^{18}F-FDG PET/CT in Patients with Suspected Recurrent or Metastatic Well-Differentiated Thyroid Cancer

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PET using ^{18}F-FDG has been shown to effectively detect various types of cancer by their increased glucose metabolism. The aim of this study was to evaluate the use of coregistered PET and CT (PET/CT) in patients with suspected thyroid cancer recurrence. **Methods:** After total thyroidectomy followed by radioiodine ablation, 61 consecutive patients with elevated thyroglobulin levels or a clinical suspicion of recurrent disease underwent ^{18}F-FDG PET/CT. Of these, 59 patients had negative findings on radioiodine (^{131}I) whole-body scintigraphy (WBS). Fifty-three of the 61 patients had both negative ^{131}I WBS findings and elevated thyroglobulin levels. PET/CT images were acquired 60 min after intravenous injection of 400–610 MBq of ^{18}F-FDG using a combined PET/CT scanner. Any increased ^{18}F-FDG uptake was compared with the coregistered CT image to differentiate physiologic from pathologic tracer uptake. ^{18}F-FDG PET/CT findings were correlated with the findings of histology, postradioiodine WBS, ultrasound, or clinical follow-up serving as a reference. The diagnostic accuracy of ^{18}F-FDG PET/CT was evaluated for the entire patient group and for those patients with serum thyroglobulin levels of less than 5, 5–10, and more than 10 ng/mL. **Results:** Thirty patients had positive findings on ^{18}F-FDG PET/CT; 26 were true-positive and 4 were false-positive. In 2 patients, increased ^{18}F-FDG uptake identified a second primary malignancy. ^{18}F-FDG PET/CT results were true-negative in 19 patients and false-negative in 12 patients. The overall sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT were 68.4%, 82.4%, and 73.8%, respectively. The sensitivities of ^{18}F-FDG PET/CT at serum thyroglobulin levels of less than 5, 5–10, and more than 10 ng/mL were 60%, 63%, and 72%, respectively. Clinical management changed for 27 (44%) of 61 patients, including surgery, radiation therapy, or chemotherapy. **Conclusion:** Coregistered ^{18}F-FDG PET/CT can provide precise anatomic localization of recurrent or metastatic thyroid carcinoma, leading to improved diagnostic accuracy, and can guide therapeutic management. In addition, the findings of this study suggest that further assessment of ^{131}I WBS–negative, thyroglobulin-positive patients by ^{18}F-FDG PET/CT may aid in the clinical management of selected cases regardless of the thyroglobulin level.

Key Words: ^{18}F-FDG; PET/CT; thyroid cancer; imaging; thyroglobulin

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Serum thyroglobulin and radioiodine whole-body scintigraphy (WBS) play an important role in the postsurgical follow-up of differentiated thyroid cancer (*1–3*). Elevated thyroglobulin levels are a sensitive marker for residual or recurrent disease (*4*). Radioiodine WBS using ^{123}I or ^{131}I allows localization of local recurrences or distant metastases and aids in the decision on subsequent radioiodine treatment (*4–6*). However, radioiodine WBS shows negative findings in 10%–15% of patients with detectable serum thyroglobulin levels (*5,7,8*). At least 2 factors may account for the discrepancy between serum thyroglobulin levels and radioiodine WBS. First, the tumor volume might be too small to be detected by WBS, and second, tumor cells may lose the ability to trap radioiodine while still retaining the ability to secrete thyroglobulin (*8,9*).

It is important to localize tumor sites to initiate the appropriate treatment, such as surgery or external-beam radiotherapy (*10,11*). Various imaging modalities including ultrasonography, CT, bone scintigraphy, and MRI are currently being used for further diagnostic evaluation. In addition, several radiopharmaceuticals such as ^{201}Tl, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, and ^{111}In-octreotide have been evaluated for detection of recurrent or metastatic thyroid cancer (*12–15*).

Cancer frequently exhibits increased glucose metabolism that can be visualized on ^{18}F-FDG PET. Differentiated thyroid cancer is not generally characterized by a marked increased ^{18}F-FDG uptake (*16*). Several groups have

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studied ^{18}F-FDG PET in detecting metastatic or recurrent non–radioiodine-avid lesions (*10,11,17–19*). However, most of these studies were conducted with relatively small patient sample sizes and exact tumor localization was often difficult because of the lack of anatomic landmarks, particularly in the neck region, and the limited spatial resolution of PET (*20,21*). Furthermore, variable physiologic ^{18}F-FDG uptake in muscle, brown adipose tissue, and lymphoid tissue or nonmalignant lesions can confound image interpretation (*20–22*).

