Comparison of ^{18}F-FDG, ^{131}I-Na, and ^{201}Tl in Diagnosis of Recurrent or Metastatic Thyroid Carcinoma

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There are several reports about the usefulness of ^{18}F-FDG PET in thyroid cancer. However, few studies have compared FDG PET with ^{131}I and ^{201}Tl scintigraphy. The aim of this study was to evaluate the clinical significance of whole-body FDG PET in differentiated thyroid cancer and to compare the results with those obtained from ^{131}I and ^{201}Tl scintigraphy. **Methods**: Whole-body FDG PET was performed on 32 patients (10 men, 22 women; age range, 30–77 y; mean age, 54 y) with differentiated thyroid cancer (5 cases of follicular cancer and 27 of papillary cancer) after total thyroidectomy. An overall clinical evaluation was performed, including cytology, thyroglobulin level, sonography, MRI, and CT, to allow a comparison with functional imaging results for each patient. Metastatic regions were divided into five areas: neck, lung, mediastinum, bone, and other. Multiple lesions in one area were defined as one lesion. The tumor-to-background ratio (TBR) was measured for the lesions that were positive for both ^{201}Tl uptake and FDG PET uptake. **Results**: The number of lesions totaled 47. Forty-one (87%) were detected by all scintigraphic methods. FDG uptake was concordant with ^{131}I uptake in only 18 lesions (38%). FDG uptake was concordant with ^{201}Tl uptake in 44 lesions (94%). Only one lesion was negative for FDG uptake and positive for ^{201}Tl uptake, and two lesions were positive for FDG uptake and negative for ^{201}Tl uptake. A significant correlation was seen between the TBR of ^{201}Tl and that of FDG ($r = 0.69$; $P < 0.05$). **Conclusion**: These data indicate that for detecting metastatic lesions, FDG PET and ^{131}I scintigraphy may provide complementary information, whereas FDG PET may provide results similar to those of ^{201}Tl scintigraphy. Thus, the combination of ^{131}I scintigraphy and FDG PET (or ^{201}Tl scintigraphy) is the method of choice for detecting metastatic thyroid cancer after total thyroidectomy.

Key Words: ^{201}Tl scintigraphy; ^{131}I scintigraphy; thyroid cancer; PET; ^{18}F-FDG

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A method that has become popular for detecting a variety of cancers is ^{18}F-FDG PET (*1*). Clinical experience with FDG PET in patients with differentiated thyroid cancer has recently been reported (*2–5*). Several investigators reported that FDG PET and ^{131}I whole-body scanning played complementary roles in the detection of recurrent or metastatic differentiated thyroid cancer (*2,3,6*). Highly differentiated thyroid cancer was positive for ^{131}I uptake and negative for FDG uptake, whereas poorly differentiated cancer was negative for ^{131}I uptake and positive for FDG uptake (*2,3,5*). On the other hand, Grünwald et al. (*4*) reported that FDG PET was more sensitive than ^{99m}Tc-sestamibi, probably because of better spatial resolution with respect to tomographic imaging and differences in the tracer uptake mechanism. However, few studies have compared FDG PET with ^{131}I scintigraphy, and particularly few have compared FDG PET with ^{201}Tl scintigraphy, which is known to be sensitive in some tumors that are negative for ^{131}I uptake (*7–12*).

The aim of this study was to evaluate the clinical significance of whole-body FDG PET in differentiated thyroid cancer by comparing the results with those obtained from whole-body ^{131}I and ^{201}Tl scintigraphy.

