

# Planar Coincidence Scintigraphy and PET in Staging Malignant Melanoma

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This study describes a comparison of simulated planar positron coincidence scintigraphy (PCS) with PET in the whole-body staging of patients with malignant melanoma using 2-<sup>18</sup>F-fluoro-2-deoxy-D-glucose (FDG). **Methods:** In 55 patients with either known metastatic or newly diagnosed malignant melanoma, whole-body PET scanning was performed on a conventional full-ring dedicated PET tomograph, and multiplanar sections were obtained. Furthermore, anteroposterior projection images simulating images of a dual-head Anger camera operating in coincidence mode were obtained from the PET raw data. Each study was evaluated separately and blindly. Imaging findings were confirmed by biopsy or by at least one imaging modality in addition to PET. **Results:** A total of 108 lesions were evaluated, of which 76 proved to be melanoma metastases. Whole-body PET correctly demonstrated 68 metastases, 6 lesions were classified as questionable metastases and 2 were missed. Whole-body PCS correctly demonstrated 14 metastases, 22 lesions were classified as questionable metastases and 40 metastases were missed. The sensitivities of whole-body PET and whole-body PCS were 89% and 18%, respectively. In PCS lesions in regions of high background activity, such as in the abdomen, were missed more often than in PET ( $p < 0.05$ ). The tumor-to-background contrast was generally lower in PCS than in PET. A further decrease in PCS detection was found in lesions of  $< 22$  mm in diameter. **Conclusion:** The lack of sensitivity precludes the clinical use of whole-body PCS in staging malignant melanoma.

**Key Words:** positron coincidence imaging; fluorine-18-fluorodeoxyglucose; melanoma; tumor staging

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Accurate tumor staging is a key prerequisite for choosing the appropriate treatment strategy in oncology in general. A single imaging modality with the potential to accurately define the extent of disease would be extremely helpful. In several reports, it has been demonstrated that PET with 2-<sup>18</sup>F-fluoro-2-deoxy-D-glucose (FDG) is a sensitive imaging modality in the staging of patients with several metastatic tumors, including melanoma, nonsmall-cell lung cancer and lymphoma (1-5). With modern PET systems, whole-body scans can be acquired in ~ 60 min. The raw data are reconstructed into several hundred transaxial sections that can be reformatted coronally or sagittally. Although these full-ring dedicated PET scanners perform well, they are costly. Radioisotopes for PET scanning also must be produced in a cyclotron, and synthesis of the radiopharmaceuticals requires well-equipped biochemistry laboratories. Hence, PET imaging has been restricted to major centers only.

Satellite PET has been proposed, in which a central cyclotron produces FDG which is delivered to various sites with PET scanning facilities (6). Manufacturers are currently developing systems that consist of coincidence detection circuitry added

onto a standard nuclear dual-head detector system used for planar scintigraphy or SPECT (7-10). This addition makes satellite PET cameras accessible for centers with a small nuclear medicine unit. Although the spatial resolution of these systems seems to be quite good for evaluating myocardial viability (11), the photon detection sensitivity of the systems is quite low for physical reasons. A coincidence detection gamma camera gets an actual counting rate of ~10,000 cps in an FDG tumor study, compared to a counting rate of 30,000 cps with PET (8). Tomographic scanning of large body parts may be not practical because long scan times are needed. For the staging of many tumors, detection of distant metastases is necessary and, thus, imaging should cover the entire body. Hence, one may be tempted to acquire whole-body planar positron coincidence scintigraphy (PCS) rather than tomographic PET slices. The major question is whether PCS has a comparable sensitivity to PET. If so, whole-body PCS would be a reasonable alternative to whole-body PET.

Therefore, we compared the ability of simulated whole-body PCS and whole-body PET to detect metastases using 55 PET scans of patients with malignant melanoma. Diagnoses of lesions was confirmed histopathologically or with at least one imaging modality in addition to PET.