The use of combined ^{18}F-FDG PET/CT has the potential to increase the diagnostic accuracy of ^{18}F-FDG PET by providing coregistered metabolic and anatomic information (*20*). There is limited information available so far describing the role of ^{18}F-FDG PET/CT in differentiated thyroid cancer patients. The aims of this study were to evaluate the use of coregistered ^{18}F-FDG PET and CT (^{18}F-FDG PET/CT) in ^{131}I WBS–negative, thyroglobulin-positive patients with suspected thyroid cancer recurrence and to assess the diagnostic performance of ^{18}F-FDG PET/CT in a subset of patients with thyroglobulin values less than 10 ng/mL or more than 10 ng/mL.

MATERIALS AND METHODS

Patients

^{18}F-FDG PET/CT scans from 61 consecutive patients studied at the University of Pittsburgh Medical Center were retrospectively examined. All data were acquired and managed with the prior approval of the Institutional Review Board at the University of Pittsburgh. All patients had undergone a previous total thyroidectomy for well-differentiated thyroid cancer followed by ^{131}I ablation of residual thyroid tissue. Ablation doses generally ranged from 3.7 to 5.5 GBq (100–150 mCi) of ^{131}I. Fifty-nine patients presented for ^{18}F-FDG PET/CT imaging after negative ^{131}I WBS results (53 of whom had both negative ^{131}I WBS results and elevated thyroglobulin levels) and 2 patients underwent ^{18}F-FDG PET/CT because of suggestive findings on other imaging modalities. Thyroglobulin status at the time of ^{18}F-FDG PET/CT was as follows: Forty-six patients had elevated thyroglobulin (>2 ng/mL) and elevated thyroid-stimulating hormone (TSH) levels upon thyroid hormone withdrawal, 7 patients had elevated thyroglobulin levels (>1 ng/mL) while on thyroid hormone medication with suppressed TSH, and the remaining 8 patients had nondetectable thyroglobulin levels (<1.0 ng/mL), with ^{18}F-FDG PET/CT performed for restaging because of elevated thyroglobulin antibodies or a high clinical suspicion of recurrent disease. For detailed patient demographics, see Table 1.

TABLE 1
Patient Demographics (n = 61)

Characteristic	Value
Sex	
Female (*n*)	39
Male (*n*)	22
Age (y)	
Average	51 ± 17
Range	15–84
Histologic type (*n*)	
Papillary thyroid cancer	49
Follicular thyroid cancer	8
Hürthle cell thyroid cancer	4
TSH (*n*)	
Elevated TSH (>20 U/mL)	53
Suppressed TSH (<0.1 U/mL)	8
Reference standard	
Histopathology (*n*)	33
Follow-up (*n*)	28
Median (mo)	18
Range (mo)	12–30

^{18}F-FDG PET/CT Imaging

Patients fasted for at least 6 h before ^{18}F-FDG PET/CT imaging with the exception of liberal water intake. An intravenous catheter was placed for radiopharmaceutical administration, and the blood glucose level was measured before tracer injection. The blood glucose levels of all patients were less than 150 mg/dL (mean, 96 ± 24 mg/dL) at the time that the ^{18}F-FDG was injected. Each patient received 400–610 MBq (11–16.5 mCi) of ^{18}F-FDG intravenously. After tracer injection, the patients rested on a comfortable chair during the ^{18}F-FDG uptake period. PET/CT was initiated 60 min after injection of the ^{18}F-FDG, and a dual-slice lutetium oxyorthosilicate PET/CT scanner (Siemens) was used. CT was performed before acquisition of the PET data in a single step with the patients supine. First, a scout scan was obtained to determine the axial range of the study. The scanning parameters for whole-body CT craniocaudal scanning were 130 kV, 80–120 mAs, 5-mm collimation, and a pitch of 1.6. During the scan, patients were asked to maintain shallow respiration. The subsequent 3-dimensional PET data acquisition included 4–6 bed positions, (4 min per bed position) over the same axial extent. The PET acquisition included a dead-time correction and online delayed coincidence subtraction to correct for random coincidences. The helical CT scan was reconstructed by filtered backprojection into 512 × 512 pixel images with a slice thickness of 2.4 mm to match the PET scan. Images were reconstructed using ordered-subset expectation maximization with 2 full iterations of 8 subsets. Rescaled CT images were used to produce attenuation correction values for the PET emission reconstruction.