MATERIALS AND METHODS

Patients

This study included 32 patients with differentiated thyroid cancer after total thyroidectomy (10 men, 22 women; age range, 30–77 y; mean age ± SD, 54 ± 11 y). The population included 5 patients with follicular cancer and 27 with papillary cancer. All the patients had stopped taking T_4 thyroid hormone for 3 wk for ^{131}I therapy. The thyroid-stimulating hormone (TSH) level was more than 50 μU/mL for all patients at the time of ^{131}I oral ingestion. Metastasis or recurrence had been diagnosed on the basis of positive thyroglobulin levels (>3 ng/mL), positive cytologic findings, or positive findings on imaging modalities including FDG PET, ^{131}I scintigraphy, ^{201}Tl scintigraphy, CT, sonography, MRI, radiography, and bone scintigraphy.

Imaging

We performed PET using a whole-body scanner (ECAT EXACT 47; Siemens/CTI, Knoxville, TN). Patients fasted for at least 5 h. Whole-body emission images were obtained 60 min after injection of 185 MBq FDG using the three-dimensional method. All patients were asked to remain resting and quiet and to void just before scanning. The images were obtained from the cerebellum to the femur in 11 patients. In 2 patients, the images were obtained

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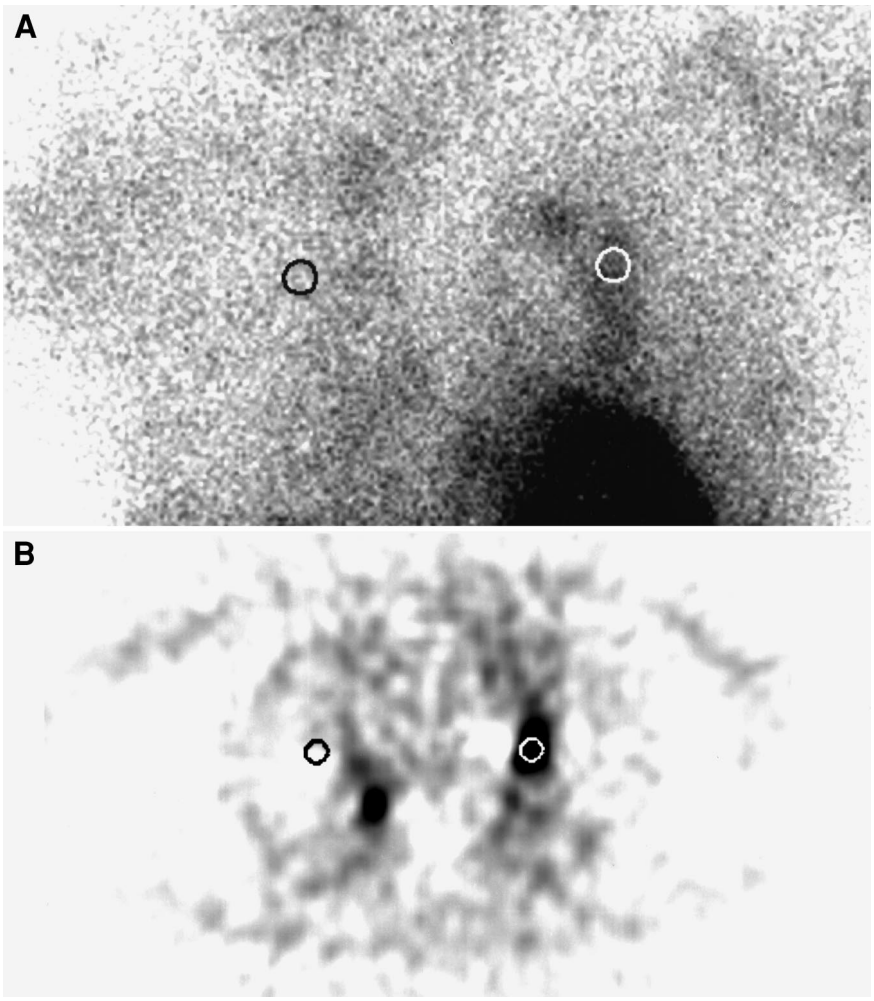

FIGURE 1. One-centimeter-diameter regions of interest drawn over tumors (white circle) and contralateral region (black circle) on spot images from ^{201}Tl scintigraphy (A) and on 5-mm-thick axial images from FDG PET (B).

from the top of the brain to the femur. These images were reconstructed by filtered backprojection using a ramp filter without attenuation correction.

