Clinical Usefulness of Positron Emission Tomography–Computed Tomography in Recurrent Thyroid Carcinoma

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Objectives: To determine the efficacy of combined positron emission tomography–computed tomography (PET-CT) in identifying recurrent thyroid cancer and to elucidate its role in the clinical management of thyroid carcinoma.

Design: Retrospective study.

Setting: Tertiary care referral academic center.

Patients: One hundred twenty-four patients with previously treated thyroid carcinoma who underwent PET-CT.

Main Outcome Measures: PET-CT images were correlated with clinicopathologic information. The influence of PET-CT findings on disease status determination and the treatment plan was evaluated.

Results: Among 121 patients undergoing iodine I 131 (131I) imaging (an 131I image was unavailable for 3 patients), 80.6% had negative findings on 131I imaging before undergoing PET-CT. Among 75 patients who had positive findings on PET-CT, 71 were true positive results. Among 49 patients who had negative findings on PET-CT, 32 were true negative results. Therefore, PET-CT demonstrated a sensitivity of 80.7%, specificity of 88.9%, positive predictive value of 94.7%, and negative predictive value of 65.3%. A significant difference was noted in the mean serum thyroglobulin levels between patients with positive vs negative PET-CT findings (192.1 vs 15.0 ng/mL, \(P = .01\)) (to convert thyroglobulin level to micrograms per liter, multiply by 1.0). Overall, distant metastases were detected in 20.2% of patients using PET-CT. There was an alteration of the treatment plan in 28.2% of patients as a result of added PET-CT information, and 21.0% of patients underwent additional surgery.

Conclusions: PET-CT is usually performed in patients with thyroid cancer having elevated thyroglobulin levels but non-131I–avid tumors and has high diagnostic accuracy for identifying local, regional, and distant metastases. Additional information from PET-CT in patients with 131I-negative and thyroglobulin-positive tumors frequently guides the clinical management of recurrent thyroid carcinoma.


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Thyroid cancer is the most common endocrine malignant neoplasm, with an incidence of approximately 37,000 cases per year in the United States and with a mortality rate of approximately 1600 cases per year.1 The incidence of thyroid cancer has more than doubled in the past few decades.2 Papillary and follicular thyroid cancer, the most common histologic types, are collectively referred to as differentiated thyroid cancer (DTC) and generally have a good prognosis. The 10-year overall survival rates for patients with papillary and follicular carcinoma are 93% and 85%, respectively.3 Clinical prognostic factors resulting in a high risk for recurrence and cancer death include age, sex, tumor size, metastasis, and histologic subtype.4 Mainstay therapy for DTC includes total or near-total thyroidectomy and postoperative iodine I 131 (131I) ablation. Surveillance of these patients for tumor recurrence involves ultrasonography (US) and measurement of serum thyroglobulin level. Increasing thyroglobulin levels represent a reliable method to identify recurrence in patients with DTC.5 In patients with elevated thyroglobulin levels, neck US, noncontrast computed tomography (CT), magnetic resonance imaging, and whole-body 131I imaging (WBI) have been used to localize residual or recurrent DTC tissue.

Patients with disease recurrence identified by positive 131I images are routinely treated with successive 131I ablation therapy, which can be curative. However, in patients with non-131I–avid recurrence, curative treatment can usually be achieved only if the tumor can be localized and surgically resected or ablated by another means. Positron emission tomography (PET) using fludeoxyglucose F 18 as a radiopharmaceutical has been widely accepted as a
method for detecting recurrence of DTC, particularly in non-\(^{131}\)I-avid disease.\(^{6,9}\) PET avidity has been shown to be a strong predictor of survival in patients with metastatic thyroid cancer.\(^{10}\) One of the limitations of PET is the absence of anatomical information. Consequently, PET-CT fusion technology allows coregistration of both image sets, enhancing diagnostic accuracy. More recently, the development of integrated PET-CT systems has further enhanced the sensitivity, specificity, and special resolution for various indications. After 1 or more \(^{131}\)I imaging sessions, recurrent tumor is less likely to be \(^{131}\)I avid, limiting the usefulness of WBI. PET-CT may provide improved detection of metastatic or recurrent lesions, differentiation between physiologic and pathologic foci, and better localization for surgical excision. Combined PET-CT was shown to be more accurate than PET or CT alone in 65 patients with head and neck squamous cell carcinoma.\(^{11}\) Studies\(^{2-10}\) have demonstrated that PET is effective in localizing recurrence in patients with DTC. The primary objective of our study was to evaluate the diagnostic accuracy of PET-CT among a large cohort for identifying recurrent disease in patients with thyroglobulin-positive tumors based on pathologic or clinical progression of disease. We also sought to elucidate the role of PET-CT in the clinical management of recurrent thyroid carcinoma.

