Thallium-201 Imaging in the Follow-Up of Differentiated Thyroid Carcinoma

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Since thallium-201 imaging has been reported as a potential means of follow-up of patients with differentiated thyroid carcinoma (DTC) during ongoing thyroid suppression therapy, the authors evaluated the diagnostic sensitivity of this procedure in 31 patients known to have metastases or local recurrence. Among 51 tumor sites ^{201}Tl imaging had a detection rate of 45% whereas 84% was noted for imaging with ^{131}I administered in therapeutic doses. Thus, even though the effectiveness of the two radionuclides is not strictly comparable due to the difference in the administered doses, Thallium imaging cannot be recommended as the only modality for the follow-up of patients with DTC. Six of the eight tumor sites negative with ^{131}I were positive with ^{201}Tl (especially metastatic cervico-mediastinal lymph nodes). So ^{201}Tl imaging may particularly be helpful in localizing metastases or recurrences in patients with a negative ^{131}I scan and abnormal levels of serum thyroglobulin.

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It has been suggested that thallium-201 (^{201}Tl) imaging could be of major clinical utility in the follow-up of patients with differentiated thyroid carcinoma (DTC) who have undergone total or sub-total thyroidectomy, with or without post operative ablative therapy using iodine-131 (^{131}I) (*1,2*). The main reasons for this suggestion are: ^{201}Tl chloride has been reported to have tumor seeking properties (*3–7*), in particular for thyroid carcinoma (*6,8*); ^{131}I imaging is not entirely reliable to allow exclusion of DTC metastatic disease (*9*); ^{201}Tl imaging, as opposed to ^{131}I imaging, can be performed during ongoing thyroid medication and can therefore help in selecting patients for withdrawal of thyroid medication and who can benefit from use of ^{131}I for imaging and treatment (*1,2*).

We have undertaken a prospective study to evaluate the reliability of ^{201}Tl whole-body scintigraphy in detecting known tumor sites of DTC, comparing the results with those obtained from ^{131}I whole-body imaging.

PATIENTS AND METHODS

We studied 31 selected patients, 18 female and 13 male, who had undergone total thyroidectomy for histologically proven nonmedullary DTC, followed by one or more courses of ^{131}I therapy. They were known to have one or more metastases or local recurrences. We excluded from this study those patients who had only ^{131}I uptake in the thyroid bed, since it was not possible to know whether this uptake corresponded to residual normal or tumoral tissue.

Of these 31 patients, two had cervical recurrences in the thyroid bed and 29 had one or several metastases of the DTC. In 23 of these patients, the metastases were identified by ^{131}I uptake outside the thyroid bed region on a previous scan, obtained after a therapeutic course of ^{131}I. All but six patients had high levels of serum thyroglobulin (Tg), above 60 ng/ml, after withdrawal of thyroid suppression therapy and one had anti-thyroglobulin antibodies. In the other six patients, who had metastases but no abnormal ^{131}I uptake, the presence of metastases was strongly suspected because of high levels of serum Tg in five. Moreover, there were pulmonary nodules seen on chest radiograph in two patients, abnormal mediastinal lymph nodes detected with CT scans in one, a bone tumor in the shoulder of one, and palpable cervical lymph nodes in one. In another patient who had a large cervical lymph node, a serum Tg measurement was unavailable due to the presence of anti-Tg antibodies. In all these six patients the abnormalities detected were confirmed to be metastases of DTC by biopsy and bronchial aspiration, with immunologic studies using monoclonal anti-Tg antibodies. In the two patients with metastatic cervical lymph nodes, biopsies of the nodes were obtained after the ^{201}Tl scan.

The histologic tumor type of the primary DTC was papillary in 15 patients, well differentiated follicular in six and moderately differentiated follicular in ten.

Thallium-201 imaging was started 20 min after an intravenous injection of 5 mCi of ^{201}Tl-chloride. First an anterior

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view of the neck using a pin hole collimator was obtained. The acquisition time was 5 min. Then two whole body scans, first an anterior then a posterior view, were acquired using a LFOV gamma camera, equipped with a low energy, high resolution collimator and moving at 6 cm/min. The entire study was completed within about 90 min after the injection of ^{201}Tl. Four hours after the injection, repeated images of the neck and whole body were obtained using the same views. Thirteen patients were receiving thyroid suppression therapy (TST) when imaged with ^{201}Tl, whereas 18 patients had no TST, since they were due to start a course of ^{131}I therapy a few days later.