^{18}F-FDG PET/CT Analysis

All ^{18}F-FDG PET/CT scans were interpreted by specialized head and neck radiologists in conjunction with nuclear medicine physicians. The ^{18}F-FDG PET portion and the CT portion of PET/CT were jointly interpreted using a dedicated image fusion workstation, and a final consensus was reached for all patients. The leading criterion for ^{18}F-FDG PET/CT interpretation was the presence of focally increased ^{18}F-FDG uptake. Therefore, any increased ^{18}F-FDG uptake was compared with the anatomic finding on CT. Areas of increased ^{18}F-FDG uptake corresponding to normal structures such as salivary glands, muscle, fat, and lymphoid tissue were not recorded. All areas with abnormally increased ^{18}F-FDG uptake corresponding to a CT abnormality (tissue mass or lymph node) were interpreted as positive for recurrent disease. In addition, focally increased ^{18}F-FDG that did not correspond to normal structures or any other structural findings was recorded as positive. Suggestive findings on CT were interpreted as negative if they did not correspond to an area of abnormally increased ^{18}F-FDG uptake.

The results of ^{18}F-FDG PET/CT were correlated with patient follow-up information, which included the results from subsequent

imaging modalities such as neck ultrasound, MRI, CT, and post-radioiodine treatment scanning; thyroglobulin levels; and histologic examination of surgical specimens. The ^{18}F-FDG PET/CT findings were classified as follows:

- Lesions were true-positive if positive findings on ^{18}F-FDG PET/CT were confirmed by the presence of carcinoma on histologic examination or were confirmed by other imaging modalities in the presence of persistent abnormal or increasing thyroglobulin levels.
- Lesions were false-positive if biopsy samples of suggestive lesions were negative for carcinoma on histologic examination or the lesions had resolved on subsequent follow-up imaging. The presence of a second primary tumor was also considered a false-positive finding.
- Lesions were true-negative if the findings of ^{18}F-FDG PET/CT were negative, if elevated thyroglobulin had normalized without treatment, and if metastatic disease was not evident on subsequent follow-up. Lesions were also true-negative if there was no change in thyroglobulin level (only for levels between 2 and 8 ng/mL) and patients had not received subsequent treatment for at least 12 mo. Follow-up was continued in all patients with true-negative lesions for at least 12 mo.
- Lesions were false-negative if the findings of ^{18}F-FDG PET/CT were negative and metastatic thyroid cancer was found at histologic examination of surgical biopsy specimens or if disease progression was seen on other imaging modalities, such as posttreatment radioiodine scans. ^{18}F-FDG PET/CT findings were also false-negative if patients had persistent elevated thyroglobulin levels (>8 ng/mL) or rising thyroglobulin levels.

Statistical Analysis

Sensitivity, specificity, positive and negative predictive values, and accuracy were calculated for ^{18}F-FDG PET/CT for all patients and for subgroups with thyroglobulin levels less than 5, 5–10, or more than 10 ng/mL. All patients in this study underwent follow-up, for a median of 18 mo (range, 12–30 mo).

RESULTS

^{18}F-FDG PET/CT

The findings of ^{18}F-FDG PET/CT were positive in 30 of 61 patients (49.2%) and negative in 31 patients (50.8%). PET/CT findings were true-positive in 26 of 30 studies; 23 of 26 true-positive findings were confirmed by histologic examination of surgical biopsy specimens; 2 of 26 underwent empiric radioiodine treatment and had positive post-treatment scan results, and 1 patient had a further increase in serum thyroglobulin levels and had progression of disease on follow-up imaging. In the true-positive group, 11 of the 26 patients had local recurrences or lymph node metastases in the neck, 9 had both local and distant recurrent disease, and 4 had distant metastases only. Illustrations of true-positive ^{18}F-FDG PET/CT findings are shown in Figures 1 and 2. Detailed ^{18}F-FDG PET/CT results are summarized in Table 2.