**METHODS**

**STUDY DESIGN**

This retrospective study was approved by the institutional review board at the University of Pittsburgh, Pittsburgh, Pennsylvania. We identified 124 consecutive patients undergoing PET-CT for evaluation of histologically proven thyroid carcinoma between January 1, 2000, and January 1, 2008. A preliminary study\(^{17}\) included a subset of these patients. All patients with DTC had undergone previous surgery for thyroid cancer, followed by \(^{131}\)I ablation therapy. There were 46 men and 78 women in the cohort, with a mean age of 45 years (age range, 5-89 years). The mean follow-up time from initial PET-CT was 36.7 months (range, 1-88 months). The histologic subtypes were papillary (106 patients), follicular (8 patients), and Hurthle cell (10 patients). Follow-up variables in our study included surgical pathologic findings, thyroglobulin levels, and results of radiographic studies, including US, WBI, CT, and magnetic resonance imaging. PET-CT was used in the setting of restaging primarily among patients with an elevated thyroglobulin level and negative WBI following initial \(^{131}\)I imaging. The sensitivity, specificity, positive predictive value, and negative predictive value of PET-CT were analyzed. A true-positive finding occurred when the PET-CT image was rated as a malignant neoplasm and the patient was found to have positive disease based on surgical pathologic findings or clinical progression of disease. Clinical progression was defined as persistently elevated thyroglobulin levels (>8.0 ng/mL), a rise in thyroglobulin levels, or progression of disease on serial imaging (to convert thyroglobulin level to micrograms per liter, multiply by 1.0). A false-positive finding occurred when the PET-CT image was rated as a malignant neoplasm but the patient was found to have negative surgical pathologic findings or no evidence of disease on serial imaging (ie, PET-CT findings were initially positive, and subsequent imaging was negative). A true-negative finding occurred when the PET-CT image was rated as benign and subsequent surgical pathologic findings were negative, thyroglobulin levels were undetectable, or serial images were negative. For patients with a thyroglobulin level between 2.0 and 8.0 ng/mL, it has been our practice to consider these true-negative clinical findings if the patients are stable over a minimum follow-up of 1 year in addition to negative serial images. A false-negative finding occurred when the PET-CT image was rated as benign and subsequent surgical pathologic findings were positive or the patient had persistently elevated thyroglobulin levels (>8.0 ng/mL), rising thyroglobulin levels, or progression of disease on serial imaging. PET-CT information was determined to definitively change the clinical management if additional findings on PET-CT were not seen on previous imaging, including WBI and US. This includes patients with negative WBI or US results with subse-quent positive PET-CT findings. Furthermore, patients with positive WBI or US results found to have new findings on PET-CT (ie, previously unidentified distant disease) would also be included. If PET-CT confirmed previous findings, this was defined as additive to the clinical management.

**PET-CT PROTOCOL**

PET-CT was performed on a dual-section lutetium oxyorthosilicate PET-CT imaging system (Siemens, Forsheim, Germany). Patients were asked to fast for 6 hours before the procedure, and blood glucose levels were measured before imaging. Patients with blood glucose levels exceeding 200 mg/dL were rescheduled for imaging at another date (to convert glucose level to millimoles per liter, multiply by 0.0555). Each patient received 400 to 600 MBq of fluorodeoxyglucose F 18 (\(^{18}\)FDG) and then rested for approximately 1 hour. Combined PET-CT was performed from the skull base through the pelvis without the use of iodinated contrast. Computed tomography data were used for attenuation correction of PET data.

All examinations were reviewed by 1 of 2 head and neck radiologists (B.F.B. and E.J.E.) with 10 and 5 years of experience in reading whole-body PET-CT images of patients with head and neck cancers. No specific standardized uptake value thresholds were applied. PET-CT images were determined to be positive or concerning for malignant neoplasms if findings met the following criteria: (1) soft tissue or lymph nodes with subjectively increased FDG avidity that could not be attributed to normal or altered physiologic uptake, (2) lymph nodes with concerning CT features such as central necrosis, (3) pulmonary nodules that were subjectively judged as suspicious based on CT criteria or increased FDG uptake, or (4) distant masses with increased FDG avidity or CT features that were suggestive of malignant neoplasm.

