The present study was to assess the detectability of differentiated thyroid carcinoma (DTC) metastases by 99mTc-tetrofosmin and to compare the results of 99mTc-tetrofosmin with 131I and 201Tl. The reliability of 201Tl and 99mTc-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 201Tl, 99mTc-tetrofosmin or 131I 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 201Tl and 99mTc-tetrofosmin (thyroxine on-and-off group). Radiologic studies (chest radiography, CT and MRI), serum thyroglobulin asays 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 did not 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 201Tl, 99mTc-tetrofosmin and 131I in diagnosing distant metastases were comparable (0.85, 0.85 and 0.78, respectively). Iodine-131 was much more sensitive than 201Tl and 99mTc-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 201Tl 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

Radioiodine (131I) scintigraphy is widely recommended and used for the follow-up of differentiated thyroid carcinoma (DTC) patients to detect residual, recurrent or metastatic disease (J). However 131I 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 (J). A large number of studies has been performed to evaluate the role of 201Tl in the follow-up of DTC with nonuniform and conflicting results. Other alternative agents such as 99mTc-sestamibi (MIBI) (2), 111In-octreotide (3), 99mTc-tetrofosmin (4) and 18F-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 the this study was to assess the detectability of DTC metastases by 99mTc-tetrofosmin and to compare the results of 99mTc-tetrofosmin with those of 131I and 201Tl. The reliability of 201Tl and 99mTc-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
FIGURE 1. (A) A 31-yr-old woman with follicular thyroid carcinoma. Thallium-201 (left upper), 99mTc-tetrofosmin (right upper) and 131I (lower) images show intense activity in right humerus in thyroxine-off images. (B) Thyroxine-on 201TI (left upper) and 99mTc-tetrofosmin (left lower) images of same patient. No difference to thyroxine-off images in site and lesion activity. CT (right) also confirms metastatic lesion in right humerus.

wk. The last 2 wk the patients did not receive any thyroid hormone replacement. All patients had 201TI, 99mTc-tetrofosmin and 131I whole-body scanning that were grouped as thyroxine-off images. Thyroglobulin (Tg) levels were assayed at the time of this maximum thyroid-stimulating hormone stimulation.

Thyroxine On-and-Off Imaging. Of the 41 patients, 14 were determined to have distant metastases on the basis of clinical, radiologic and histopathologic findings. Eight of these 14 patients also were imaged when they were on thyroxine therapy, both with 201TI and 99mTc-tetrofosmin, which were grouped as thyroxine on-and-off images.

Imaging

The whole-body scans and 5-min static images of the cranium, neck, chest, abdomen and pelvis from anterior and posterior positions were obtained with a low-energy, all-purpose (LEAP)
collimator 20 min after the intravenous injection of 74 MBq (2 mCi) $^{201}$Tl. Twenty minutes after the intravenous injection of 740 MBq (20 mCi) $^{99m}$Tc-tetrofosmin, whole-body scans and 5-min spot images of the same positions above were recorded with a LEAP collimator. Forty-eight hours after the oral administration of 185 MBq (5 mCi) $^{131}$I, 150,000 counts were collected for each of the anterior and posterior head, neck, chest, abdomen and pelvis images using a high-energy collimator.

Other Diagnostic Studies
Clinical follow-up, radiologic studies (chest radiography, CT and MRI), serum Tg assays and histopathologic examinations were performed to clarify the presence of metastasis with positive uptake on any of three radionuclide studies.

Image Interpretation
The scintigraphic findings on each of three scans were evaluated independently for the presence of thyroid cancer metastases. Thallium-201, $^{99m}$Tc-tetrofosmin and $^{131}$I scans were visually interpreted as positive when increased focal activity was present with respect to background activity. Any focal uptake in the thyroid bed after completion of ablation was regarded as positive for the presence of local recurrence. If ablation was not completed, uptake in the thyroid bed was attributed to postsurgical residual thyroid tissue after surgery. Serum Tg levels were considered positive if the values were above 10 ng/ml (normal range: 0–90 ng/ml) (10).

Statistical Analysis
To calculate the lesion-to-background ratio (L:B) the same region of interest was drawn around the metastatic area (L) and its symmetric contralateral site (B). The ratio of lesion-to-background regions was named the index. The mean indices of $^{201}$Tl, $^{99m}$Tc-tetrofosmin and $^{131}$I were calculated. The Student’s t-test was used to assess significance. A p value of <0.05 was considered statistically significant.

The sensitivity of $^{201}$Tl, $^{99m}$Tc-tetrofosmin and $^{131}$I for diagnosing DTC metastases was calculated. The McNemar test was used to investigate the significance of the difference between the sensitivity values.

RESULTS
According to the thyroxine-off images, patients were classified into four groups on the basis of distant metastases (lung, bone and cervicomedial lymph node metastases). Residual thyroid tissue and local recurrent cancer in the thyroid bed were not considered.