Iodine-131 imaging was performed a few days or weeks after ^{201}Tl imaging and 5 days after a scheduled therapeutic course using 100–150 mCi of ^{131}I-iodide. The views obtained were the same as for the ^{201}Tl imaging. But the camera speed was 15 cm/min for the whole body scanning. The patients had discontinued hormone suppressive therapy (1 mo for administration of l-thyroxin and 2 wk for triiodothyronin) and the plasma TSH levels ranged from 35 to 136 micro U/ml. The urinary concentration of "cold" iodine had been checked in all patients by using the Sandell-Kolthoff technique, based on the catalytic effect of Iodide ions on the oxidation-reduction reaction of Cerium ions by arsenous salts. Iodide normal excretion is inferior to 2000 nmol/24 hr. In this group of patients the value was 889 ± 602 (s.d.) nmol/24 hr.

RESULTS

A comparison of the results of imaging with ^{201}Tl and ^{131}I is summarized in Table 1. Among 51 tumor sites, 23 were detected with ^{201}Tl (45%) and 43 with ^{131}I (84%). Thallium was least effective in recognizing bone (2/16) and liver (0/2) metastases. The latter result was probably due to the significant liver background (Figs. 1 and 2). Reasonably good results with ^{201}Tl were obtained for lung metastases (6/11) and cervico-mediastinal metastatic lymph nodes (13/20). The histologic type of DTC was not associated with any statistically significant difference in positive ^{201}Tl results, which were generally seen only in the early scan. Thallium-201 imaging was usually negative in the thyroid bed of patients who had residual ^{131}I uptake, except for the two cases of local recurrence. No statistically significant difference in thallium positivity was noted between patients on or off TST. In three cases transient diffuse lung ^{201}Tl uptake noted in the early images was interpreted as presumably false positive, on the basis of the negativity of all other investigations including high resolution CT and absence of ^{131}I uptake in the lungs.

Eight tumor sites in seven patients were not visualized with ^{131}I imaging. They comprised three cases of lung metastases (moderately differentiated follicular carcinomas) of which two were positive with ^{201}Tl, four metastatic sites of cervico-mediastinal lymph nodes (papillary carcinomas), which were all positive with ^{201}Tl and one bone metastasis from a moderately differentiated follicular carcinoma which was also negative with ^{201}Tl imaging. All these patients had a normal urinary level of "cold" iodine. So, among eight tumor sites which were not visualized with ^{131}I, six were positive with ^{201}Tl, especially metastatic lymph nodes and to a lesser extent lung metastases (Fig. 3). In these cases serum thyroglobulin ranged from 64 to 8,200 ng/ml (with the exception of one patient with anti-Tg antibodies) after withdrawal of TST, and from "undetectable value" (one patient) to 2,000 ng/ml on TST. It may be noted that one patient with a bone metastasis imaged after ^{131}I administration, also had multiple pulmonary nodules which were proven to be DTC and which were not visualized on ^{131}I nor ^{201}Tl scans. This may possibly be due to a different degree of differentiation at the two tumor sites.

TABLE 1
Comparison of Scintigraphy Using ^{201}Tl and ^{131}I to Image 51 Tumor Sites*

Tumor site	Number	Positive with ^{201}Tl	Positive with ^{131}I
Bone metastases	16	2	15
Cervico mediastinal metastatic lymph nodes	20	13	16
Lung metastases†	11	6	8
Liver metastases†	2	0	2
Local recurrences	2	2	2
Total	51	23 (45%)	43 (84%)

* Radionuclide uptake in the thyroid bed was not considered to correspond to a tumor site, except when there was a clinical evidence of local recurrence.
† Multiple lung or liver metastases were counted as one tumor site.

DISCUSSION

The relatively poor overall results obtained here with ^{201}Tl in detecting tumor sites from DTC should be compared with those of Ling et al. (*1*) and Hoefnagel et al. (*2*) who found, respectively, that sensitivities using ^{201}Tl imaging were 88% and 94%. Hoefnagel et al. (*2*) reported that ^{131}I imaging had a low sensitivity (48%) but the highest specificity (99%). Specificity of thallium imaging is not clearly discussed by these authors.

