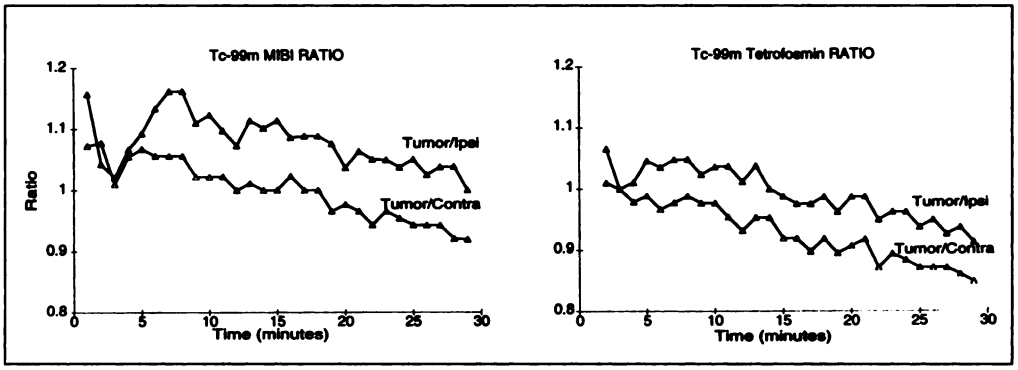

FIGURE 3. Time-activity curves show the ratios of tumor and contralateral background activity and of tumor and ipsilateral background activity from Figure 2.

TABLE 2
Mean ± s.d. and Mean Values of the Quotients

	^{99m}Tc-MIBI			^{99m}Tc-Tetrofosmin			
	Mean	s.d.	Median	Mean	s.d.	Median	p value
Tumor/Contralateral background	2.79	1.73	2.19	2.51	1.16	2.13	0.14
Tumor/Ipsilateral background	2.51	1.26	2.09	2.30	0.91	2.22	0.25

tumor activity while the background activity remained essentially stable. This is confirmed by the falling curves in Figure 3, which shows the ratios with the time between tumor and contralateral background activity as well as between tumor and ipsilateral background activity from Figure 2. On the basis of these observations, it was decided to perform the final evaluation of both radiopharmaceuticals during the period of 10–15 min after injection.

Comparison Between MIBI and Tetrofosmin

Except for Patient 12, who had a negative examination with ^{99m}Tc-MIBI (Table 1), all tumors showed increased uptake compared to both background regions on visual evaluation of all recordings. The activity ratios for each patient, calculated during the 10–15 min period after tracer injection, are shown in Table 1. The mean, median and ± s.d. values of the quotients in the different groups are given in Table 2. The values are slightly higher for ^{99m}Tc-MIBI than for ^{99m}Tc-tetrofosmin at both comparisons. The differences are not significant. A similar analysis of the seven osteosarcoma patients also only revealed an insignificant tendency toward higher values for ^{99m}Tc-MIBI than for ^{99m}Tc-tetrofosmin with regard to both background regions.

DISCUSSION

Technetium-99m-MIBI is incorporated in metabolically active tissues and retained in the mitochondria (*23*). Despite the fact that this entails a normal uptake in various organs and tissues and makes the distribution nonspecific (*24*), aberrant accumulation may add considerable information in a given clinical situation in a tumor patient. Although the chemical structures of ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin are different, their physical properties are similar. Both are weakly lipophilic cationic complexes, which condition is supposed to entail the same uptake mechanism in the myocard (*25*). This mechanism is probably similar for accumulation in tumors.

The aim of the study was to compare the tumor detectability of the two agents. Consequently, the evaluation was made with regard to the tumor-to-background activity ratio. More elaborate analyses such as activity distribution within the tumor or absolute uptake, which would require tomographic acquisition, were not performed. The idea was to compare the uptake in primary tumors outside disturbing abdominal activity and with a symmetrical contralateral structure serving as one background reference. This was achieved with the present series of patients, while a rather heterogeneous group of tumors had to be accepted. The two pelvic malignancies were located outside disturbing soft-tissue activity and could be included. Due to the possibility of an unspecifically altered background activity in a tumor-bearing limb, an ipsilateral background region was also included. The rather low activity, 250 MBq for both radiopharmaceuticals, administered to keep the total radiation burden down in these potentially curable patients undergoing many radiologic examinations, was adequate for the spot examinations of these large tumors.

The optimal time for assessing tumor uptake of ^{99m}Tc-MIBI has never been evaluated and the examination is usually performed soon after administration. Different kinetics in neoplastic and normal tissue was described early on (*3*) and this forms the basis for the double-phase investigation with ^{99m}Tc-MIBI in parathyroid disease (*26*). The curves in Figure 3 show a continuously decreasing ratio between tumor and background activity. Consequently, registration soon after the stabilization period, as performed here should be preferable. This is also desirable from a practical point of view. We have not systematically studied how long the relatively decreasing tumor activity lasts. However, in two patients outside this study with soft-tissue sarcomas showing increased uptake of ^{99m}Tc-MIBI, compared to surrounding tissue, at early acquisition, specimens removed at surgery 20–24 hr later showed reduced activity compared to surrounding normal tissue (unpublished data). The reason for a more rapid washout from a tumor is not known, but an increased metabolism or turnover of neoplastic tissue may be considered. Consequently, we find it it highly unprobable that late scans (1–2 hr after injection) would contribute to the detection of these tumors.