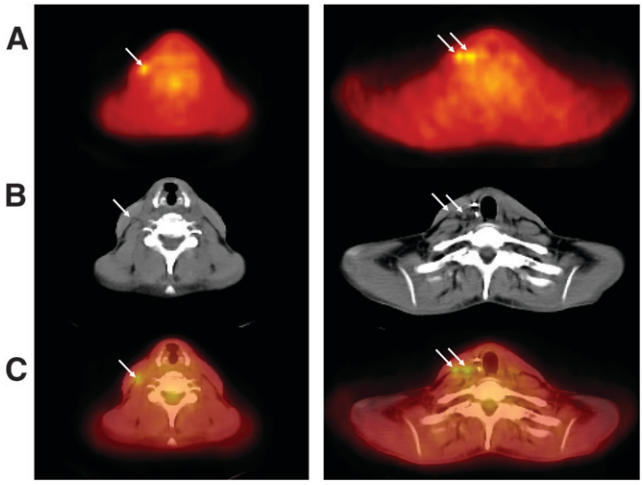

FIGURE 1. A 47-y-old woman with history of papillary thyroid cancer who underwent thyroidectomy and radioiodine ablation. Two years later, patient presented with thyroglobulin level of 6.1 ng/mL (TSH suppressed) and negative findings on ^{131}I WBS. ^{18}F-FDG PET (A) demonstrates small foci of increased ^{18}F-FDG uptake (arrows) corresponding to small lymph nodes in right lower neck on CT (B). These are clearly visualized on fused ^{18}F-FDG PET/CT (C) and were subsequently proven to be thyroid cancer metastases.

The findings of ^{18}F-FDG PET/CT were false-positive in 4 patients. One patient had a histologically confirmed parathyroid adenoma; 1 had a focal abscess that had formed at the area of prior surgery, 1 underwent surgery that revealed only fat and lymphoid tissue on histologic examination, and 1 had a second primary malignant tumor in the lung.

The findings of ^{18}F-FDG PET/CT were true-negative in 19 of 61 patients as validated by thyroglobulin levels or histologic examination of surgical specimens. On follow-up 17 of these 19 patients had decreasing or negative levels of serum thyroglobulin levels (2–8 ng/mL for at least 12 mo was considered stable). Two patients underwent surgery for suggestive findings identified by other imaging modalities, but histologic examinations of the surgical specimens were negative for thyroid carcinoma; these patients also had

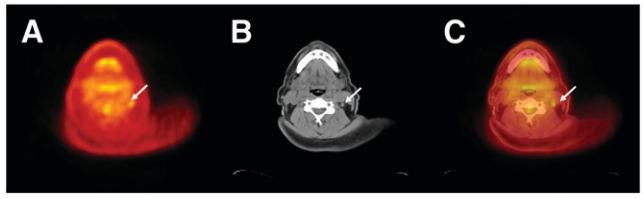

FIGURE 2. A 62-y-old man with history of papillary thyroid cancer. ^{131}I WBS and ^{18}F-FDG PET/CT were performed 1 y previously and had negative findings (thyroglobulin, 6.9 ng/mL). At current presentation, patient has thyroglobulin level of 29 ng/mL and small focal area of increased ^{18}F-FDG uptake in left neck (arrow). Focus was proven by histopathology to be thyroid cancer metastasis. Shown are ^{18}F-FDG PET (A), CT (B), and fused ^{18}F-FDG PET/CT (C) images.

TABLE 2
^{18}F-FDG PET/CT Results

^{18}F-FDG PET/CT	All patients (n = 61)	Thyroglobulin < 5 ng/mL (n = 21)	Thyroglobulin 5–10 ng/mL (n = 11)	Thyroglobulin > 10 ng/mL (n = 29)
Positive (n)	30	4	5	21
Negative (n)	31	17	6	8
True-positive (n)	26	3	5	18
True-negative (n)	19	15	3	1
False-positive (n)	4	1	0	3
False-negative (n)	12	2	3	7
Sensitivity (%)	68.4	60.0	62.5	72.0
Specificity (%)	82.4	93.8	100	25.0
PPV (%)	86.7	75.0	100	85.7
NPV (%)	61.3	88.2	50.0	12.5
Accuracy (%)	73.8	85.7	72.7	65.5

PPV = positive predictive value; NPV = negative predictive value.

stable thyroglobulin levels (<8 ng/mL). For at least 12 mo, none of these patients had received a specific treatment.