Our study was prospective and was performed within a period of 5 mo (June to October 1986) on a highly selected group of patients, known to have metastases or local recurrences. Furthermore we have not considered an uptake of ^{131}I located in the thyroid bed as indicative of a tumor site, unless there was clinical evidence of local recurrence, because it was not possible to deter-

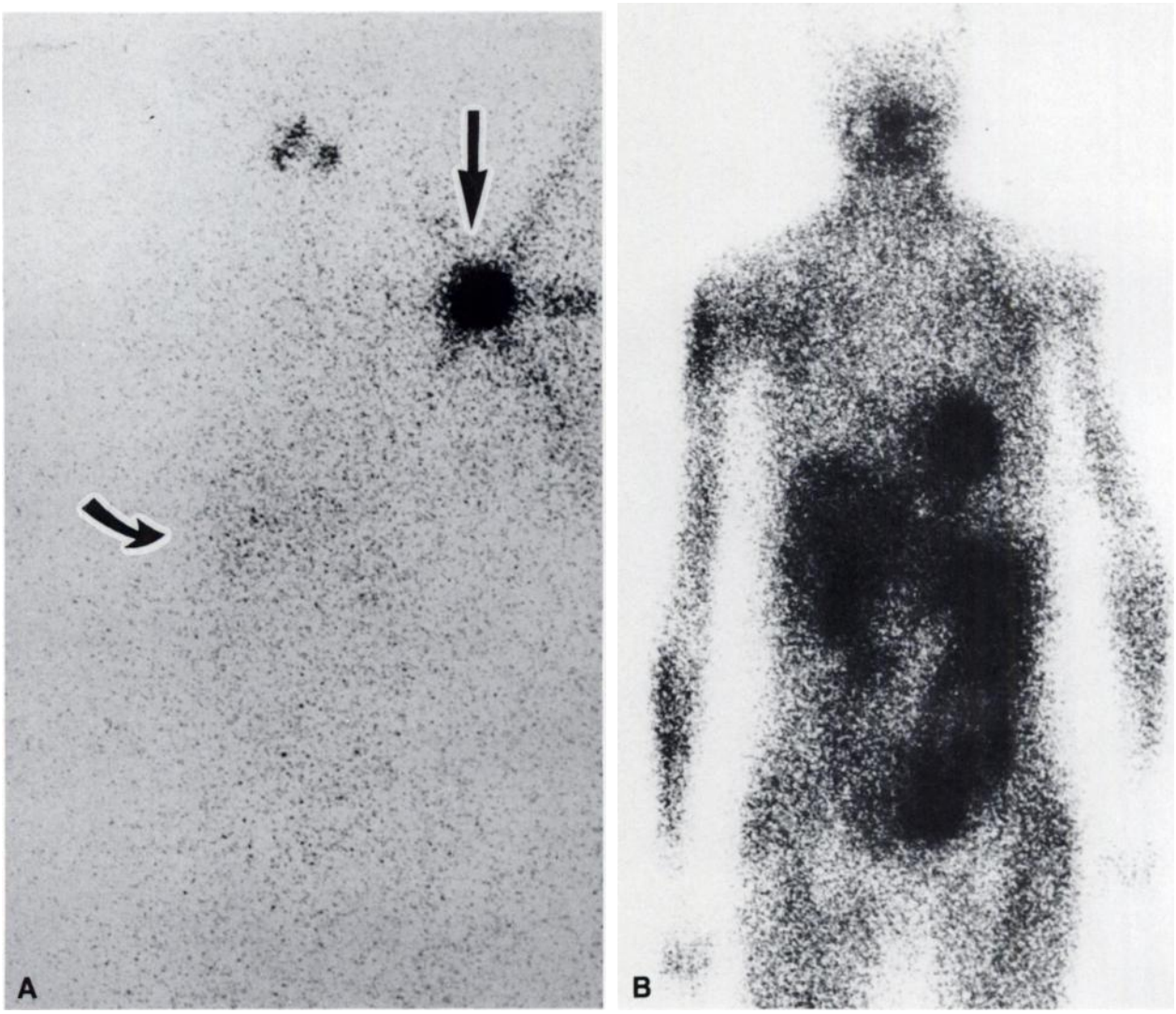

FIGURE 1
A positive ^{131}I image with a negative ^{201}Tl scan. A: The anterior view of the whole-body scan obtained with ^{131}I shows intense uptake in the superior part of the left humerus (straight arrow) where there is a pathological fracture at a metastatic site. The curved arrow shows faint liver activity. B: The anterior view of the early ^{201}Tl whole-body scan shows no uptake in the metastasis. The posterior view and images obtained after 4 hr were also negative.

mine whether the uptake corresponded to normal or tumoral tissue. Also, for this study, we have excluded medullary carcinoma of the thyroid, which together with nonmedullary DTC has been studied by other authors using thallium imaging (*1,2*).