Statistical analysis was performed using commercially available software (SPSS 15.0 for Windows; SPSS Inc, Chicago, Illinois). We determined sensitivity, specificity, negative predictive value, and positive predictive value of PET-CT in evaluating disease as already described. Unpaired \(t\) test was used to calculate 2-tailed \(P\) values. Statistical significance was set at \(P<.05\).

**RESULTS**

Among 124 patients in our cohort undergoing PET-CT for surveillance of recurrent thyroid carcinoma, 75 images were interpreted as positive at the time of imaging. After histologic, clinical, or radiographic follow-up, 71 images were determined to be true positives. Of these, 60 patients had positive findings on both PET and CT, 6 patients had positive CT findings only, and 5 patients had positive PET findings only. Of these, 57 patients had a confirmed positive pathologic diagnosis by surgical excision or fine-needle aspiration biopsy, while 14 patients had a confirmed positive pathologic diagnosis by...
clinical progression of disease, radiographic follow-up results, or increasing thyroglobulin levels. Among 71 true-positive images, 49 represented local (central compartment) or lateral lymph node recurrence only.

Distant metastases were detected in 25 patients on initial PET-CT at the following sites: 14 lung, 10 bone, 3 brain, and 3 liver. Among these, 11 patients also had local recurrence, and 6 patients also had regional recurrence. Eight patients had distant metastases only.

Seven patients had a secondary primary tumor identified on PET-CT. These tumors included lung adenocarcinoma, lung squamous cell carcinoma, renal cell carcinoma, renal eosinophilic oncocytoma, retroperitoneal leiomyosarcoma, Hodgkin lymphoma, and hemangioblastoma in the spinal cord.

**PET-CT DIAGNOSTIC ACCURACY**

Four patients had false-positive PET-CT findings (2 based on surgical pathologic findings and 2 based on subsequent serial imaging). One patient underwent neck exploratory surgery that revealed no disease. One patient underwent excision of FDG-avid tissue that proved to be a focal abscess. One patient had US results and CT images that were negative for recurrent disease at follow-up. One patient with FDG-avid mediastinal lymph nodes and pulmonary nodules was found to have sarcoidosis.

Among 124 patients who underwent PET-CT, 49 images were interpreted as negative. Of these, 32 were determined to be true negative results, and 17 were determined to be false negative results. In the true-negative group, 20 patients showed undetectable, low, or stable (2.0-8.0 ng/mL) thyroglobulin levels along with negative serial imaging; 7 patients had disease confirmed histologically; and 5 patients demonstrated negative serial imaging alone during observation. In the false-negative group, 9 patients had positive histologic findings, 7 patients showed persistently elevated thyroglobulin levels, and 1 patient demonstrated progressive disease on serial imaging.

The sensitivity of PET-CT for identifying recurrent or residual thyroid cancer was 80.7%, and the specificity was 88.9%. The positive predictive value was 94.7%, and the negative predictive value was 65.3%. This information is summarized in **Table 1**.

Among 124 patients in our cohort, PET-CT confirmed or altered the clinical management in 60 patients. Of these, 22 underwent selective neck dissection, 30 had local excision of the disease, and 4 received fine-needle aspiration biopsy. Five patients had radiation therapy, and 2 patients had empiric chemotherapy. PET-CT was the deciding diagnostic modality for determination of the treatment course in 35 patients. Among these, 23 patients had a negative WBI. Five patients had both negative WBI and US results. Among 8 patients with positive WBI, PET-CT identified distant metastasis in 5 patients that was not detected on WBI. Negative PET-CT findings prevented unnecessary surgery in 3 patients with indeterminate or suspicious nodules on US. The patient shown in **Figure 1** was found to have regional disease on PET-CT and subsequently underwent neck dissection.

**SERUM THYROGLOBULIN LEVEL**

Among 64 patients with reported laboratory values, the mean serum thyroglobulin level in 16 patients with positive PET-CT images was 192.1 ng/mL (range, 0.5-4015.0 ng/mL), while the mean serum thyroglobulin level in 48 patients with negative PET-CT images was 15.0 ng/mL (range, 0.3-165.0 ng/mL). A significant difference was noted between the 2 groups (P = .01). Furthermore, the mean serum thyroglobulin levels in patients

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**Table 1. Positron Emission Tomography–Computed Tomography (PET-CT) Findings Among the Cohort**

<table>
<thead>
<tr>
<th>Disease Outcome</th>
<th>Positive (n=75)</th>
<th>Negative (n=49)</th>
<th>Total (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>71</td>
<td>17</td>
<td>88</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>32</td>
<td>36</td>
</tr>
</tbody>
</table>

*a The sensitivity of PET-CT for identifying recurrent or residual thyroid cancer was 80.7%; specificity, 88.9%; positive predictive value, 94.7%; and negative predictive value, 65.3%.