The findings of ^{18}F-FDG PET/CT were false-negative in 12 of 61 patients. Four patients underwent surgery because of suggestive findings on other imaging modalities, with histologic examination of surgical specimens revealing thyroid carcinoma. Another 4 patients had rising thyroglobulin levels (>8 ng/mL) during follow-up, and the remaining 4 patients underwent empiric radioiodine treatment and had positive findings on posttreatment scans.

^{18}F-FDG PET/CT showed a second primary tumor in 2 patients, a breast carcinoma in one and lung cancer in the other. The findings of ^{18}F-FDG PET/CT in the first patient were classified as true-positive because an area of increased ^{18}F-FDG uptake in the neck turned out to be a local recurrence of papillary thyroid cancer. An additional area of focally increased ^{18}F-FDG uptake in the right breast was moderately differentiated infiltrating ductal carcinoma of the breast. The findings of ^{18}F-FDG PET/CT in the second patient, a 64-y-old woman with a history of Hürthle cell thyroid cancer, were classified as false-positive because the focus of increased ^{18}F-FDG uptake turned out to be a moderately differentiated adenocarcinoma of the lung with mucinous differentiation, which did not explain the increased thyroglobulin level.

Diagnostic Accuracy of ^{18}F-FDG PET/CT and Serum Thyroglobulin Levels

When the sensitivity of ^{18}F-FDG PET/CT was compared for different thyroglobulin levels, the sensitivity increased from 60% for thyroglobulin levels less than 5 ng/mL to 62.5% for thyroglobulin levels ranging from 5 to 10 ng/mL and to 72% for thyroglobulin levels higher than 10 ng/mL (Table 2). The findings of ^{18}F-FDG PET/CT were true-positive in 14%, 45%, and 62% of patients with thyroglobulin levels less than 5, 5–10, and more than 10 ng/mL, respectively. Table 3 shows true-positive ^{18}F-FDG PET/CT findings with respect to serum thyroglobulin and TSH levels.

Change in Treatment After ^{18}F-FDG PET/CT

In 27 of the 61 patients (44%), ^{18}F-FDG PET/CT resulted in subsequent treatment changes. Surgery was performed on 23 patients for whom ^{18}F-FDG PET/CT suggested resectable tumor recurrence. ^{18}F-FDG PET/CT showed local recurrences or metastases in the neck in 20 of 23 patients who underwent selective neck dissection. Eleven of these 20 patients had recurrent disease in the neck only, but 9 patients had additional tumor localizations in the mediastinum (n = 3), lungs (n = 3), and bone (n = 3). The remaining 3 of 23 patients showed no evidence of recurrences or metastases in the neck, and ^{18}F-FDG PET/CT correctly identified distant metastases in the lungs (n = 2) and mediastinum (n = 1). Two of 27 patients had multiple nonresectable metastases identified by ^{18}F-FDG PET/CT and received chemotherapy. Four patients underwent external-beam radiation, and 2 of these 4 underwent this treatment after initial surgery for tumor recurrence. ^{18}F-FDG PET/CT identified a second primary tumor in 2 patients, breast carcinoma in one and lung cancer in the other.

DISCUSSION

In our study of 61 patients, we found an overall sensitivity and specificity of 68.4% and 82.4%, respectively, for detecting and localizing recurrent or metastatic differentiated thyroid cancer on coregistered ^{18}F-FDG PET/CT. An

TABLE 3
True-Positive ^{18}F-FDG PET/CT Findings Compared with Serum Thyroglobulin Levels for Stimulated and Suppressed TSH Levels

Serum thyroglobulin (ng/mL)	True-positive ^{18}F-FDG PET/CT	
	Stimulated TSH (>25 U/L)	Suppressed TSH (<1 U/L)
<5	2/9 (22.2%)	1/12 (8.3%)
5–10	2/7 (28.5%)	3/4 (75.0%)
>10	14/23 (60.8%)	4/6 (66.7%)

important advantage of PET/CT is its high specificity, compared with previously reported specificities using ^{18}F-FDG PET alone (*10,11,17,18,21*). There are several potential sources for false-positive findings, including difficult-to-interpret ^{18}F-FDG uptake in muscle and brown fat, the salivary glands, vocal cords, tonsils, and other lymphoid tissues (*23*). In our study, the coregistered metabolic and anatomic information from PET/CT allowed for improved differentiation between physiologic and pathologic ^{18}F-FDG uptake. A recent study compared the PET results of PET/CT with combined PET/CT and found an increase in specificity from 50% to 89% (*20*). Other groups reported similar results (*24,25*). The 4 false-positive cases in our series—a histologically confirmed parathyroid adenoma, a focal abscess in the surgical bed, a specimen containing fat and lymphoid tissue, and a second primary tumor in the lung—are not unexpected in a larger patient sample size. A second primary tumor was classified as false-positive because the positive PET finding did not explain the source of the increased thyroglobulin level.