## MATERIALS AND METHODS

Of the patients who were referred to our clinic for PET staging of a known metastatic or a newly diagnosed high-risk melanoma (Breslow  $> 1.5$  mm), 55 consecutive cases were selected. For PET scanning, patients were asked to fast for at least 4 hr before the examination to suppress myocardial glucose utilization. FDG (300-400 MBq) was injected intravenously. FDG was produced in our own radiopharmaceutical laboratory by well-known techniques (12). After an uptake phase of 40 min, emission scanning was started. PET scanning was performed on a commercially available PET scanner (PET Advance; GE Medical Systems, Milwaukee, WI) using the whole-body mode. In this mode, the scanner acquired two-dimensional data over an axial field of view of 14.4 cm for 5 min. Up to 13 increments could be preprogrammed, resulting in an axial field of view of 187 cm. Transmission images were not acquired because this would have prolonged the total acquisition time beyond patient tolerance. To simulate whole-body PCS, anteroposterior projection images were reconstructed from the PET raw data. The two-dimensional projection images were formed by resorting the sinogram data after normalization of the data efficiencies.

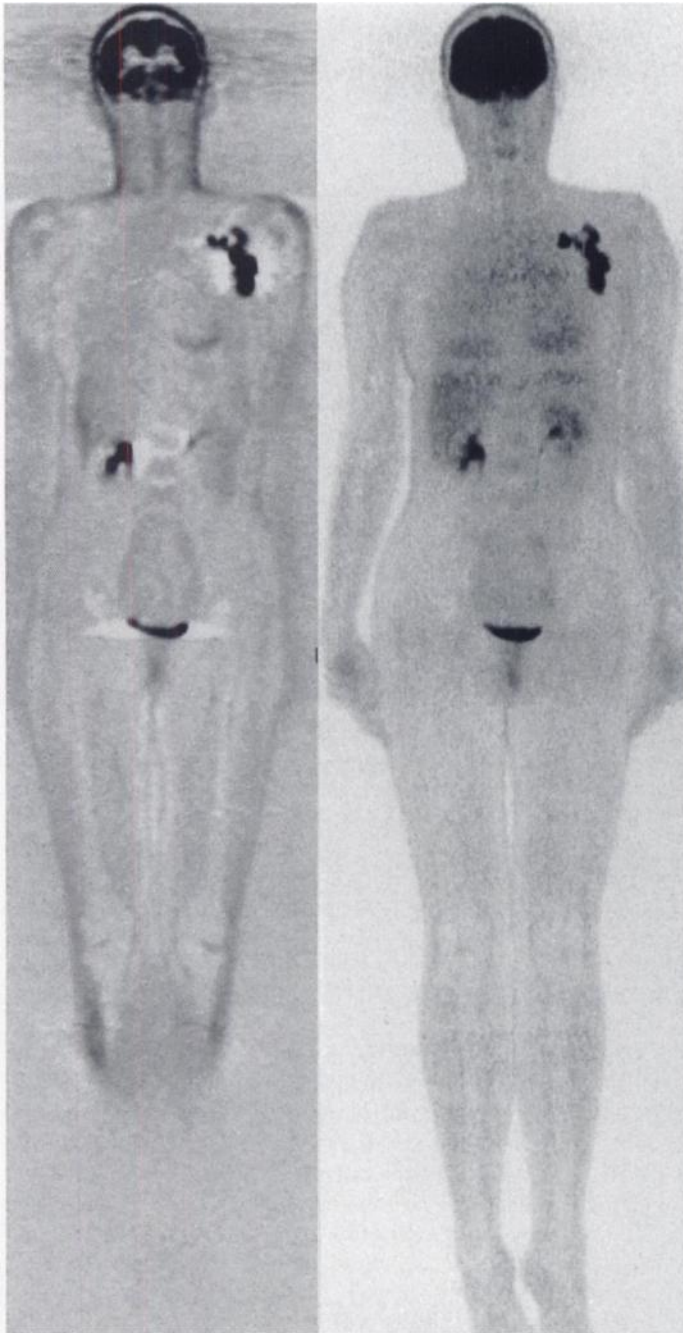
Positron coincidence scintigraphy and PET images were documented by using a 600-dpi laser printer with a digital interface (A&S; Münster, Germany). The paper copies of PCS and PET images were used for interpretation. To assure relative uniformity in scan appearance, a level and window setting were used that brought the brain into an intensity range just below the upper window level, as described elsewhere (13). Positron coincidence

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**TABLE 1**  
Imaging Results of Detection of Suspicious Lesions (n = 83)