Group 1
Thallium-201, Technetium-99m-Tetrofosmin and Iodine-131 Whole-Body Scan Negative. All three scans were negative for metastases in 26 patients. Except for 4 patients the Tg levels were low in this group. In 2 patients the elevated Tg level was attributed to postsurgical residual thyroid tissue. No satisfactory explanation for the elevated Tg level could be found in the remaining 2 patients using other imaging methods.

Group 2
Thallium-201, Technetium-99m-Tetrofosmin and Iodine-131 Whole-Body Scan Positive. The second group consisted of 9 patients in whom all three scans were positive for distant metastases in identical sites. The Tg levels were elevated in all patients in this group. (Fig. 1).

Group 3
Thallium-201 and Technetium-99m-Tetrofosmin Whole-Body Scan Negative with Iodine-131 Whole-Body Scan Positive. Three patients had positive $^{131}$I scans and negative $^{201}$Tl and
Thallium-201 and Technetium-99m-Tetrofosmin Whole-Body Scan Positive with Iodine-131 Whole-Body Scan Negative. In 3 patients 201TI and 99mTc-tetrofosmin whole-body scans could localize bone and cervicomediastinal lymph node metastases that were not visualized with 131I (Fig. 3). The Tg levels were elevated in all these patients. The presence of metastases was established by CT and histopathologic examinations.

Uptake in the thyroid bed due to postsurgical residual thyroid tissue was present in the radioiodine scans of 9 patients with only 3 of them having corresponding 201TI and 99mTc-tetrofosmin accumulation. Seven of these patients had distant metastases, and the thyroglobulin levels were elevated in all 9 patients. No case of local neck recurrence was encountered in the study group.

FIGURE 3. (A) Anterior 201TI (left upper) and 99mTc-tetrofosmin (left lower) images show increased uptake in left frontal and left upper mediastinal regions. These regions showed no detectable 131I (right) uptake. N = nose; C = chin; J = jugular (suprasternal) notch. (B) Corresponding CT scans show lesions in left frontal bone (left) and left mediastinal lymph nodes (right).
A comparison of the results of imaging with $^{131}$I, $^{201}$Tl and $^{99m}$Tc-tetrofosmin is presented in Table 1. Thallium-201 and $^{99m}$Tc-tetrofosmin were clearly superior to $^{131}$I in diagnosing bone metastases. Iodine-131 was much more sensitive than $^{201}$Tl and tetrofosmin for demonstrating residual thyroid tissue.

The mean indices of $^{201}$Tl, $^{99m}$Tc-tetrofosmin and $^{131}$I were 1.69 ± 0.36, 2.3 ± 1.38 and 9.13 ± 6.84, respectively. There was no significant difference between the mean $^{201}$Tl and $^{99m}$Tc-tetrofosmin indices. There was a significant difference between the mean $^{201}$Tl and $^{131}$I and $^{99m}$Tc-tetrofosmin and $^{131}$I indices (p = 0.006, p = 0.01, respectively).

The results of the thyrroxine on-and-off images are presented in Table 2. The mean index of $^{201}$Tl on and off thyrroxine medication was 1.51 ± 0.36 and 1.56 ± 0.39, respectively. The $^{99m}$Tc-tetrofosmin indices on-and-off thyrroxine treatment were 1.56 ± 0.32 and 1.61 ± 0.32. No significant difference in lesion uptake was present between thyrroxine-on and thyrroxine-off scanning with $^{201}$Tl and $^{99m}$Tc-tetrofosmin.

The sensitivity and specificity values of $^{201}$Tl, $^{99m}$Tc-tetrofosmin and $^{131}$I for detecting DTC metastases are shown in Table 3. Thallium-201 and $^{99m}$Tc-tetrofosmin were equally sensitive. The sensitivity difference between $^{131}$I and $^{201}$Tl/$^{99m}$Tc-tetrofosmin was not significant.

**DISCUSSION**

Iodine-131 imaging is accepted as the gold standard for demonstrating thyroid carcinoma metastases. However, not all DTC metastases take up radiiodine. This study was conducted to evaluate the possible alternative or complementary role of $^{201}$Tl and the new tumor agent $^{99m}$Tc-tetrofosmin in following up DTC patients.

Conflicting results about the efficacy of $^{201}$Tl imaging have been reported. Hoefnagel et al. (1) in a study of 326 patients found a sensitivity of 94% and a specificity of 97% whereas Dadparvar et al. (11) reported significantly lower sensitivity and specificity values (60% and 82%, respectively). Brendel et al. (12) in their study of 31 patients concluded that $^{201}$Tl imaging cannot be recommended for the follow-up of DTCs because of its poor sensitivity in detecting tumor sites (45%). The view of Brendel et al. was shared in a recent article by Lorberboym et al. (13) who found $^{131}$I imaging with diagnostic doses more accurate than $^{201}$Tl imaging in DTC patients. In an independent study that was conducted previously in our department, results similar to those of Hoefnagel et al. were obtained (14). In another study Dadparvar et al. compared $^{201}$Tl, MIBI and $^{131}$I imaging in 34 patients with DTC and found a poor sensitivity (36%) for MIBI; the specificity was considerably high (89%) (2). The study of Yen et al. (15) about the role of MIBI in diagnosing metastatic Hürthle cell carcinoma revealed more encouraging results for the tracer (81.8% sensitivity, 100% specificity) in 37 patients. In 60 patients with DTC, Meyer et al. (16) reported MIBI scintigraphy to be the best diagnostic method for detecting metastasis in patients with oxyphilic carcinoma and a complementary imaging to $^{131}$I scanning in patients with follicular thyroid carcinoma.