The sensitivity of ^{18}F-FDG PET/CT in our patient group is comparable to previously reported sensitivities (*10,11,17*). In one of the largest ^{18}F-FDG PET studies, on 64 patients with suspected recurrent disease (*11*), the sensitivity was 69.4%, which favorably compares with 68.4% in our study. The sensitivity of ^{18}F-FDG PET is generally determined by the metabolic activity of recurrent or metastatic thyroid cancer. An inverse relationship has been reported between the ability to concentrate radioiodine and the uptake of ^{18}F-FDG in thyroid cancer (*8,16,18*). In most tumors, ^{18}F-FDG uptake increases with the level of dedifferentiation (*16*) and was, for example, found to correlate with the expression of the glucose transporter protein 1 (*26*).

^{18}F-FDG PET is especially helpful for detecting recurrent or metastatic lesions in patients with increased thyroglobulin levels and negative radioiodine WBS findings (*10,11,16–19*). In our study, 59 of 61 patients presented with negative ^{131}I WBS findings, 53 of whom had both negative WBS findings and elevated thyroglobulin levels. The sensitivities of ^{18}F-FDG PET/CT at serum thyroglobulin levels of less than 5, 5–10, and more than 10 ng/mL were 60%, 63%, and 72%, respectively. In the United States, most insurance providers cover ^{18}F-FDG PET in patients with a thyroglobulin level greater than 10 ng/mL. However, our results suggest that ^{18}F-FDG PET/CT could also be helpful in selected cases of thyroglobulin levels less than 10 ng/mL. The low specificity in the subgroup with thyroglobulin levels less than 10 ng/mL was related to the 3 false-positive findings, which were, however, independent of the thyroglobulin level. As shown in Table 3, we found no obvious difference in the diagnostic performance of ^{18}F-FDG PET/CT carried out at suppressed ($<$1 U/L) or stimulated ($>$25 U/L) TSH.

An important observation is that in 20 of 26 true-positive cases, local recurrences or lymph node metastases were located in the neck. Physical palpation is limited in the postsurgical neck, and various imaging modalities are therefore applied to detect recurrent disease. CT of the neck is difficult to interpret without administering intravenous contrast material, and MRI, although a sensitive tool, lacks specificity (*27*). Ultrasound has an emerging role, with advances in technology such as high-resolution phased-array transducers, color flow Doppler, and power Doppler providing detailed information and improved detection of local recurrences and lymph node metastases (*28*). In addition, ultrasound offers the advantage of immediate biopsy of suggestive lesions. Future studies will be needed to compare both the clinical effectiveness and the cost effectiveness of neck ultrasound versus ^{18}F-FDG PET/CT. Of note, in 14 patients, ^{18}F-FDG PET/CT identified tumor deposits outside the neck, predominantly in the chest and bone. An invaluable advantage of ^{18}F-FDG PET and ^{18}F-FDG PET/CT is the ability to identify thyroid cancer recurrences and metastases in soft tissue, lymph nodes, liver, lungs, and bone in a single imaging procedure.

^{18}F-FDG PET/CT provided important diagnostic information that changed patient management in 27 (44%) of 61 patients. A crucial advantage of coregistered ^{18}F-FDG PET/CT is the precise localization of local recurrences and distant metastatic disease. This information, for example, improved surgical planning and target definition for external-beam radiation. ^{18}F-FDG PET/CT directed the treatment to neck dissections, thoracotomy, wedge resections of the lungs, radiation therapy, or chemotherapy in cases with multiple metastases. Although the exact contribution of ^{18}F-FDG PET/CT to patient management is difficult to quantify, its clinical relevance is probably best illustrated by the fact that most patients had previous negative findings on radioiodine WBS and underwent an extensive diagnostic work-up before being referred for ^{18}F-FDG PET/CT. Our findings are in line with the findings of other studies: In one, a change in management was found in 22 (67%) of 33 patients (*24*), and in another, 17 (74%) of 23 patients showed increased ^{18}F-FDG uptake (*25*).