^{201}Tl whole-body scintigraphy was performed 15 min after injection of 111 MBq ^{201}Tl using a dual-head gamma camera (Millennium MG; Elgems, Tirat Carmel, Israel) with low-energy collimators. Spot images of the lesions were obtained after the completion of whole-body scans.

^{131}I whole-body scintigraphy was performed using a Millennium MG gamma camera with high-energy collimators. The images were acquired 5–7 d after oral ingestion of the therapeutic dose, 3.7–5.55 GBq ^{131}I.

All images were visually interpreted by at least two experienced nuclear physicians by consensus. The lesions were considered positive if a definite localized area of higher uptake than in the surrounding normal tissue was present, except for physiologic uptake. The regions of metastasis or recurrence were divided into five areas: neck, lung, mediastinum, bone, and other. Multiple lesions in one area were defined as one lesion.

Analysis

FDG PET findings were compared with those from ^{131}I and ^{201}Tl scintigraphy using the χ^2 test for independence to determine if the frequency of FDG uptake was significant compared with ^{131}I and ^{201}Tl uptake. $P < 0.05$ was considered statistically significant.

Semiquantitative analysis was also performed for patients who had lesions positive for both ^{201}Tl and FDG uptake. We could not identify all lesions on ^{131}I scintigraphy because of poor spatial resolution. Therefore, we did not analyze lesions that were positive for both ^{131}I uptake and FDG uptake. A region of interest with a 1-cm diameter was drawn over the tumors and the contralateral side of the lesion on spot images from ^{201}Tl scintigraphy and on 5-mm-thick axial images from FDG PET (Fig. 1). The regions of interest were settled in tumors that were more than 1.5 cm in diameter. Tumor uptake ratio was semiquantitatively determined as tumor-to-background ratio (TBR).

RESULTS

Recurrence or metastasis—47 lesions in total—was diagnosed in all patients. Forty-one of 47 lesions (87%) were