Localization	Positron coincidence scintigraphy score							PET score						
	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Axillary lymph node	2	1	3	—	2	1	1	—	—	—	1	4	1	4
Inguinal lymph node	2	1	3	1	—	—	—	—	—	1	1	4	1	—
Abdominal lymph node	1	—	—	—	2	—	2	—	—	—	—	—	—	5
Curtis, subcutis, soft tissue	9	1	—	—	1	—	—	—	—	1	2	4	1	3
Brain	7	—	—	—	—	—	—	1	—	—	—	3	—	3
Face, neck	7	—	—	—	2	—	2	—	—	2	—	4	—	5
Liver, pancreas, spleen	9	—	—	—	1	—	1	1	—	—	—	4	1	5
Lung	7	2	2	1	—	—	—	—	—	3	—	7	1	1
Bone	6	1	—	2	—	—	—	—	—	2	1	5	—	1
Total	50	6	8	4	8	1	6	2	—	9	5	35	5	27



**FIGURE 1.** Coronal emission PET scan (left) and positron coincidence scintigraphy scan (right) in a 40-yr-old patient. Both PET and position coincidence scintigraphy show the lymph node metatases in the left axilla.



**FIGURE 2.** Coronal emission PET scan (left) and positron coincidence scintigraphy scan (right) in a 30-yr-old patient. The lymph node metastasis is shown clearly in PET. Positron coincidence scintigraphy shows only a spot of slightly increased FDG accumulation.



**FIGURE 3.** Coronal emission PET scan (left) and positron coincidence scintigraphy scan (right) in a 34-yr-old patient. PET shows a lymph node metastasis in the soft tissues of the left upper leg. Positron coincidence scintigraphy does not demonstrate any pathologic FDG uptake.

scintigraphy and PET scans were interpreted independently and without knowledge of the results of other examinations or of the other scanning study.

FDG accumulation in the lesions was scored visually with one of seven grades, from 0 (no accumulation) to 6 (high accumulation, similar to the FDG uptake in the brain). This grading actually represented the visual tumor-to-background ratios. A lesion was defined as a focus of increased FDG uptake above the intensity of the surrounding activity, excluding the renal pelvis, urinary bladder and myocardium, if present. A lesion with no enhanced FDG uptake was interpreted as nonmalignant. A lesion that showed an intense FDG uptake (score = 4–6) and had a nodular appearance was very likely to be malignant. Focal lesions of distinct but clearly lower FDG uptake as compared with brain FDG uptake were possibly malignant. A lesion that showed a less circumscribed appearance and was localized in the arms or legs was very likely to represent an inflammatory process after subcutaneous injection of interferon.

At first PET scans were interpreted prospectively. In a second step, corresponding PCS scans were presented to three experienced



**FIGURE 4.** Coronal emission PET scan (left) and positron coincidence scintigraphy scan (right) in a 48-yr-old patient. PET shows a metastasis in the left brain and the edge of a metastasis in the right lung. In addition, PET shows increased FDG uptake in the muscles of both lower legs. No increased FDG uptake is seen in the positron coincidence scintigraphy image.

nuclear physicians. Again, image reading was performed by separate observers who had no knowledge of histopathologic data or other scanning results.

All patients were evaluated with clinical history, physical examination, routine clinical laboratory tests, chest radiography and ultrasound (US) of the regional lymph nodes and of the abdomen. Any lesion that was suspicious for metastasis was either confirmed histopathologically or with CT, MRI or both imaging modalities. The melanoma metastases verified in this way represented the gold standard in our study.

In a consequent matching step, the findings of all readers could be defined as true- or false-positive. Interobserver variability was tested by comparing the scores of the three readers in a  $3 \times 2$  contingency table. Consequently, discordant findings were discussed and a consensus was reached on the importance of the observed lesions. Sensitivity was calculated for very likely malignant findings only (highly specific evaluation) and for all findings (highly sensitive reading).