Although this study reports on one of the largest patient groups examined with ^{18}F-FDG PET or PET/CT, the number of patients is still limited in the subgroup analysis. We did not perform an independent analysis of ^{18}F-FDG PET versus ^{18}F-FDG PET/CT because the limitations of ^{18}F-FDG PET alone for tumor detection are well documented (*29*). We also did not compare the diagnostic accuracy of ^{18}F-FDG PET versus CT because, on patients with differentiated thyroid cancer, CT is generally performed without intravenous contrast material, which compromises the diagnostic information provided. Follow-up, including histopathologic results, served as the endpoint for assessing the diagnostic accuracy of ^{18}F-FDG PET/CT. After thyroidectomy and radioiodine ablation, rising thyroglobulin levels are generally a reliable indicator of recurrent thyroid cancer. We assumed the presence of disease in patients with persistent elevated ($>$8 ng/mL) or rising thyroglobulin levels, although this assumption might not

be true in all cases. In addition, verification of true-negative findings is difficult in these patients. ^{18}F-FDG PET/CT was considered true-negative in 19 of 61 patients defined by stable (2–8 ng/mL), decreasing, or negative follow-up thyroglobulin levels. Thyroglobulin autoantibodies or heterophilic antibodies (human antimurine antibodies), which could interfere with thyroglobulin measurements, were not available for all patients.

CONCLUSION

Coregistered ^{18}F-FDG PET/CT provided precise anatomic localization of recurrent or metastatic thyroid carcinoma, leading to improved diagnostic accuracy. The use of ^{18}F-FDG PET/CT altered patient management and was also helpful in guiding the site of therapeutic intervention. ^{18}F-FDG PET/CT appears to be useful, specifically in patients with elevated thyroglobulin levels and negative radioiodine whole-bode scintigraphy findings. Our results also show that ^{18}F-FDG PET/CT adds valuable diagnostic information in selected cases regardless of the thyroglobulin level.

