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The value of Tc-99m tetrofosmin thyroid scintigraphy in patients with nodular goiter

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The aim of this study is to investigate the value of Tc-99m tetrofosmin (Tc-99m-TF) in conjunction with conventional Tc-99m-pertechnetate (Tc-99m-P) scintigraphy in the differentiation of malignant nodules from benign thyroid nodules. Forty-two patients [(32 females, 10 males; mean age 41 ± 13 years; twenty-two multinodular goiter (MNG) patients with 58 nodules and 20 solitary thyroid nodules (STN)] were included in the study. Thyroid scintigraphy with Tc-99m-P and Tc-99m-TF, thyroid ultrasonography and fine needle aspiration cytology (FNAC) were performed. After IV injection of 370–550 MBq Tc-99m-TF, images were obtained at 15 minutes and evaluated semiquantitatively by using a five point (0–4) scoring system. Four patients with a hypoactive STN, and 1 patient with a hypoactive MNG was found to have thyroid malignancy by histopathological examination; 2 of these patients had false negative benign FNAC results. The tetrofosmin uptake score (TUS) was 2-3-3-3 and 3 in these 5 malignant nodules. Five hyperactive (hot or warm) STN with benign FNAC had a TUS of 2-3-3-3-3. All hypoactive (cold) MNG nodules with benign FNAC (n = 21) had TUS ≤ 2. Our preliminary results suggest that follicular adenomas and thyroid cancers have higher tetrofosmin uptake than benign colloidal goiter nodules. Mitochondrial sequestration of tetrofosmin in benign or malignant follicular cells that proliferate more rapidly than normal follicular cells and/or hypervascularity may be responsible for this. The use of Tc-99m-TF in conjunction with Tc-99m-P thyroid scintigraphy will be helpful in the evaluation of patients with nodular goiter (NG). In patients with a STN, a hypoactive nodule with a high TUS has a higher probability of malignancy; whereas a hyperactive nodule with a high TUS is a follicular adenoma. In patients with MNG, a hypoactive nodule with a high TUS may be suggestive of malignancy despite a benign FNAC result. We think that further studies with Tc-99m-TF are required to confirm these results.

Key words: nodular goiter, thyroid cancer, technetium-99m tetrofosmin thyroid scintigraphy

INTRODUCTION

IN PATIENTS with nodular goiter (NG), differentiation of malignant from benign nodules and selection of patients for operation is a common and important clinical problem. Clinical characteristics of the nodule, ultrasonography (US), radionuclide thyroid imaging and fine needle aspiration cytology (FNAC) results are used in combination in this respect.[1] Although FNAC is currently considered the 'gold standard,' false negative and false positive results may occur[2]; this is especially true in patients with multinodular goiter (MNG) in whom it is clinically important to identify the suspicious nodule to perform FNAC.

In solitary thyroid nodule (STN) and in MNG, there are no specific ultrasonographic findings which can differentiate a benign from malignant nodule.[3] With I-131 thyroid scintigraphy, the probability of malignancy in a hypoactive STN is 15–20%; this probability is 5–10% in hypoactive MNG and 0–4% in hyperactive STN. Because I-131 is

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non-specific in diagnosis of malignancy, different radionuclides such as Cs-131 chloride, Ga-67 citrate, Se-75 chloride, Tl-201 chloride and technetium-99m methoxy-isobutyl-isonitrile have been tried, but specific diagnosis of a malignant nodule could not be established.[1]

Technetium-99m tetrofosmin which is a radionuclide used in myocardial perfusion studies, is also a non-specific tumor seeking agent, probably due to its mitochondrial uptake by rapidly proliferating malignant cells.[4]

In the light of these facts, we decided to investigate the possible value of Tc-99m-TF thyroid scintigraphy in the evaluation of patients with NG.