The ^{131}I scans of this work were obtained after therapeutic doses ranging from 100 to 150 mCi. Such high doses obviously increase the sensitivity of the ^{131}I imaging compared to that of 5 mCi of [^{201}Tl]chloride. But this does not explain the intrinsically poor results of our ^{201}Tl imaging. Furthermore among the 25 patients who had ^{131}I in metastases or tumor recurrences, all but two had a high level of uptake which probably would not have been missed if diagnostic doses of ^{131}I had been used. We consider it is probable that the results of comparison between the two radiopharmaceuticals would not have been very different had we used lower doses of ^{131}I. But we acknowledge that the detection rate of 84% obtained with therapeutic doses of ^{131}I was overestimated in comparison with the detection rate of diagnostic doses of this radionuclide. However, the main intention of this work was to study the effectiveness of thallium imaging for detection of known tumor sites. It was relatively poor as a method independent of the effectiveness of ^{131}I.

The scanning speed of 6 cm/min used for thallium whole-body imaging was perhaps too high for the detection of lesions with a very low uptake of ^{201}Tl. The

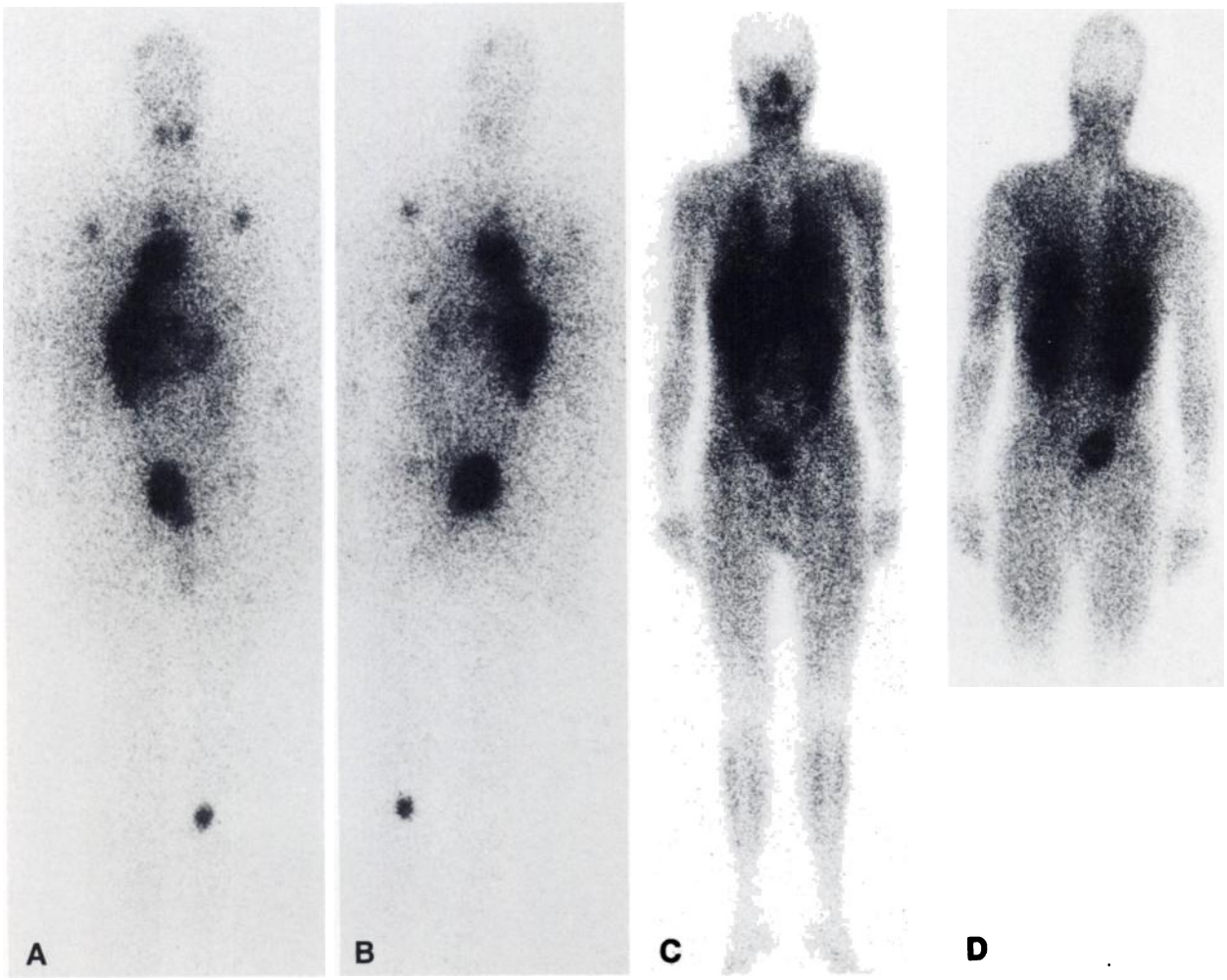

FIGURE 2
Whole-body scans of a patient with multiple metastases. A and B show, respectively, anterior and posterior views of a ^{131}I scan. There is bone uptake in shoulders, left elbow, sacrum, and left knee, multiple liver foci and uptake in the right hilar region of the mediastinum. C and D, respectively, show anterior and posterior views obtained from the early ^{201}Tl scans. Only uptake in the sacral metastasis is visible. A diffuse uptake in the lungs is apparent in the anterior view. It is very faint in the posterior view and disappeared in the images recorded after 4 hr. This was interpreted as transient, false-positive ^{201}Tl uptake. Note the intense abdominal background precluding interpretation in this region.