The curves in Figures 2 and 3 were made to depict the change in contrast between the tumor and background with time to establish the optimal moment for evaluation and consequent examination and do not allow further conclusions. Since the values in Figure 2 are related to the maximal activity of each ROI, the difference in level between the curves in Figures 2 and 3 does not represent differences in activity. Consequently, it may reflect a difference in tracer extraction efficiency between normal and neoplastic tissue in combination with different blood-flow dynamics between the normal and the tumor-bearing limb, including the choice of different regions between the limbs.

The extreme variability of the ratios among patients examined with the same radiopharmaceutical may have several causes. Variations of biological properties such as metabolic activity, vascularization and the proportion of tumor necrosis, as well as of production of P-glycoprotein by the neoplastic cells causing efflux of the radiopharmaceutical (*22*), can all account for this. In addition, since only planar registrations were acquired, the uptake strongly depends on the tumor volume and the depth of the tumor, both varying in the different patients. The latter facts also preclude any comparison of ratios between different patients. It is believed that the negative result of the ^{99m}Tc-MIBI examination in Patient 12 may also be explained by the biological factors mentioned.

There is a small difference in favor of ^{99m}Tc-MIBI with regard to both background regions. This is far from significant, despite the fact that the study was performed as a paired investigation. Although there is no significant difference between the groups of patients, there is a certain variation in individual patients with regard to the radiopharmaceuticals. This may indicate some difference in the uptake mechanism for the agents either in the tumor or in the background tissue, which cannot be further elucidated. There was no difference between the agents in the osteosarcoma patients in a separate analysis, and there is no clear tendency with other variables either (Table

1). Consequently, the most suitable agent to use in the individual patient cannot be predicted from this study.

CONCLUSION

In practice, either ^{99m}Tc-MIBI or ^{99m}Tc-tetrofosmin can be used to depict musculoskeletal sarcomas. The choice of agent may depend on which radiopharmaceutical is used routinely for myocardial studies in the particular laboratory.

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Total-Body Scintigraphy with Thallium-201 and Iodine-131 in the Follow-up of Differentiated Thyroid Cancer

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We analyzed the significance of total body scintigraphy with ^{201}Tl in the follow-up of patients with differentiated thyroid cancer, both in the preablation and ablated stages. **Methods:** Prospective assessment was performed in 116 patients who were involved in 178 studies (115 in preablation and 63 after ablation). For ablation, an absence of uptake in the thyroid bed was required in the total ^{131}I follow-up scan after ^{131}I ablation therapy. Each study consisted of a ^{201}Tl scan performed while the patient was receiving thyroid hormone therapy, an ^{131}I scan performed when endogenous thyroid-stimulating hormone levels were higher than 50 mIU/ml and determination of thyroglobulin (Tg) concentration using the same sample. **Results:** In the 115 scans in the preablation group, the findings for ^{201}Tl and ^{131}I agreed in 26 scans and disagreed in 89 scans. In 59 discordant studies, only ^{131}I detected focal accumulation, and, in 54 of these, Tg levels were undetectable. Of the other 30 discordant studies, ^{201}Tl and ^{131}I detected focal uptake in 27 studies, although they did not reveal the same lesions, and in 3 studies, only ^{201}Tl detected focal accumulation; in these 30 studies, the association of detectable Tg predominated. Of the 63 studies in the ablated group, the results agreed for the two tracers in 49 and disagreed in 14 studies. In 13 of the 14 discordant studies, ^{201}Tl detected focal uptake, and, in 10 of these, Tg was detectable. Thus, 31 of the 116 patients assessed (15 preablation and 16 ablated) had at least one lesion that was detected by ^{201}Tl but not detected by ^{131}I. A definitive diagnosis could be established in 26 patients, and the presence of thyroid cancer was confirmed in 23. The sensitivity and specificity in the ablated group were 94% and 96%, respectively, for ^{201}Tl and 29% and 100%, respectively, for ^{131}I. **Conclusion:** The high sensitivity of ^{201}Tl scintigraphy in detecting tumor tissue indicates that the inclusion of this technique in the follow-up of patients with differentiated thyroid carcinoma should be considered in both the preablation and the ablated stages.

Key Words: differentiated thyroid cancer; thallium-201; iodine-131; thyroglobulin

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Total body scintigraphy with ^{131}I is the established technique for the follow-up of differentiated thyroid cancer (DTC). However, the inherent limitations of the technique are also well known. In recent years, therefore, the introduction of ^{201}Tl total

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