Table 1 Clinical characteristics of the patients

	STN	MNG
Number of Patients (n)	20	22
Age (Years)	38 ± 13	43 ± 13
Sex (Male/Female)	5/15	5/17
Number of Nodules	20	58
Hypoactive Nodules	15	34*
Hyperactive Nodules	5**	24

STN: Solitary thyroid nodule
MNG: Multinodular goiter
*: FNAC was performed to 22 clinically dominant nodules
**: All thyrotoxic

MATERIALS AND METHODS

Patients

Forty-two patients (10 males, 32 females; mean age 41 ± 13 years) with NG who attended the outpatient clinic of the Department of Endocrinology and Metabolism, Medical School of Akdeniz University were included in the study. The study design was explained to the patients and informed consent was obtained from them. Thyroid ultrasonography, Tc-99m-P, Tc-99m-TF thyroid scintigraphy and FNAC were performed in all patients. Twenty-two patients had MNG with 58 nodules (34 hypoactive, 24 hyperactive). FNAC was performed from the hypoactive nodule which was the dominant nodule by physical examination (i.e. FNAC was performed from 22 hypoactive MNG nodules). Twenty patients had STN; five had a hyperactive nodule and were thyrotoxic (toxic adenoma) whereas 15 had a hypoactive nodule and were euthyroid. FNAC was performed on all hypoactive and hyperactive nodules of patients with STN.

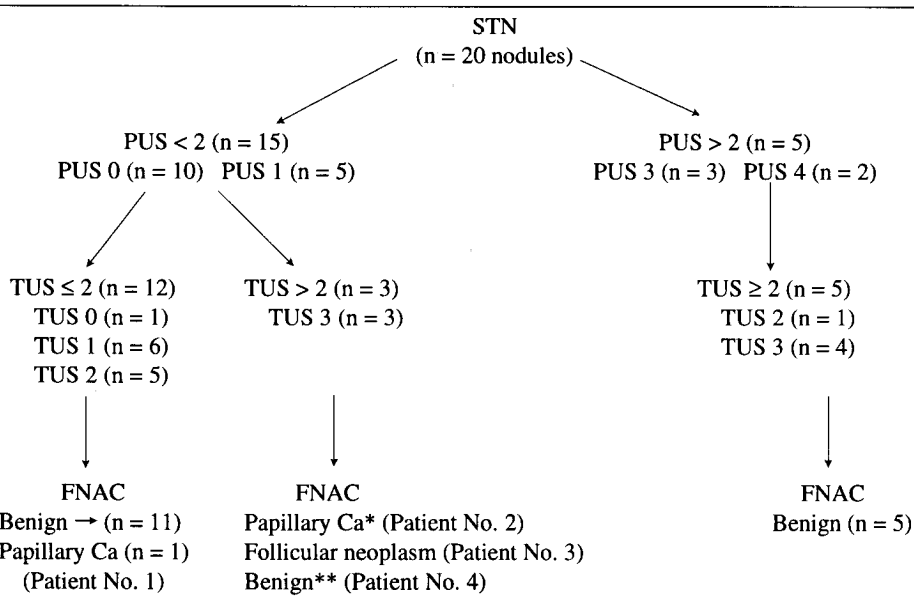
The characteristics of the patients are summarized in Table 1.

Methods

Tc-99m-TF thyroid scintigraphy protocol:

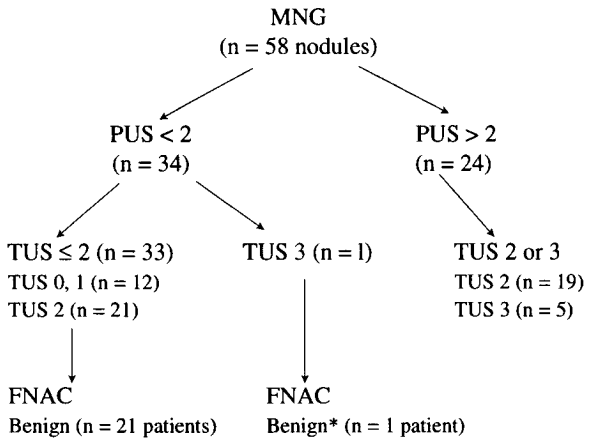
After IV injection of 370–550 MBq Tc-99m-TF, images were obtained at 15 minutes and evaluated semiquantitatively by two Nuclear Medicine specialists with a 5 point