count density of "spot images" obtained by Hoefnagel et al. (*2*) was probably higher than that of our whole body images. However our scanning time for these images was approximately one hour, which is a long time for a patient. It would perhaps be better to spend the imaging time, concentrating on certain regions of the body, such as the head, neck, and thorax, which are more likely to bear metastases, and to exclude areas such as the abdomen and pelvis, where the ^{201}Tl background virtually precludes detection of metastases, and the limbs where metastases are less likely to occur. In this way a higher count density would be obtained for the selected areas.

The major difference in the effectiveness of the two radionuclides was noted for bone metastases, of which ^{201}Tl only detected two among 16, compared to 15 for ^{131}I. A part of the explanation of this fact may be the difference in energy of the two radionuclides. If bone metastases are dealt with separately in calculating detection rates, then the difference between ^{201}Tl and ^{131}I is not so marked: 60% for ^{201}Tl and 80% for ^{131}I.

An interesting point for discussion is possibly related to the kinetics of ^{201}Tl in malignant tumors. In a study including nonthyroid tumors Sahweil et al. (*10*) showed that the optimal time for scanning with ^{201}Tl is ~15 min after the i.v. injection. But one cannot perform whole-body imaging between 10 and 20 min after injection of the ^{201}Tl. It may be possible that our best ^{201}Tl results, which were obtained for cervicomediastinal metastatic nodes, were partially explicable by the fact that neck and anterior chest areas were imaged at the beginning of the thallium scan. In any case, it should be kept in mind that the uptake mechanism is different for ^{131}I and ^{201}Tl. It is therefore expected that the results