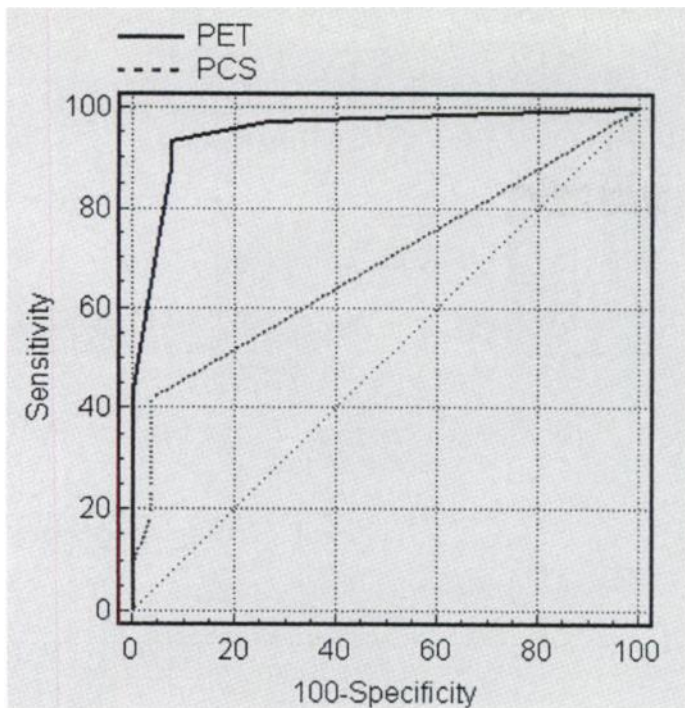


FIGURE 5. Receiver operating characteristic analysis.

The seven scores also were used for a receiver operating characteristic (ROC) analysis. A standard PC spreadsheet application was used to calculate false- and true-positive fractions for both PET and PCS. The same program was used for diagram plotting and calculating the area under the curves.

To assess a possible correlation between intensity of PCS findings and intensity of PET findings, the Spearman rank correlation was calculated. Linear regression was not used because our data apparently were not normally distributed.

## RESULTS

By using the histopathologic and combined imaging information (PET, PCS, US, CT and MRI), we found a total of 108 lesions in the 55 patients. In correlation with clinical history, 19 lesions in 11 patients with an increased but less circumscribed FDG uptake were due to inflammation caused, for example, by subcutaneous injection of interferon or by postoperative reparative process. Three lesions in two patients with enhanced FDG accumulation obviously represented muscle activity, and another three lesions in three patients obviously demonstrated reconstruction artifacts in PCS. After these lesions were excluded, 83 suspicious lesions in 24 patients remained in the study. Of these lesions, 76 proved to be metastases of melanoma, and 7 represented benign lesions (Table 1 and Figs. 1–4). Diagnoses were confirmed with histologic examination in 25 of 83 lesions and in 17 of 24 patients, respectively. Fifty-eight lesions were clearly identified with at least one other imaging modality.

With PET, 68 metastases were correctly identified, 6 metastases were questionable and 2 metastases (1 in the brain and 1 in the liver) were missed. The calculated sensitivity of PET was 89%, using a highly specific reading. With PCS, 14 lesions were correctly identified as metastases, 22 lesions were possibly metastatic and 40 metastases were missed. Taking only highly malignant lesions into account, the sensitivity of PCS was 18%.

The ROC curves for PET and PCS interpretation were very different (Fig. 5). While PET interpretation started with 42% sensitivity at the maximum specificity level, PCS only reached a 41% point at a 96% specificity. The area under the curve was

TABLE 2  
Influence of High Versus Low Background Activity for Lesion Detection in the Trunk

Localization	PCS score						PET score							
	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Central	29	4	5	3	2	—	3	—	—	4	3	25	3	11
Lateral	2	2	3	—	2	1	1	—	—	—	1	4	1	5

Central = high background activity; Lateral = low background activity.

0.955 for PET and 0.688 for PCS. The p value for the difference of the areas under the curves was  $< 0.005$ .

To analyze the influence of the background activity for lesion detection in the trunk, two groups of regions were created. The group with low background activity, in other words the axillary lymph nodes, represented the lateral lesions. Lesions closer to the midline with high background activity represented the central lesions. The detection of lateral metastases was significantly higher than that of central metastases (chi-square test,  $p = 0.01248$ ) (Table 2).