Table 2 The TUS, PUS and FNAC results of patients with STN



STN: Solitary Thyroid Nodule, PUS: Pertechnetate Uptake Score, TUS: Tetrofosmin Uptake Score, FNAC: Fine Needle Aspiration Cytology
*: Although FNAC result was papillary Ca, histopathology revealed follicular Ca
**: Although FNAC was benign, a thyroidectomy was performed and papillary Ca was found

Table 3 The TUS, PUS and FNAC results of patients with MNG



MNG: Multinodular Goiter, PUS: Pertechnetate Uptake Score, TUS: Tetrofosmin Uptake Score, FNAC: Fine Needle Aspiration Cytology, *: Although FNAC was benign, a thyroidectomy was performed and follicular Ca was found (Patient No. 5)

Table 4 Summary of the results of STN and MNG patients

		STN (%)	MNG (%)
1) PUS ≥ 3 and TUS 2 or 3	⇨ benign	→ 5/5 (100)	24/24 (100)
2) PUS 2	⇨ —		
3) PUS 0,1 and TUS 3	⇨ malignant	→ 3/3 (100)	1/1 (100)
4) PUS 0,1 and TUS 2	⇨ malignant	→ 1/7 (14)	0/22 (0)
5) PUS 0,1 and TUS 0,1	⇨ benign	→ 5/5 (100)	11/11 (100)

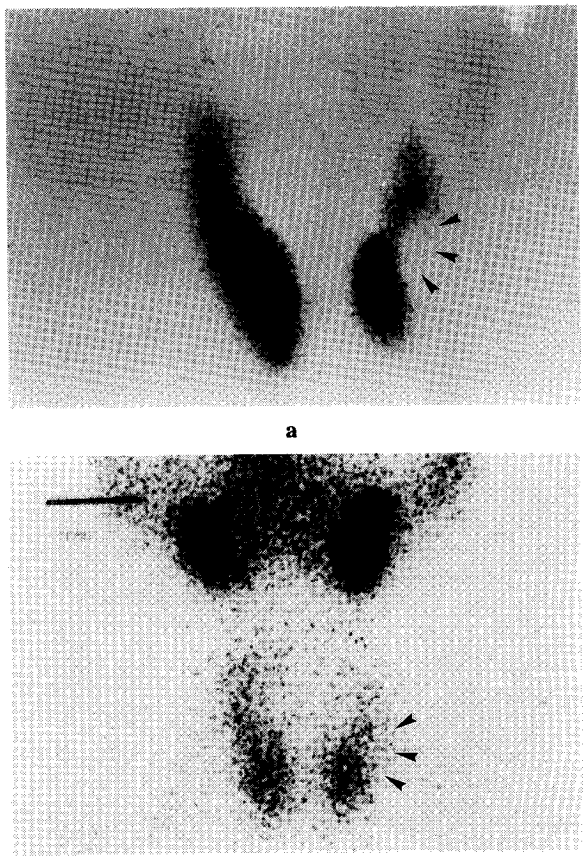
scoring system [Tetrofosmin Uptake Score (TUS): 0 = no significant uptake, 1 = uptake greater than background but less than thyroid, 2 = uptake equal to thyroid, 3 = uptake greater than thyroid, 4 = prominent uptake and no visualization of extra nodular thyroid tissue]. A Toshiba GCA-602A gamma camera with a LEAP collimator was used and static images were obtained for 5 minutes with a 256 × 256 matrix.

Tc-99m-P thyroid scintigraphy protocol:

After IV injection of 111 MBq Tc-99m-P, static images were obtained at 30 minutes from the anterior position for 400,000 counts with a pinhole collimator. The same 5 point scoring system was used for Tc-99m-P [Pertechnetate Uptake Score (PUS)].

FNAC:

FNAC was performed from the solitary nodule or from the dominant nodule/or nodules of MNG patients by the same clinician. A 22 gauge needle was used and a standard technique was used as described elsewhere.[5] The smear of the aspirates was stained with Papanicalau and examined by the same Cytopatholog. The results were interpreted as malignant, benign, suspicion of malignancy and interpretation not possible (a second FNAC was performed on these patients).