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REFERENCES

1. Ronga G, Fiorentino A, Paserio E, et al. Can iodine-131 whole-body scan be replaced by thyroglobulin measurement in the post-surgical follow-up of differentiated thyroid carcinoma? *J Nucl Med.* 1990;31:1766–1771.
2. Roelants V, Nayer PD, Bouckaert A, Beckers C. The predictive value of serum thyroglobulin in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med.* 1997;24:722–727.
3. Filesi M, Signore A, Ventroni G, Melacrinis FF, Ronga G. Role of initial iodine-131 whole-body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. *J Nucl Med.* 1998;39:1542–1546.
4. Helal BO, Merlet P, Toubert ME, et al. Clinical impact of ^{18}F-FDG PET in thyroid carcinoma patients with elevated thyroglobulin levels and negative ^{131}I scanning results after therapy. *J Nucl Med.* 2001;42:1464–1469.
5. Ashcraft MW, Van Herle AJ. The comparative value of serum thyroglobulin measurements and iodine 131 total body scans in the follow-up study of patients with treated differentiated thyroid cancer. *Am J Med.* 1981;71:806–814.
6. Galligan JP, Winship J, van Doorn T, Mortimer RH. A comparison of serum thyroglobulin measurements and whole body ^{131}I scanning in the management of treated differentiated thyroid carcinoma. *Aust N Z J Med.* 1982;12:248–254.
7. Pacini F, Agate L, Elisei R, et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic ^{131}I whole body scan: comparison of patients treated with high ^{131}I activities versus untreated patients. *J Clin Endocrinol Metab.* 2001;86:4092–4097.
8. Schlumberger M, Arcangioli O, Piekarski JD, Tubiana M, Parmentier C. Detection and treatment of lung metastases of differentiated thyroid carcinoma in patients with normal chest x-rays. *J Nucl Med.* 1988;29:1790–1794.
9. Pineda JD, Lee T, Ain K, Reynolds JC, Robbins J. Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab.* 1995;80:1488–1492.
10. Alnafisi NS, Driedger AA, Coates G, Moote DJ, Raphael SJ. FDG PET of recurrent or metastatic ^{131}I-negative papillary thyroid carcinoma. *J Nucl Med.* 2000;41:1010–1015.
11. Schluter B, Bohuslavizki KH, Beyer W, Plotkin M, Buchert R, Clausen M. Impact of FDG PET on patients with differentiated thyroid cancer who present with elevated thyroglobulin and negative ^{131}I scan. *J Nucl Med.* 2001;42:71–76.
12. Baudin E, Schlumberger M, Lumbroso J, Travagli JP, Caillou B, Parmentier C. Octreotide scintigraphy in patients with differentiated thyroid carcinoma: contribution for patients with negative radioiodine scan. *J Clin Endocrinol Metab.* 1996;81:2541–2544.
13. Carril JM, Quirce R, Serrano J, et al. Total-body scintigraphy with thallium-201 and iodine-131 in the follow-up of differentiated thyroid cancer. *J Nucl Med.* 1997;38:686–692.
14. Iwata M, Kasagi K, Misaki T, et al. Comparison of whole-body ^{18}F-FDG PET, ^{99m}Tc-MIBI SPET, and post-therapeutic ^{131}I-Na scintigraphy in the detection of metastatic thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2004;31:491–498.
15. Unal S, Menda Y, Adalet I, et al. Thallium-201, technetium-99m-tetrofosmin and iodine-131 in detecting differentiated thyroid carcinoma metastases. *J Nucl Med.* 1998;39:1897–1902.
16. Grunwald F, Kalicke T, Feine U, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in thyroid cancer: results of a multicentre study. *Eur J Nucl Med.* 1999;26:1547–1552.
17. Dietlein M, Scheidhauer K, Voth E, Theissen P, Schicha H. Fluorine-18 fluorodeoxyglucose positron emission tomography and iodine-131 whole-body scintigraphy in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med.* 1997;24:1342–1348.
18. Feine U, Lietzenmayer R, Hanke JP, Held J, Wohrle H, Muller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. *J Nucl Med.* 1996;37:1468–1472.
19. Joensuu H, Ahonen A. Imaging of metastases of thyroid carcinoma with fluorine-18 fluorodeoxyglucose. *J Nucl Med.* 1987;28:910–914.
20. Israel O, Mor M, Guralnik L, et al. Is ^{18}F-FDG PET/CT useful for imaging and management of patients with suspected occult recurrence of cancer? *J Nucl Med.* 2004;45:2045–2051.
21. Zimmer LA, McCook B, Meltzer C, et al. Combined positron emission tomography/computed tomography imaging of recurrent thyroid cancer. *Otolaryngol Head Neck Surg.* 2003;128:178–184.
22. Cook GJ, Maisey MN, Fogelman I. Normal variants, artefacts and interpretative pitfalls in PET imaging with 18-fluoro-2-deoxyglucose and carbon-11 methionine. *Eur J Nucl Med.* 1999;26:1363–1378.
23. Jabour BA, Choi Y, Hoh CK, et al. Extracranial head and neck: PET imaging with 2-[F-18]fluoro-2-deoxy-D-glucose and MR imaging correlation. *Radiology.* 1993;186:27–35.
24. Nahas Z, Goldenberg D, Fakhry C, et al. The role of positron emission tomography/computed tomography in the management of recurrent papillary thyroid carcinoma. *Laryngoscope.* 2005;115:237–243.
25. Palmedo H, Bucerius J, Joe A, et al. Integrated PET/CT in differentiated thyroid cancer: diagnostic accuracy and impact on patient management. *J Nucl Med.* 2006;47:616–624.
26. Schonberger J, Ruschoff J, Grimm D, et al. Glucose transporter 1 gene expression is related to thyroid neoplasms with an unfavorable prognosis: an immunohistochemical study. *Thyroid.* 2002;12:747–754.
27. Gross ND, Weissman JL, Talbot JM, Andersen PE, Wax MK, Cohen JI. MRI detection of cervical metastasis from differentiated thyroid carcinoma. *Laryngoscope.* 2001;111:1905–1909.
28. Torlontano M, Attard M, Crocetti U, et al. Follow-up of low risk patients with papillary thyroid cancer: role of neck ultrasonography in detecting lymph node metastases. *J Clin Endocrinol Metab.* 2004;89:3402–3407.
29. Branstetter BF IV, Blodgett TM, Zimmer LA, et al. Head and neck malignancy: is PET/CT more accurate than PET or CT alone? *Radiology.* May 2005;235:580–586.