TABLE 1
FDG and ^{131}I Findings

FDG finding	^{131}I finding	
	Positive	Negative
Positive	13	9
Negative	20	5

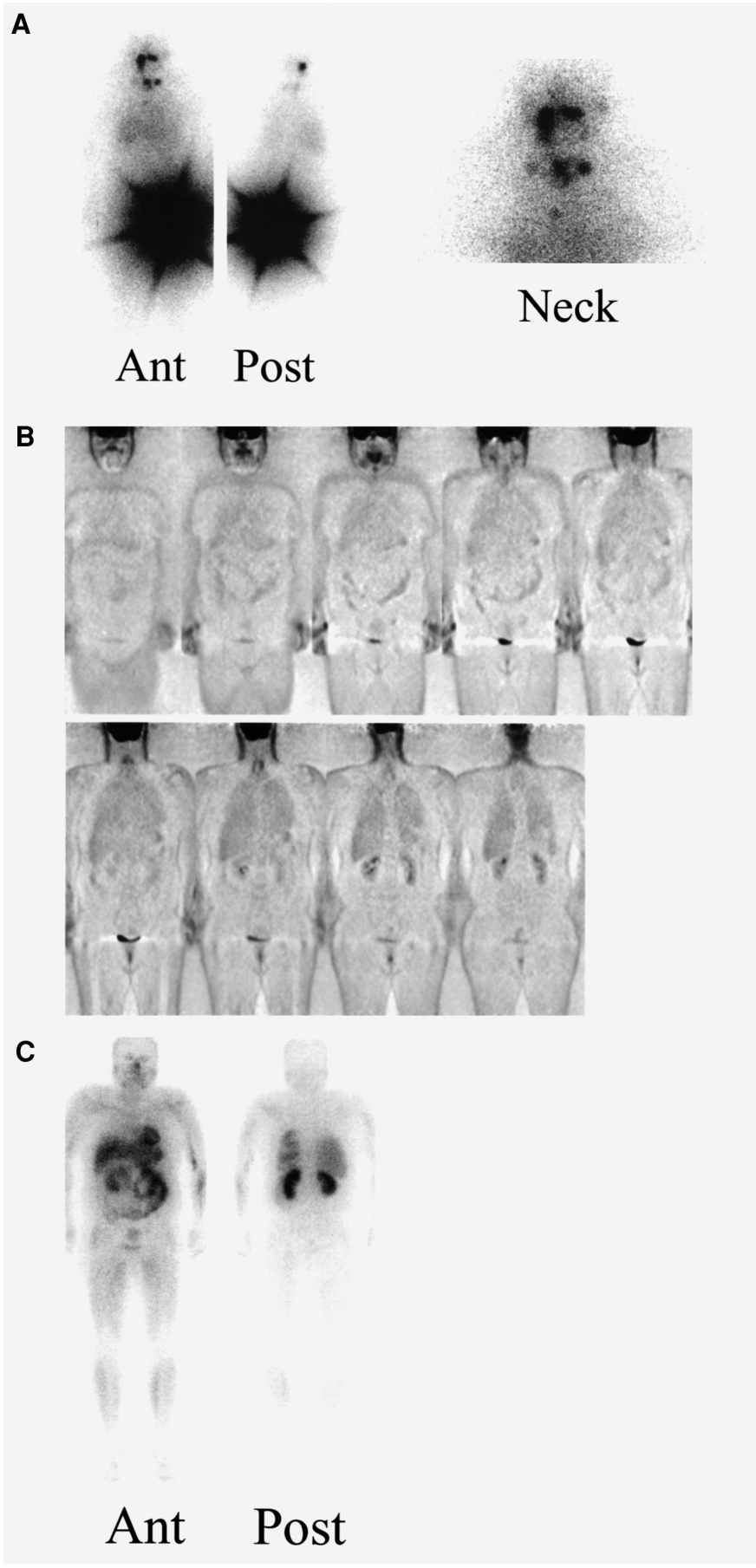

FIGURE 2. A 46-y-old woman with thyroid papillary cancer with metastases to neck lymph node, mediastinal lymph node, and pelvic bone. (A) ^{131}I scans show focal uptakes in neck and mediastinum and strong uptake in pelvic bone. However, FDG PET (B) and ^{201}Tl (C) scans show no definite abnormality. Thyroglobulin level = 291.8 ng/mL; thyroglobulin antibody level = 5.85 U/mL; TSH level = 145 μU/mL.

TABLE 2
FDG and ^{201}Tl Findings

FDG finding	^{201}Tl finding	
	Positive	Negative
Positive	20	2
Negative	1	24

detected by FDG PET, ^{131}I, or ^{201}Tl scintigraphy, whereas 6 (13%) were not. Those 6 lesions were in the brain, bone, neck, and lung of 6 patients and were detected by MRI, CT, sonography, or bone scintigraphy. Four of the 6 patients had other lesions that were detected by FDG PET, ^{131}I scintigraphy, or ^{201}Tl scintigraphy.

^{131}I scintigraphy revealed 33 (70%) of 47 metastatic or recurrent lesions. The relationship between FDG PET and ^{131}I scintigraphy is shown in Table 1. FDG uptake was concordant with ^{131}I uptake in 18 lesions (38%). FDG uptake was discordant with ^{131}I uptake in the remaining 29 lesions (62%) (Figs. 1 and 2). No significant association existed between FDG uptake and ^{131}I uptake.