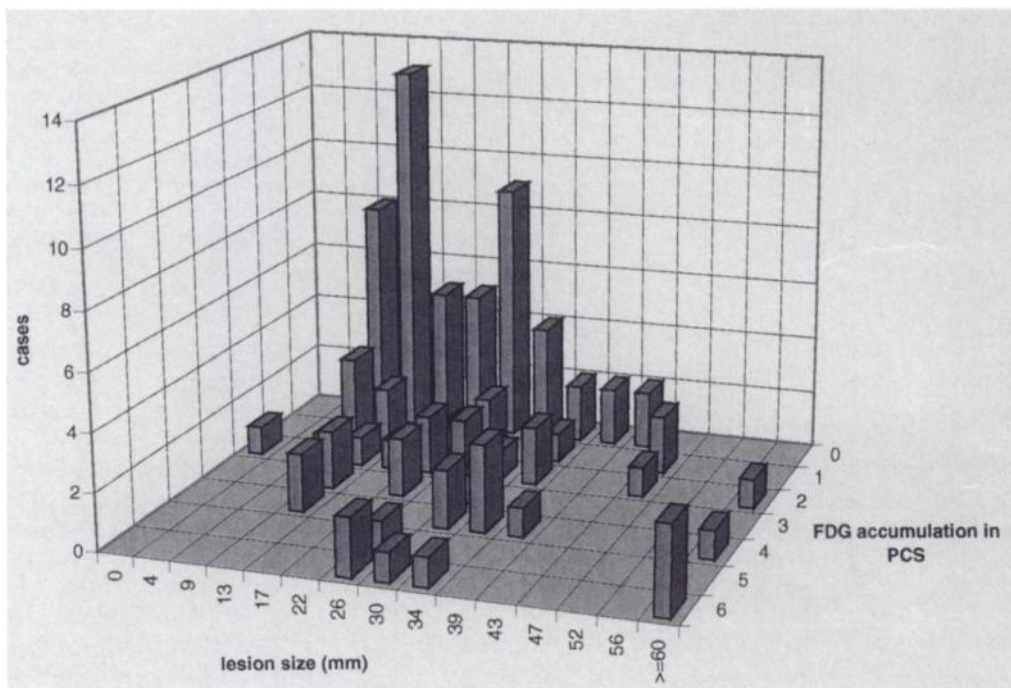
We further compared the tumor-to-background ratios of PET and PCS findings. In 16% the findings had a comparable FDG accumulation in PET and PCS, and in 84% the findings had a lower FDG accumulation in PCS than in PET. The Spearman correlation coefficient was 0.37.

Some of the very intense PET findings that were missed in PCS reading were obviously small lesions. To assess the hypothesis of a lower threshold of lesion size for PCS detection, tumor-to-background ratios of PCS were plotted against the size of the findings (Fig. 6). Lesions of a size of 22 mm or smaller were missed significantly more often (FDG accumulation = 0) than larger lesions (Wilcoxon signed rank test,  $p < 0.05$ ). The statistical analysis of the interobserver variability did not show significant differences between the three readers ( $p > 0.05$ ).

## DISCUSSION

PET cameras with the ability to tomographically evaluate the entire body of a patient are expensive. To make PET more widely available, it would be desirable to have cheaper detection systems available. Currently, equipment manufacturers are working on dual-head, camera-based coincidence detection schemes. Their major drawback is their inability to tolerate high counting rates, making the systems substantially less efficient (14). The question may be asked of whether tomographic imaging is at all necessary, because tomographic data acquisition is time-consuming. To our knowledge, this is the first study that compares the clinical value of whole-body PET and simulated whole-body PCS in the detection of metastases.

The results of this study show that adequate whole-body staging, at least in malignant melanoma, requires tomographic data because the sensitivity of lesion detection is less than half if only planar data of coincidence detection are used. In particular, small lesions cannot be identified with PCS. However, it is the detection of small lesions which makes PET scanning so attractive for tumor staging. The cross-sectional imaging modalities of US, CT and MRI are excellent in demonstrating lesions once they have attained a size of 1.0–1.5 cm. The only criteria of these anatomical imaging modalities for tumor involvement is morphologic. That is, the criteria rely on the size and shape of lymph nodes. Especially, normal-sized lymph nodes or lesions of  $< 1$ –1.5 cm, if at all seen on anatomical imaging, cannot be classified as benign or malignant. It is in this crucial size range that FDG PET seems to be superior.