Technetium-99m-tetrofosmin is a new myocardial perfusion imaging agent with similar chemical properties to sestamibi. Both are cationic agents and are accepted to be concentrated in mitochondria (5). Accumulation of $^{99m}$Tc-tetrofosmin in various tumors has been reported (8,9). Technetium-99m-tetrofosmin uptake in DTC metastases has not been studied extensively. Recently Lind and Gallowitsch (17) published a prospective trial on 146 patients in which $^{99m}$Tc-tetrofosmin was concluded to be a promising tracer to detect malignant recurrence and distant metastases of DTC. Successful visualization of DTC metastases with $^{99m}$Tc-tetrofosmin also were reported in two recent case reports (5, 18).

This study shows that $^{99m}$Tc-tetrofosmin and $^{201}$Tl are at least as sensitive as $^{131}$I in detecting distant metastases. Among 23 tumor sites, 21 were visualized with $^{201}$Tl and $^{99m}$Tc-tetrofosmin and 17 with $^{131}$I. Thallium-201 and $^{99m}$Tc-tetrofosmin were clearly superior to radiiodine in diagnosing bone metastases. Similar successful results for $^{99m}$Tc-tetrofosmin were obtained by Lind and Gallowitsch (17) in 146 patients in whom, among 47 tumor sites, 36 were $^{99m}$Tc-tetrofosmin positive whereas $^{131}$I was only possible in 21 sites. In contrast to our study, Brendel et al. found $^{201}$Tl to be more sensitive in lung metastases than MIBI (12). Dadparvar et al. (2) found MIBI, which is chemically similar to $^{99m}$Tc-tetrofosmin, to be more sensitive than $^{131}$I in bone metastases. The sensitivity of MIBI for
pulmonary metastases, however, was poor. In cervicomediastinal lymph nodes the results were similar for 201Tl and MIBI as for 201Tl and 99mTc-tetrofosmin in this study (2). Thallium-201 and 99mTc-tetrofosmin may be useful in locating metastatic disease when 131I scintigraphy is negative. In the study of Brendal et al. six 201Tl-positive distant metastases were negative with 131I. In the study of Hoefnagel et al. 201Tl scintigraphy revealed metastases in 39 patients that were not visualized with radioiodine. Lind and Gallowitsch report detecting 17 radioiodine-negative metastases with 99mTc-tetrofosmin (17). Similar to these studies we also had three 201Tl and 99mTc-tetrofosmin-positive distant metastases that were missed with 131I.

In this study residual thyroid tissue was successfully demonstrated with 131I in 9 patients whereas the concomitant 201Tl and 99mTc-tetrofosmin showed uptake in only 3 of them. All published studies agree that 131I is the best imaging method for delineating residual thyroid tissue (1,2,13,17).

The reliability of 201Tl and 99mTc-tetrofosmin scanning during suppression therapy also was demonstrated in this study since no difference was found between thyroxin on-and-off images in the thyroxin on-and-off group. Dadparvar et al., Hoefnagel et al., Lind and Gallowitsch and Nemec et al. also proposed that 201Tl, 99mTc-tetrofosmin scans could be performed without withdrawal of thyroid suppressive therapy (1,2,17,19).

CONCLUSION

Although no significant difference was found between 201Tl and 99mTc-tetrofosmin images in detecting DTC metastases, 99mTc-tetrofosmin has some advantages over 201Tl as a kit-based radiopharmaceutical that allows imaging whenever needed and permits administration of higher doses, resulting in better quality imaging.

The sensitivity of 201Tl, 99mTc-tetrofosmin and 131I for diagnosing distant metastases of DTC were comparable. Radioiodine is more sensitive than 201Tl and 99mTc-tetrofosmin for demonstrating postsurgical residual thyroid tissue.

Before 131I imaging, thyroid hormone medication should be discontinued which not only places patients in a hypothyroid state but also may promote tumor growth. Technetium-99m-tetrofosmin or 201Tl scanning on thyroxine medication combined with a Tg assay may be used to follow-up DTC patients after successful ablation of postsurgical residual thyroid tissue. If either of the tests is suspicious for recurrent DTC 131I whole-body scintigraphy should be performed to determine whether the lesions are amenable to radioidine therapy.

Thallium-201 and 99mTc-tetrofosmin can detect 131I-negative metastases in patients with high Tg levels. In patients with high Tg levels but negative radioiodine scans a further attempt to localize metastases can be made with either a 201Tl or 99mTc-tetrofosmin whole-body scan. No metastases will be missed by combining 131I imaging with either 201Tl or 99mTc-tetrofosmin imaging.

REFERENCES