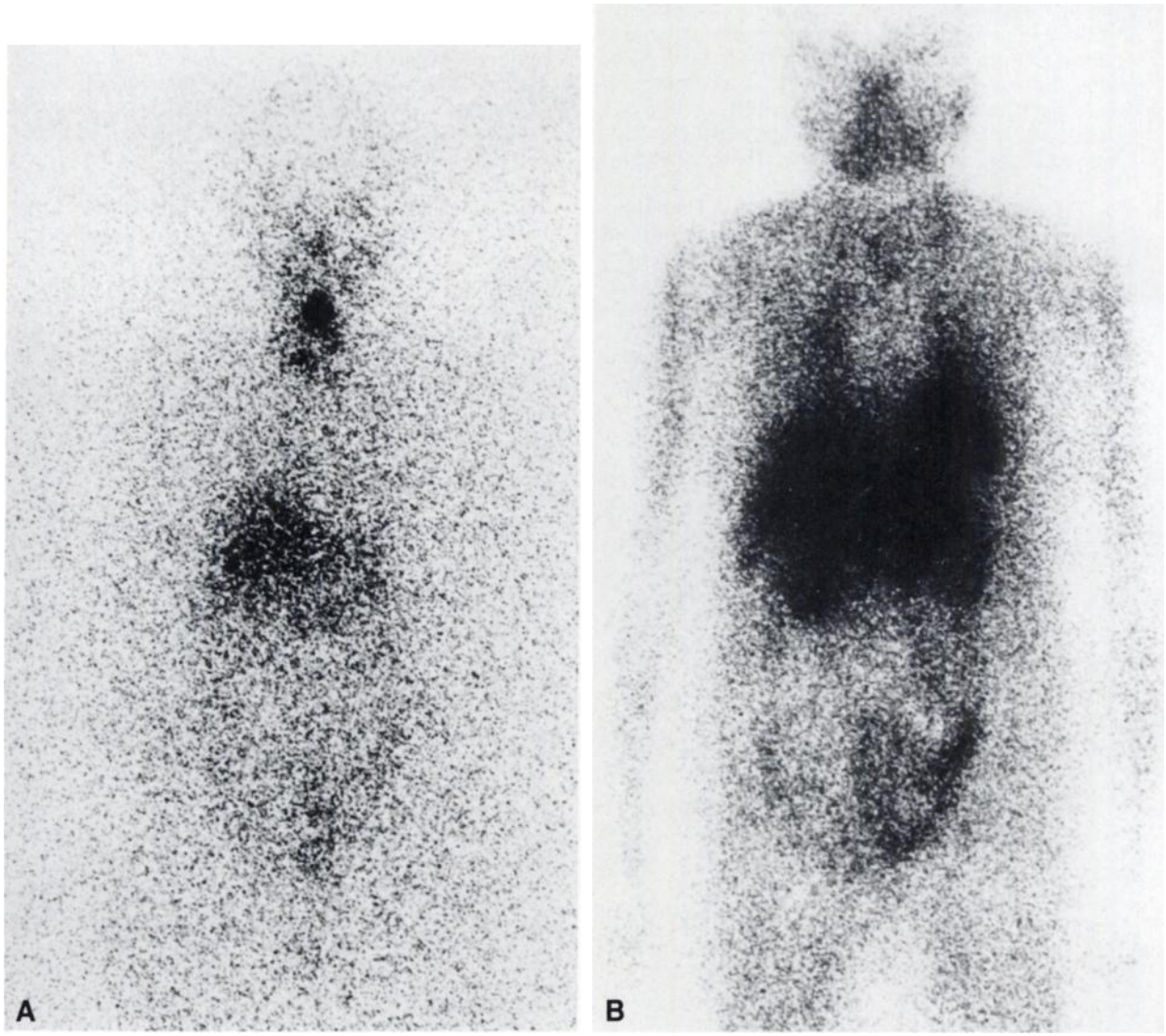

FIGURE 3
Positive ^{201}Tl imaging recorded with a negative ^{131}I scan. Multiple lung metastases were shown on the chest radiograph. A: No lung uptake was noted 5 days after a 100 mCi dose of ^{131}I. The cervical uptake of ^{131}I in the thyroid bed area corresponds to postsurgical remnants. B: Diffuse ^{201}Tl uptake is noted on the early scan and was also present in the 4-hr images.

will not be identical regardless of the imaging technologies used.

Our results seem to indicate that ^{201}Tl imaging cannot be recommended for follow-up of (nonmedullary) differentiated thyroid carcinomas, since its overall sensitivity in detecting tumor sites is relatively poor, even though its effectiveness is better for extraosseous lesions. Furthermore the main advantage of thallium imaging for this purpose is that the patient does not have to interrupt his thyroid suppression therapy. But these patients are also monitored with serum thyroglobulin measurements, which are known to be more reliable when plasma levels of TSH are elevated. It may then be argued that there should be periodic interruption of TST to allow the TG levels to be checked and that ^{131}I images could be obtained during this interruption. It should be added that our results have also demonstrated an interesting point about ^{201}Tl imaging. It may be helpful in localizing metastases, especially metastatic lymph nodes on patients with abnormal levels of serum Tg and for whom results of ^{131}I scans are negative. In this case, thallium images should probably be obtained 15 min after the ^{201}Tl injection, with high count density images of the most suspicious areas.

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