**FIGURE 6.** Accumulation of FDG in positron coincidence scintigraphy compared to lesion size.

The results reveal that small lesions (< 2.2 mm) and lesions in regions of high relative background are more often missed with positron coincidence scintigraphy and that the tumor-to-background ratio is, in general, less in positron coincidence scintigraphy than it is in PET.

Other groups have reported the detection of malignancies using single-photon technology with special collimated gamma cameras using FDG. Holle et al. (15) studied 50 patients with breast carcinoma. Studies were performed with a dual-head gamma camera equipped with a 0.5-inch thick crystal for better photon detection efficiency. Whole-body scans and additional SPECT scans were acquired. All primary tumors with an extension of > 2.3 cm could be identified. In smaller tumors, sensitivity showed a marked decrease. Holle et al. (15) stated that the detection of distant metastases depended on the size and the location. Macfarlane et al. (16) compared the results of a triple-head SPECT camera fitted with ultra-high-energy collimators and PET in oncology with FDG. With SPECT, only 5 of 14 lesions that were < 3 cm were detected. The authors concluded that the lack of sensitivity in lesions that were < 2–3 cm hampered the clinical application of gamma cameras in tumor detection with FDG. It can be expected that the resolution will increase with newer camera systems.

Our study clearly has some drawbacks, but we do not feel that they diminish its value. First, we have used only data from one tumor, i.e., melanoma. This is justified because melanoma has a relatively high FDG uptake into lesions (1,2). Hence, they are often intensely visible, which should make projection imaging more rather than less adequate to visualize lesions. With a sensitivity of 18%, this is apparently not the case, and in other tumors in which the lesions have less FDG uptake, even worse sensitivities have to be expected.

The second drawback is that data of whole-body positron coincidence scintigraphy had to be simulated by reconstructing anteroposterior-projection images from PET raw data. Again, we believe that this is not a severe drawback of the study and that our findings can be extrapolated to whole-body positron coincidence scintigraphy obtained with dual-head coincidence detection cameras. Although it could be stated that our data are simulated planar positron emission scintigrams, physically we

are not performing any data simulation. In fact, as with a dual-head, NaI Anger camera retrofitted with a coincidence circuitry, we acquired projection images with the bismuth germanate-based coincidence circuitry of our PET scanner. This set-up is actually more sensitive than a NaI set-up, and so the projection data as acquired by us should be better than those acquired with a coincidence dual-head Anger camera. If anything, the spatial resolution of standard PET cameras is higher. So the only difference between an actual and a simulated situation is in the type of detector system.

Finally, one might argue that, using planar techniques, the data collection time could be extended to provide a better signal-to-noise ratio. Although this is true, the projection images reconstructed with PET incorporate data from all detectors and contain a counting rate that, due to detector sensitivity, is higher than that of a dual-head coincidence detection system. The total scanning time of 1 hr as used in our scans would not provide a higher signal-to-noise in planar dual-head coincidence systems. The only factor that would favor such systems is that their axial field of view is 2–2.5 times larger than that of top-of-the-line PET equipment.

## CONCLUSION

Our data suggest that tumor staging with PET has to be performed tomographically in most settings because position coincidence scintigraphy imaging has a far inferior sensitivity. It must be demonstrated whether or not tomographic imaging with dual-head systems will provide extensive body coverage in the time required by most tumor staging procedures.

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# Thallium-201, Technetium-99m-Tetrofosmin and Iodine-131 in Detecting Differentiated Thyroid Carcinoma Metastases