FDG PET revealed 22 (47%) of 47 metastatic or recurrent lesions, whereas ^{201}Tl scintigraphy detected 21 lesions (45%). The results of FDG PET and ^{201}Tl scintigraphy are shown in Table 2. FDG uptake was concordant with ^{201}Tl uptake in 44 lesions (94%) (Figs. 2 and 3). Only one lesion, in the neck, was negative for FDG uptake and positive for ^{201}Tl uptake, and two lesions, in the neck and lung, were positive for FDG uptake and negative for ^{201}Tl uptake. The association was significant between the findings for FDG PET and those for ^{201}Tl scintigraphy ($P < 0.01$).

Fifteen lesions were more than 1.5 cm in diameter, and the TBRs of FDG and ^{201}Tl were compared for these lesions. A significant correlation was observed between the TBR of ^{201}Tl and that of FDG ($r = 0.69$; $P < 0.05$) (Fig. 4).

DISCUSSION

This study revealed discrepancies between the findings for FDG PET and the findings for ^{131}I scintigraphy with respect to accumulation in metastatic thyroid cancer, whereas the findings for FDG PET and ^{201}Tl scintigraphy were similar. Previous studies have shown that ^{131}I scintigraphy and FDG PET play complementary roles in the detection of recurrent or metastatic thyroid cancer (*2–4,6*). Our results confirmed those data. Tumors are positive for FDG uptake mainly in the high-grade type of differentiated thyroid cancer (*4,5*), because glucose metabolism is generally increased, particularly in poorly differentiated cancer. Joensuu and Ahonen (*13*) reported that metastases showing high FDG uptake but low ^{131}I uptake grow rapidly in cases of thyroid cancer. On the other hand, a tumor that takes up ^{131}I represents functionally differentiated tumor cells. Therefore, cancer positive for ^{131}I uptake and negative for FDG uptake is thought to consist of functionally differen-