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b

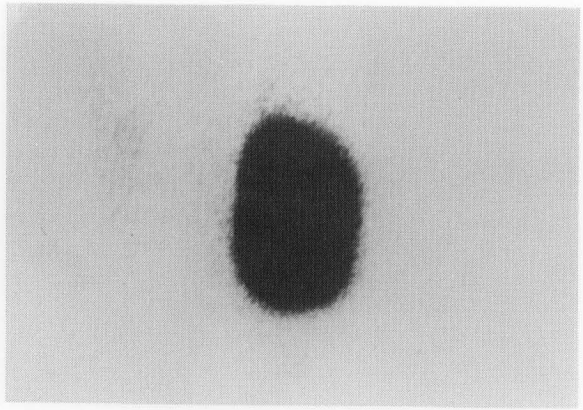
Fig. 1 Thyroid scintigraphies of a patient with a STN which proved to be a papillary thyroid carcinoma. a) Tc-99m pertechnetate scan shows a hypoactive nodule (2 × 2 cm; PUS = 0) at the mid-lateral portion of the left lobe, b) TUS of the nodule was 2 on Tc-99m-TF scan.

RESULTS

The TUS, PUS and FNAC results for patients with STN and MNG are shown in Tables 2 and 3, respectively.

Twenty patients had STN; 15 were hypoactive (PUS < 2) and 5 were hyperactive (PUS = 3 or 4). Twelve of the hypoactive nodules had a TUS of 0 (n = 1), 1 (n = 6) or 2 (n = 5). One patient with a TUS of 2 had papillary carcinoma (Fig. 1). The other 3 hypoactive nodules had a TUS of 3-3-3 (2 patients had follicular and one patient had papillary carcinoma). The TUSs of 5 hyperactive nodules were 2-3-3-3-3 and the FNAC of these nodules was benign (Fig. 2).

Twenty-two patients had MNG with 58 nodules. All hypoactive MNG nodules (n = 34, PUS < 2) with benign FNAC had TUS ≤ 3 [TUS = 0, 1 (n = 12); TUS = 2 (n = 21) (Fig. 3) and TUS = 3 (n = 1)]. One patient with a benign FNAC was operated on because of clinical suspicion of malignancy and was found to have follicular Ca. The TUS of this patient was 3 (Fig. 4). On the other hand, hyperactive MNG nodules [PUS > 2 (n = 24)] with benign FNAC had a TUS of 2 (n = 19) or 3 (n = 5).



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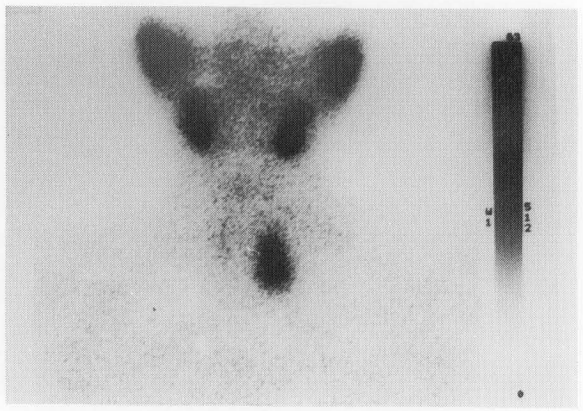

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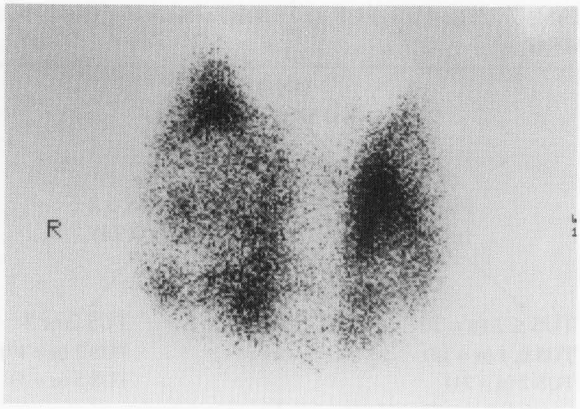
Fig. 2 Thyroid scintigraphies of a patient with a STN, thyrotoxicosis and a benign FNAC. a) Tc-99m pertechnetate scan shows a hyperactive nodule (PUS = 3), b) TUS of the nodule was 3 on Tc-99m-TF scan.