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The purpose of this study was to assess the detectability of differentiated thyroid carcinoma (DTC) metastases by <sup>99m</sup>Tc-tetrofosmin and to compare the results of <sup>99m</sup>Tc-tetrofosmin with <sup>131</sup>I and <sup>201</sup>Tl. The reliability of <sup>201</sup>Tl and <sup>99m</sup>Tc-tetrofosmin scanning during suppression therapy also has been studied. **Methods:** A prospective study was performed on 41 patients (30 females, 11 males) with DTC (30 papillary, 11 follicular) who had undergone total thyroidectomy and received an average dose of 117 mCi (4329 MBq) of radioiodine for ablation of postsurgical residual thyroid tissue. All patients (n = 41) had <sup>201</sup>Tl, <sup>99m</sup>Tc-tetrofosmin or <sup>131</sup>I whole-body imaging after discontinuation of thyroid hormone replacement (thyroxine-off group). Eight of 14 patients with distant metastases also were imaged when they were on thyroxine therapy both with <sup>201</sup>Tl and <sup>99m</sup>Tc-tetrofosmin (thyroxine on-and-off group). Radiologic studies (chest radiography, CT and MRI), serum thyroglobulin assays and histopathologic examinations were performed to clarify the presence of metastases with positive uptake on any of three radionuclide studies. **Results:** In 26 of 41 patients all three scans were negative. These patients also clinically didn't show any evidence of metastases. Fourteen patients were considered to have distant metastases on the basis of clinical, radiologic and histopathologic findings. The sensitivities of <sup>201</sup>Tl, <sup>99m</sup>Tc-tetrofosmin and <sup>131</sup>I in diagnosing distant metastases were comparable (0.85, 0.85 and 0.78, respectively). Iodine-131 was much more sensitive than <sup>201</sup>Tl and <sup>99m</sup>Tc-tetrofosmin for demonstrating residual thyroid tissue after surgery (1.00, 0.33 and 0.33, respectively). The only false-positive case involved radioiodine uptake in a tuberculoma. Thyroxine-on images of 8 patients with distant metastases showed no difference from their thyroxine-off images regarding the site, number and uptake of metastases. **Conclusion:** Technetium-99m-tetrofosmin and <sup>201</sup>Tl imaging are highly sensitive for detecting differentiated thyroid carcinoma metastases and do not require prior withdrawal of thyroid hormone suppressive therapy.

**Key Words:** differentiated thyroid carcinoma; iodine-131; thallium-201; technetium-99m-tetrofosmin

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**R**adioiodine (<sup>131</sup>I) scintigraphy is widely recommended and used for the follow-up of differentiated thyroid carcinoma (DTC) patients to detect residual, recurrent or metastatic disease (1). However <sup>131</sup>I scintigraphy has several disadvantages. Before radioiodine scanning, thyroid hormone medication should be discontinued, which promotes a hypothyroid state stimulating tumor growth. A relatively high radiation burden is given to the patient. Finally, a negative radioiodine scan does not exclude the presence of thyroid cancer.

Thallium-201 scintigraphy is used increasingly for detecting and following up DTC. Thallium-201 scanning can be used while the patient is receiving thyroxine replacement therapy and requires only one visit (1). A large number of studies has been performed to evaluate the role of <sup>201</sup>Tl in the follow-up of DTC with nonuniform and conflicting results. Other alternative agents such as <sup>99m</sup>Tc-sestamibi (MIBI) (2), <sup>111</sup>In-octreotide (3), <sup>99m</sup>Tc-tetrofosmin (4,5) and <sup>18</sup>F-fluorodeoxyglucose (6) also have been tried for detecting DTC metastases.

Technetium-99m-tetrofosmin is being used currently to study myocardial perfusion (7) and has been reported to localize in various types of malignant tumors (8,9). The purpose of this study was to assess the detectability of DTC metastases by <sup>99m</sup>Tc-tetrofosmin and to compare the results of <sup>99m</sup>Tc-tetrofosmin with those of <sup>131</sup>I and <sup>201</sup>Tl. The reliability of <sup>201</sup>Tl and <sup>99m</sup>Tc-tetrofosmin during suppression therapy also has been studied.

## MATERIALS AND METHODS

### Patients

A prospective study was performed on 41 patients (30 females, 11 males) with DTC who were referred to the nuclear medicine department for evaluation of the presence of metastatic disease. The age range was 8-78 yr with a median age of 44.4 yr. The histopathologies studied were: 30 papillary carcinomas and 11 follicular thyroid carcinomas (among them one case of Hürthle cell carcinoma). All patients had undergone near total thyroidectomy and received an average dose of 117 mCi (4329 MBq) radioiodine for ablation of residual thyroid tissue.

**Thyroxine-Off Imaging.** Eight weeks before imaging, thyroxine therapy was discontinued and switched to triiodothyronine for 4

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