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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 asses the detectability of differentiated thyroid carcinoma (DTC) metastases by ^{99m}Tc-tetrofosmin and to compare the results of ^{99m}Tc-tetrofosmin with ^{131}I and ^{201}Tl. The reliability of ^{201}Tl and ^{99m}Tc-tetrofosmin scanning during supression 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 ^{201}Tl, ^{99m}Tc-tetrofosmin or ^{131}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 ^{201}Tl and ^{99m}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 ^{201}Tl, ^{99m}Tc-tetrofosmin and ^{131}I in diagnosing distant metastases were comparable (0.85, 0.85 and 0.78, respectively). Iodine-131 was much more sensitive than ^{201}Tl and ^{99m}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 ^{201}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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Radioiodine (^{131}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 ^{131}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 ^{201}Tl in the follow-up of DTC with nonuniform and conflicting results. Other alternative agents such as ^{99m}Tc-sestamibi (MIBI) (*2*), ^{111}In-octreotide (*3*), ^{99m}Tc-tetrofosmin (*4,5*) and ^{18}F-fluorodeoxyglucose (*6*) also have been tried for detecting DTC metastastases.

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 asses the detectability of DTC metastases by ^{99m}Tc-tetrofosmin and to compare the results of ^{99m}Tc-tetrofosmin with those of ^{131}I and ^{201}Tl. The reliability of ^{201}Tl and ^{99m}Tc-tetrofosmin during supression 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