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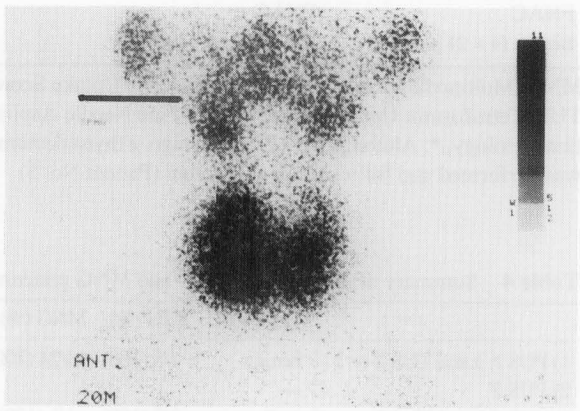

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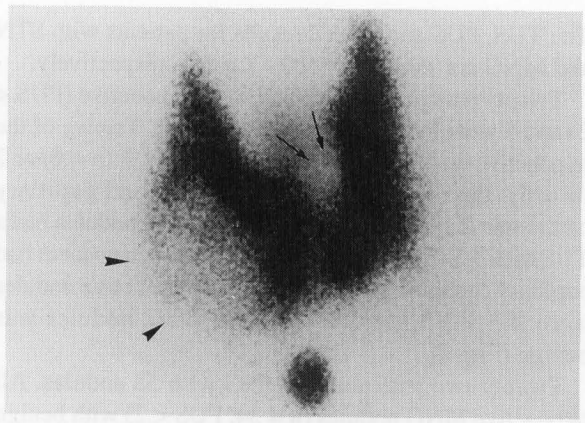
Fig. 3 Thyroid scintigraphies of a patient with MNG and benign FNAC. a) Tc-99m pertechnetate scan shows multiple hypoactive nodules (PUS = 1). b) TUS of the corresponding nodules were 2 on Tc-99m-TF scan.



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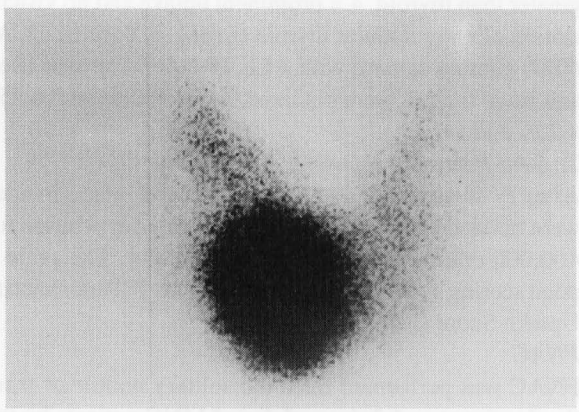

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Fig. 4 Thyroid scintigraphies of a patient with MNG, benign FNAC, but histopathologically proven follicular thyroid carcinoma. a) Tc-99m pertechnetate scan shows a prominent hypoactive nodule (4 × 3 cm; PUS = 0) at the lower part of the right lobe (arrow heads) and a small one (1.5 × 1 cm; PUS = 0) at the junction of the isthmus and left lobe (arrows). Hot spot indicates sternal notch. b) TUS of the prominent nodule was 3; whereas it was 2 in the smaller nodule on Tc-99m-TF scan.

Table 5 The characteristics of patients with thyroid cancer

No.	Age, Sex	STN-MNG	US	PUS	TUS	FNAC	Histopathology
1	46, F	STN	Solid	0	2	Papillary Ca	Papillary Ca (Fig. 1)
2	27, F	STN	Solid	0	3	Papillary Ca	Follicular Ca
3	45, F	STN	Solid	0	3	Follicular neoplasm	Follicular Ca
4	34, F	STN	Mixed	0	3	Benign	Papillary Ca
5	21, M	MNG	Solid	0	3	Benign	Follicular Ca (Fig. 4)

STN: Solitary Thyroid Nodule, MNG: Multinodular Goiter, PUS: Pertechnetate Uptake Score, TUS: Tetrofosmin Uptake Score, FNAC: Fine Needle Aspiration Cytology, US: Ultrasonography

Results for the STN and MNG patients are summarized in Table 4.