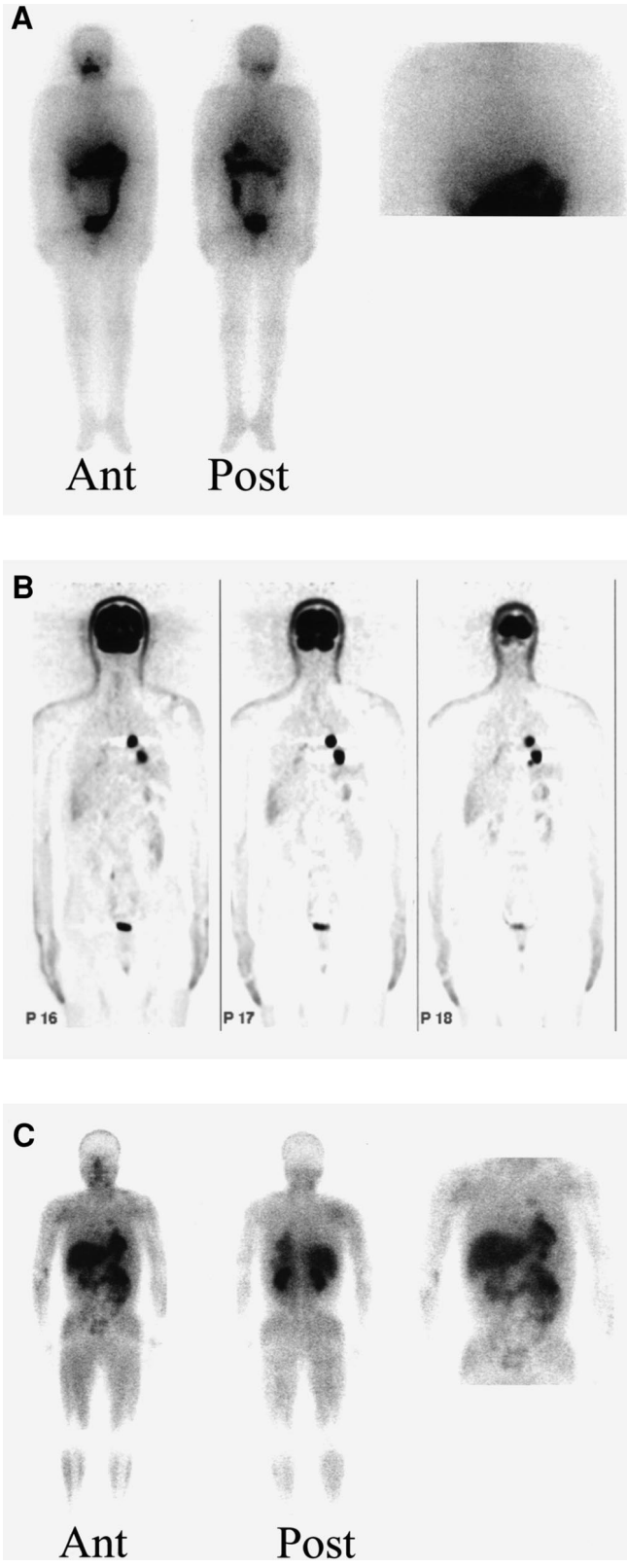

FIGURE 3. A 55-y-old man with thyroid papillary cancer with metastasis to mediastinal lymph node. (A) ^{131}I scans show no definite abnormality. However, FDG PET (B) and ^{201}Tl (C) scans show mediastinal lymph node metastasis. Thyroglobulin level = 1,494 ng/mL; thyroglobulin antibody level = 0.32 U/mL; TSH level = 97 μU/mL.

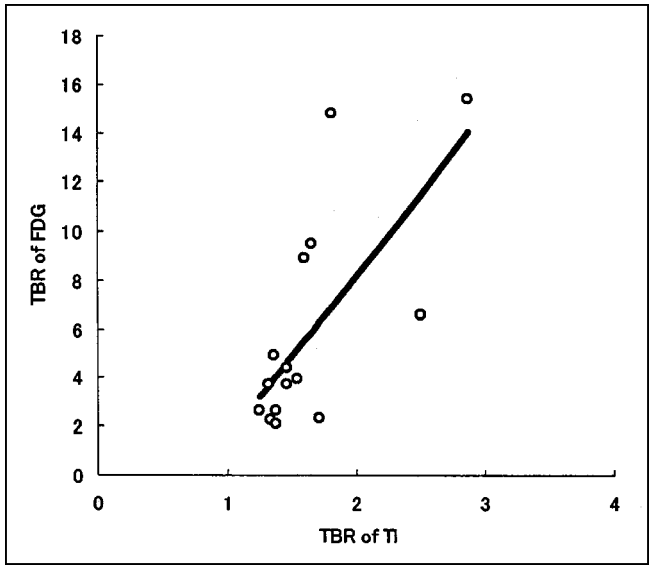

FIGURE 4. Relationship between TBRs of ^{201}Tl and FDG PET (TBR of FDG = 6.6 × TBR of ^{201}Tl − 5.1; $r = 0.69$; $P < 0.05$; $n = 15$).

tiated low-grade tumor cells, whereas cancer negative for ^{131}I uptake and positive for FDG uptake is thought to consist of functionally dedifferentiated and more aggressively growing tumor cells, even in differentiated types. For 4 of 32 patients in our study, these different types of tumors existed in the same patient. In this respect, both ^{131}I and FDG whole-body scans are necessary to detect metastatic lesions, although ^{131}I scintigraphy is cumbersome because of the requirement for total thyroidectomy and withdrawal of hormones.

FDG uptake was concordant with ^{131}I uptake in only 38% of the lesions in this study. The percentage of agreement was higher than that reported by Feine et al. (*5*) but similar to that reported by Grünwald et al. (*2*). The difference may be attributed to the serum TSH level at the time of examination. FDG PET images were acquired from patients receiving thyroid hormone therapy in the former study, whereas almost all the patients had stopped receiving thyroid hormone in the latter study, similar to ours. Many well-differentiated thyroid cancers exhibit TSH receptors coupled to an adenyl cyclase system (*14,15*). Thyroid hormone must be withdrawn so that rising levels of endogenous TSH will stimulate residual thyroid cancer to increase ^{131}I uptake for radioiodine therapy. TSH has also been reported to stimulate FDG uptake (*16*). Elevated TSH in our patients in this study may explain the higher rate of FDG uptake.