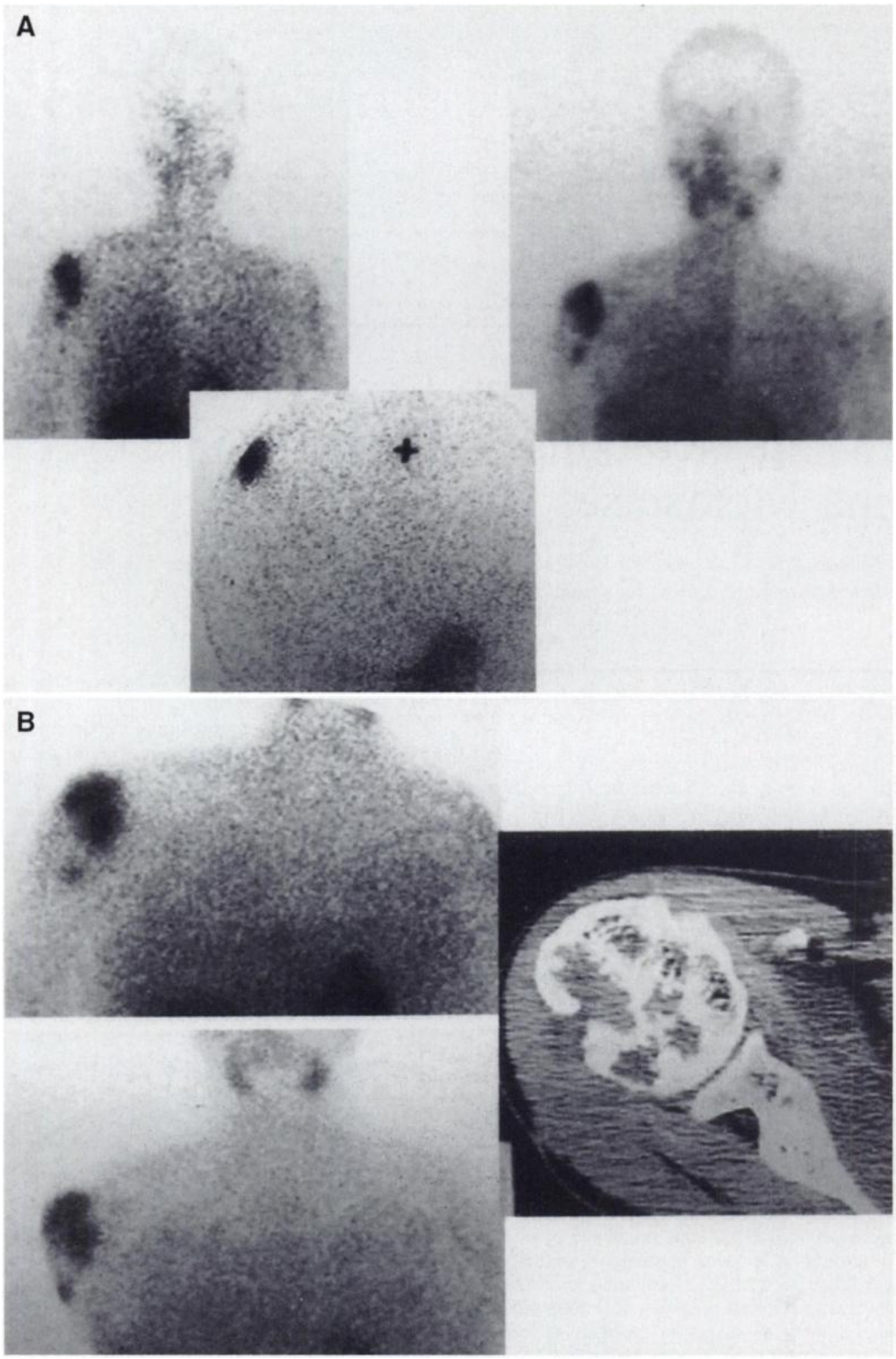

FIGURE 1. (A) A 31-yr-old woman with follicular thyroid carcinoma. Thallium-201 (left upper), ^{99m}Tc-tetrofosmin (right upper) and ^{131}I (lower) images show intense activity in right humerus in thyroxine-off images. (B) Thyroxine-on ^{201}Tl (left upper) and ^{99m}Tc-tetrofosmin (left lower) images 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 ^{201}Tl, ^{99m}Tc-tetrofosmin and ^{131}I 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 ^{201}Tl and ^{99m}Tc-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)

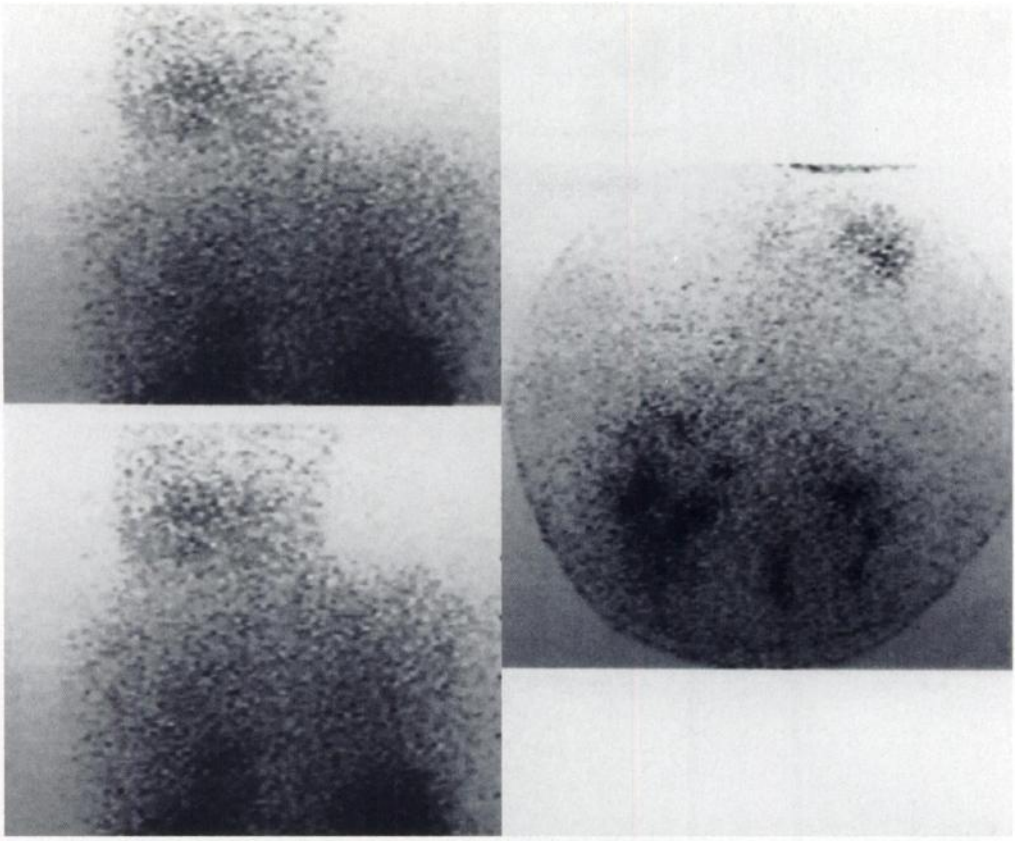

FIGURE 2. A 54-yr-old woman with papillary thyroid carcinoma. Posterior thorax view of ^{201}Tl (left upper), ^{99m}Tc-tetrofosmin (left lower) and ^{131}I (right) scans. Although ^{201}Tl and ^{99m}Tc-tetrofosmin scans are normal, corresponding radioiodine scan of posterior thorax demonstrates multiple increased activities in both lungs.