FNAC of STN revealed 2 malignant, 17 benign and 1 suspicious nodule. In MNG patients, there were 20 benign and 2 suspicious nodules. Ten patients were operated on (5 STN and 5 MNG) either because of malignant or suspicious FNAC or clinical judgment of a high probability of malignancy. Histopathological examination revealed that 5 (50%) of these nodules were malignant (2 papillary and 3 follicular thyroid cancers).

The characteristics of these 5 malignant cases are summarized in Table 5. Four were found in STN and 1 was found in MNG. All had a PUS of 0 (hypoactive) and TUS of 2-3-3-3-3. Four nodules were solid and 1 had a mixed echo pattern on US. Two patients with benign FNAC were operated on because of clinical suspicion of malignancy and were found to have papillary and follicular Ca. The TUSs of these patients were 3 and 3.

DISCUSSION

In the evaluation of patients with NG, there is a need for a better imaging method. This is especially true in areas of iodine deficiency for patients with MNG, since the clinician wants to perform FNAC on the nodules most highly suspected of malignancy. In addition to this, in these patients, the rate of malignancy may in fact be higher than currently expected, since many patients with benign FNAC and low probability of clinical suspicion of malignancy are not operated on. This may explain the higher rates of thyroid cancer found at autopsy than clinical thyroid cancer prevalence.

Tl-201 and Tc-99m methoxyisobutylisonitrile (MIBI) have been proposed as useful radionuclides in the differentiation of malignant from benign nodules by some authors,[6,7] but FNAC is currently considered the gold standard in this respect.[8]

Tc-99m-TF, which is primarily used as a myocardial perfusion scanning agent,[9–11] has also been reported to accumulate in different malignancies such as breast[12,13] and lung cancer.[14–17] Recently its value in evaluation of thyroid cancer metastasis has been shown.[18,19] Although the exact mechanism of uptake in malignant tissues is not clear, it is currently thought that mitochondrial sequestration in highly proliferating malignant cells may be responsible for this.[4]

In patients with a hypoactive STN and benign FNAC, we found low (≤ 2) TUS, whereas in 4 hypoactive STN with thyroid cancer, TUS was high. This means that, high TUS in a hypoactive STN greatly increases the probability of thyroid cancer and these patients should be operated on. Conversely, low TUS in these patients decreases thyroid cancer probability, and if there is no clinical suspicion they should be followed up.

It is currently accepted that hyperactive nodules with autonomous function (toxic adenomas) are, for all practical purposes, benign.[20] High TUS found in 5 hyperactive benign STN suggests that, benign follicular adenomas whose cell proliferation rates are higher than normal thyroid follicular cells, also accumulate more Tc-99m-TF than normal thyroid tissue.

In patients with MNG, all hypoactive benign nodules were found to have low TUS. Nevertheless, a follicular carcinoma was found in a hypoactive nodule whose FNAC was benign, but who had a TUS of 3. We suggest that, in patients with MNG and hypoactive nodules, if the TUS of the nodule is high, operation should be considered regardless of the result of FNAC. Such a protocol may increase the underestimated rate of thyroid cancer in MNG, and we have decided to start this protocol in our center to those patients who have no contraindication for thyroidectomy.

In patients with MNG and hyperactive, benign nodules, high TUS may reflect high follicular cell proliferation rates of autonomous foci of goitrous tissue. These patients must be carefully evaluated for subclinical thyrotoxicosis with a TRH test. We believe that the probability of thyroid cancer is very low and they should not be operated on for this reason.

In conclusion, our study suggests that a high TUS is not specific for thyroid cancer; this may also occur in thyroid adenomas and autonomous goitrous tissue. But when used appropriately as described in conjunction with conventional thyroid scintigraphy and FNAC, Tc-99m-TF thyroid scintigraphy may prove to be an important diagnostic tool in the evaluation of patients with NG, a hypoactive nodule with high TUS has a higher probability of malignancy, whereas a hyperactive STN with high

TUS is a follicular adenoma. Further studies with Tc-99m-TF are required to confirm these results.

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