**Figure 1.** Patient with regional disease on positron emission tomography–computed tomography (PET-CT) who subsequently underwent neck dissection. A, Coronal PET-CT image shows multiple foci of increased metabolic activity within the right aspect of the neck and a subtle area in the left aspect of the neck (arrows). B, Axial attenuation-corrected fused PET-CT image through the lowest area seen in A shows increased metabolic activity in the right paratracheal region (arrow) overlying multiple nodules. C, Axial CT image at the same level as in B shows the multiple small nodes present within this area of metabolic activity. Four metastatic lymph nodes were resected from this region at surgery.
with true-positive and true-negative findings were 201.0 and 2.4 ng/mL, respectively ($P = .007$). These thyroglobulin levels were obtained under thyrotropin suppression (thyrotropin level $<5$ mIU/L) in 47 patients and under thyrotropin stimulation (thyrotropin level $>10$ mIU/L) in 55 patients. The range of thyroglobulin levels and the associated PET-CT images are compared under thyrotropin suppression vs thyrotropin stimulation in Figure 2. The thyroglobulin levels under thyrotropin stimulation were significantly higher than those under thyrotropin suppression (39.7 vs 19.7 ng/mL, $P = .04$). Among 71 patients with true-positive PET-CT findings, 16 had a thyroglobulin level below 10.0 ng/mL.

The diagnostic accuracy of PET-CT findings and the changes in the clinical management were compared between patients with elevated thyroglobulin levels ($\geq 10.0$ ng/mL) and patients with low thyroglobulin levels ($<10.0$ ng/mL). This information is summarized in Table 2. Patients having elevated thyroglobulin levels had lower PET-CT sensitivity than patients having low thyroglobulin levels (74.6% vs 93.8%). Additional PET-CT information was more likely to change the clinical management among patients having elevated thyroglobulin levels ($P = .001$).

**Table 2. Outcomes and Thyroglobulin Levels**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thyroglobulin Level, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$&lt;10.0$ (n=50)</td>
</tr>
<tr>
<td>Disease, No.</td>
<td></td>
</tr>
<tr>
<td>True positive</td>
<td>16</td>
</tr>
<tr>
<td>False positive</td>
<td>2</td>
</tr>
<tr>
<td>True negative</td>
<td>31</td>
</tr>
<tr>
<td>False negative</td>
<td>1</td>
</tr>
<tr>
<td>PET-CT, %</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>93.8</td>
</tr>
<tr>
<td>Specificity</td>
<td>93.9</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>88.9</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>96.9</td>
</tr>
<tr>
<td>Change in clinical management, No. (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>36 (72.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>10 (20.0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (8.0)</td>
</tr>
</tbody>
</table>

**Comment**

The standard treatment for DTC includes total thyroidectomy, followed by $^{131}$I ablation therapy and levothyroxine sodium treatment. The standard protocol for detecting recurrence involves serum thyroglobulin level monitoring and US. PET has been widely accepted as a method for detecting recurrence of DTC.6-9 However, PET alone does not provide specific anatomical localization of recurrent lesions. The advent of coregistered PET-CT has allowed enhanced anatomical localization of metabolically active sites of recurrent thyroid carcinoma and distant metastases, facilitating surgical excision for diagnostic or therapeutic purposes.20 Furthermore, PET-CT can potentially explain false-positive FDG uptake in brown fat, muscles, and sites of inflammation. In addition, when PET-CT includes "diag-

**PET-CT AND US**

Fifty-nine patients had US performed before undergoing PET-CT. These US results were compared with PET-CT findings reported in Table 3. Seven patients who had negative US findings were later found to have disease on PET-CT. Two patients who had positive US findings were found to have no disease on subsequent PET-CT. Three patients who had positive PET-CT findings and negative US findings were subsequently found to have distant metastasis.
The use of serial thyroglobulin levels to monitor recurrence is well documented.\(^3\) Postoperative thyroglobulin levels of 10.0 ng/mL or higher are a significant prognostic factor in patients with DTC.\(^22\) Lagarr et al\(^12\) demonstrated a significant difference in the mean serum thyroglobulin levels between patients with positive vs negative PET-CT findings. In our study, the mean serum thyroglobulin levels in patients with positive and negative PET-CT findings were 192.1 and 15.0 ng/mL, respectively (P = .01). Therefore, in the setting of elevated thyroglobulin levels, PET-CT can help detect and localize possible recurrence. To increase the specificity for detecting recurrent or metastatic disease, we suggest that PET-CT should be reserved for patients whose thyroglobulin levels are 10.0 ng/mL or higher for patients whose thyroglobulin levels are rising.