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 cervicomediastinal 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

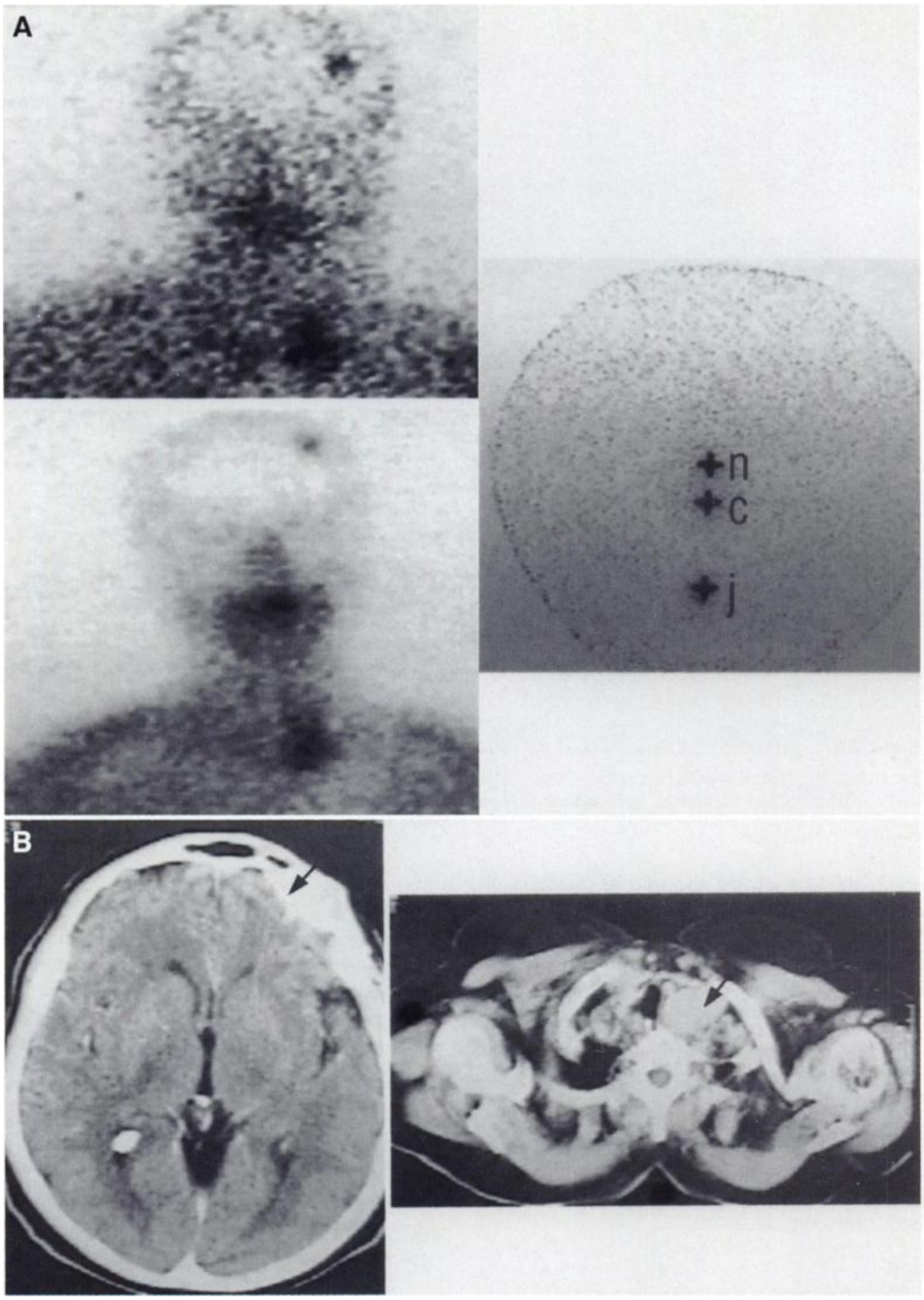

FIGURE 3. (A) Anterior ^{201}Tl (left upper) and ^{99m}Tc-tetrofosmin (left lower) images show increased uptake in left frontal and left upper mediastinal regions. These regions showed no detectable ^{131}I (right) uptake. N = nose; C = chin; J = jugular (suprasternal) notch. (B) Corresponding CT scans show lesions in left frontal bone (left) and left mediastinal lymph nodes (right).

^{99m}Tc-tetrofosmin whole-body scans. In 2 patients metastases corresponding to ^{131}I accumulation in the lungs (Fig. 2) were confirmed by CT. Thyroglobulin levels in these patients were 49.2 and 15 ng/ml. The ^{131}I scan of the third patient showed uptake in the epigastric region. The thyroglobulin level in the patient was 5.18 ng/ml. Surgically a tuberculoma was found between the left hepatic lobe and gastric corpus so that this was accepted as false-positive ^{131}I scintigraphy.