^{201}Tl scintigraphy has been proven to be useful for detecting radioiodine-negative metastatic thyroid cancer (*7–12*). To our knowledge, this study is the first to directly compare scintigraphy findings for ^{201}Tl and FDG uptake in patients with differentiated thyroid cancer after total thyroidectomy. The results indicate that FDG has a distribution pattern similar to that of ^{201}Tl, although FDG PET provides much better image quality than does ^{201}Tl scintigraphy. Higashi et al. (*17*) also reported a significant positive correlation between FDG and ^{201}Tl uptake in lung cancer. The reason for the concordance between FDG and ^{201}Tl uptake is not clear. The mechanisms of uptake for the two tracers are different. However, tumors with high proliferative activity seem to accumulate both tracers in a high concentration. We previously reported that ^{201}Tl uptake correlated well with the proliferating cell nuclear antigen index, which represents proliferative activity (*18*). On the other hand, FDG is taken up by less differentiated cancers, which generally grow faster than well-differentiated cancers (*19,20*). Although FDG uptake, unlike ^{201}Tl uptake, has not been proven to have a relationship with the proliferating cell nuclear antigen index, FDG must have some relationship to the proliferative activity of tumors. In addition, considering our results, we speculate that patients with tumors positive for FDG uptake may have a poorer prognosis than patients with tumors negative for FDG uptake, as we previously proved in patients with tumors positive for ^{201}Tl uptake (*21,22*).

Although both FDG and ^{201}Tl were distributed similarly, FDG PET provided a much higher contrast than did ^{201}Tl scintigraphy in our semiquantitative analysis. This fact may be the reason that two lesions were positive for FDG uptake and negative for Tl uptake. The difference in findings may have been caused by the different image displays, planar versus tomographic. Most lesions were better evaluated with tomographic images than with planar images because a higher spatial resolution, contrast, and sensitivity can be expected for tomographic images. The difference in findings may also have been caused by the different acquisition methods used for the gamma camera and PET camera. A PET camera has a much higher sensitivity and spatial resolution than does a SPECT system (*23*). FDG PET was superior to ^{201}Tl scintigraphy in detecting recurrence or metastasis, providing better image quality than did ^{201}Tl SPECT in a few patients who underwent ^{201}Tl SPECT. Some small lesions were detected easily with FDG but only with difficulty with ^{201}Tl because of poor spatial resolution. However, ^{201}Tl scintigraphy may provide adequate information clinically when well-trained nuclear physicians interpret the images.

This study had some limitations. Because an individual comparison of small, multiple lesions was difficult, five lesion areas were compared. Adjoining tumor sites were observed as one site with ^{201}Tl or ^{131}I scintigraphy in some patients because of low spatial resolution. In this study, the lesion findings were almost the same in many patients. However, when FDG PET and ^{201}Tl scintigraphy are compared lesion by lesion, FDG PET may have greater advantages. Comparing different image modalities—planar and tomographic—is another problem. The differences in findings may have been caused mainly by the different imaging modalities, not by differences in tracer uptake. Further study is needed to compare ^{201}Tl SPECT findings with FDG PET findings.

CONCLUSION

For metastatic lesion detection after total thyroidectomy, FDG PET and ^{131}I scintigraphy provided complementary information whereas FDG PET and ^{201}Tl scintigraphy provided similar information. In addition, FDG PET provided better image quality than did ^{201}Tl scintigraphy. Therefore, the combination of ^{131}I scintigraphy and FDG PET (or ^{201}Tl scintigraphy if FDG PET is not available) is the method of choice for detecting metastatic thyroid cancer after total thyroidectomy.

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