Tumor recurrence in patients with non-\(^{131}\)I–avid disease cannot be detected with WBI, and other imaging modalities must be used. The rate of \(^{131}\)I nonavidity in our cohort was 80.6% before PET-CT. Among 124 patients in our study, PET-CT was the deciding diagnostic modality for changing the treatment course in 35 patients. Of these, 27 patients underwent additional surgery, and 5 patients received radiation therapy or chemotherapy. The other 3 patients with negative PET-CT prevented unnecessary therapy. Although there has been no randomized trial to date showing increased survival in patients undergoing early treatment for recurrence, surgery can be potentially curative. Hamy et al\(^23\) recommended cervical reexplanation in patients with persistently elevated thyroglobulin levels because of the high level of regional recurrence. PET-CT allows precise anatomical localization of non-\(^{131}\)I–avid recurrence, potentially identifying surgically resectable tumors and preventing unnecessary surgical exploration.

An additional benefit of PET-CT is its ability to detect unrecognized distant metastatic disease. PET can accurately identify non-\(^{131}\)I–avid metastatic lesions, and PET avidity has been shown to be a strong predictor of survival in patients with metastatic thyroid cancer.\(^10\) PET can also identify lesions in which continued growth near critical structures can lead to serious morbidity. These include lesions in the brain, weight-bearing bones, and structures near the great vessels.\(^24\) In our series, initial PET-CT findings were positive for distant metastases in 25 patients at the following sites: 14 lung, 10 bone, 3 brain, and 3 liver. Overall, the additional information following PET-CT influenced the clinical management in 18 of 25 patients. Among these 18, PET-CT was the definitive imaging modality that led to a treatment plan change in 16 patients. In patients
undergoing radiation therapy or chemotherapy, PET-CT provided additional information about surgically unresectable disease. Therefore, the ability of PET-CT to detect distant metastatic disease can guide the clinical management and aid in palliative measures among patients with incurable disease. We believe that the recent proliferation of clinical trials for recurrent or advanced DTC, which often requires diagnosis of measurable disease or progression, will mandate greater use of this modality to document responses to targeted therapeutic agents.

The primary limitation of this study is the lack of prospective data collection. Although PET-CT was primarily used in the setting of patients with negative WBI results, the indication for PET-CT was not clearly documented for each patient. The objective of this study was not to compare PET-CT with US but to identify clinical situations in which PET-CT would be a valuable adjunct. These would include scenarios in which WBI or US findings are negative or equivocal, especially when thyroglobulin levels remain high. Furthermore, PET-CT is useful when there is a high suspicion of distant disease. The study was also limited by the fact that PET-CT was obtained at different time points during surveillance. A prospective study is warranted to better characterize the benefit of PET-CT compared with standard methods of surveillance and to identify whether PET-CT can be a clinical prognostic factor of survival.

In conclusion, in the setting herein of elevated thyroglobulin levels and non-131I–avid disease, patients with a history of DTC seem to benefit from the use of PET-CT, with a high diagnostic accuracy for identifying local, regional, and distant metastases. Additional information from PET-CT frequently guides the clinical management of recurrent thyroid carcinoma and aids in the selection of appropriate salvage or palliative therapies.

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Author Contributions: Mr Razfar and Drs Branstetter, Christopoulos, Lebede, Heron, and Ferris had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Razfar, Branstetter, Escott, and Ferris. Acquisition of data: Razfar, Branstetter, Christopoulos, Lebede, Heron, and Ferris. Analysis and interpretation of data: Razfar, Branstetter, Lebede, Hodak, and Ferris. Drafting of the manuscript: Razfar and Ferris. Critical revision of the manuscript for important intellectual content: Razfar, Branstetter, Christopoulos, Lebede, Hodak, Heron, Escott, and Ferris. Statistical analysis: Razfar and Hodak. Obtained funding: Ferris. Administrative, technical, and material support: Razfar, Branstetter, Christopoulos, Heron, and Ferris. Study supervision: Branstetter and Ferris.

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