Group 4

Thallium-201 and Technetium-99m-Tetrofosmin Whole-Body Scan Positive with Iodine-131 Whole-Body Scan Negative. In 3 patients ^{201}Tl and ^{99m}Tc-tetrofosmin whole-body scans could localize bone and cervicomediastinal lymph node metastases that were not visualized with ^{131}I (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 ^{201}Tl and ^{99m}Tc-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.

TABLE 1
Comparison of Imaging Results with Iodine-131, Thallium-201 and Technetium-99m-Tetrofosmin

Tumor site	Number of sites	Positive with thallium-201	Positive with tetrofosmin	Positive with iodine-131
Bone metastases	15	15	15	10
Cervicomediastinal metastatic lymph nodes	4	4	4	3
Lung metastases	4	2	2	4
Total	23	21	21	17
Residual thyroid tissue	Number of patients	3	3	9

A comparison of the results of imaging with ^{131}I, ^{201}Tl and ^{99m}Tc-tetrofosmin is presented in Table 1. Thallium-201and ^{99m}Tc-tetrofosmin were clearly superior to ^{131}I in diagnosing bone metastases. Iodine-131was 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 thyroxin on-and-off images are presented in Table 2. The mean index of ^{201}Tl on-and-off thyroxine medication were 1.51 ± 0.36 and 1.56 ± 0.39, respectively. The ^{99m}Tc-tetrofosmin indices on-and-off thyroxine treatment were 1.56 ± 0.32 and 1.61 ± 0.32. No significant difference in lesion uptake was present between thyroxine-on and thyroxine-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-201and ^{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 radioiodine. 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 Brendal 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 Hürtle 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 radioiodine in diagnosing bone metastases. Similar successful results for ^{99m}Tc-tetrofosmin were obtained by Lind and Gallowitsch (*17*) in 146 patients in whom, among 44 tumor sites, 36 were ^{99m}Tc-tetrofosmin positive whereas ^{131}I was positive only in 21 sites. In contrast to our study, Brendel et al. found ^{201}Tl to be more sensitive in lung metastases than bony lesions (*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

TABLE 2
Comparison of Thyroxine-On and -Off Scans

Group	Number of patients	Thallium-201 Thyroxine on/off	Technetium-99m-tetrofosmin Thyroxine on/off	Iodine-131 Off
2	4	+/+	+/+	+
3	3	−/−	−/−	+
4	1	+/+	+/+	−

TABLE 3
Sensitivity and Specificity Values of Thallium-201, Technetium-99m-Tetrofosmin and Iodine-131 Imaging for Detecting Differentiated Thyroid Carcinoma Metastases Separately and in Combination

Radiopharmaceutical	Sensitivity	Specificity
Thallium-201	0.85	1.00
Technetium-99m-Tetrofosmin	0.85	1.00
Iodine-131	0.78	0.96
Thallium-201 + Iodine-131 or Technetium-99m-Tetrofosmin + Iodine-131	1.00	0.96

pulmonary metastases, however, was poor. In cervicomediastinal lymph nodes the results were similar for ^{201}Tl and MIBI as for ^{201}Tl and ^{99m}Tc-tetrofosmin in this study (*2*). Thallium-201 and ^{99m}Tc-tetrofosmin may be useful in locating metastatic disease when ^{131}I scintigraphy is negative. In the study of Brendal et al. six ^{201}Tl-positive distant metastases were negative with ^{131}I. In the study of Hoefnagel et al. ^{201}Tl scintigraphy revealed metastases in 39 patients that were not visualized with radioiodine. Lind and Gallowitsch report detecting 17 radioiodine-negative metastases with ^{99m}Tc-tetrofosmin (*17*). Similar to these studies we also had three ^{201}Tl and ^{99m}Tc-tetrofosmin-positive distant metastases that were missed with ^{131}I.

In this study residual thyroid tissue was successfully demonstrated with ^{131}I in 9 patients whereas the concomittant ^{201}Tl and ^{99m}Tc-tetrofosmin showed uptake in only 3 of them. All published studies agree that ^{131}I is the best imaging method for delineating residual thyroid tissue (*2,12,13,17*).

The reliability of ^{201}Tl and ^{99m}Tc-tetrofosmin scanning during supression 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 ^{201}Tl, ^{99m}Tc-tetrofosmin scans could be performed without withdrawal of thyroid supressive therapy (*1,2,17,19*).

CONCLUSION

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

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

Before ^{131}I 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 ^{201}Tl 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 ^{131}I whole-body scintigraphy should be performed to determine whether the lesions are amenable to radioiodine therapy.

Thallium-201 and ^{99m}Tc-tetrofosmin can detect ^{131}I-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 ^{201}Tl or ^{99m}Tc-tetrofosmin whole-body scan. No metastases will be missed by combining ^{131}I imaging with either ^{201}Tl or ^{99m}Tc-tetrofosmin imaging.

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