The Role of Preoperative Positron Emission Tomography/Computed Tomography (PET/CT) in Patients With High-Risk Melanoma

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Background: Positron emission tomography/computed tomography (PET/CT) scanning is commonly used for the preoperative staging of patients with at least intermediate thickness (>1 mm) melanomas. Its role in staging at initial diagnosis for clinically asymptomatic patients is not yet established.

Methods: We examined records of all patients receiving an operation for at least an intermediate thickness melanoma from June 2005 to June 2011. Results of preoperative PET/CT scans were evaluated in asymptomatic patients with a negative physical exam. Outcome measures included changes in clinical management, as well as incidence of true- and false-positives.

Results: PET/CT scans were performed for 149 patients with at least an intermediate thickness melanoma. Positive scans were identified in 28% (41/149) of patients. An invasive procedure to further aid in diagnosis was performed in 44% (18), yet only 6 (15%) patients were diagnosed with metastatic cancer (85% false positive rate). Each of these patients had regional disease subsequently diagnosed by a sentinel lymph node biopsy. No distant metastatic disease was identified.

Conclusions: Preoperative PET/CT in asymptomatic patients is of limited benefit in staging asymptomatic melanoma patients with at least an intermediate thickness melanoma and may lead to unnecessary invasive procedures.


INTRODUCTION

There are approximately 62,000 new cases of invasive melanoma diagnosed in the US every year with a mortality rate of 13.5% [1]. Prognosis is highly dependent on stage at initial diagnosis; the 5-year survival rate decreases from 92% at stage I to 15–20% at stage IV [1]. Imaging plays an important role in the staging process and can help guide management decisions. While computed tomography (CT) has been accepted for detection of metastasis, it has limited sensitivity [2,3]. Positron emission tomography (PET) using [F-18]-fluoro-2-deoxy-D-glucose (FDG) as a radioactive tracer improves sensitivity and has been useful in patients at suspicion for systemic spread as noted by symptoms such as cough, dyspnea, and paresthesias and signs such as tenderness, jaundice, and neurological deficits. Studies have shown that PET has over 90% sensitivity in patients with suspected distant metastasis [3,4] and is confirmatory for those with clinically suspicious nodal disease [5]. However, it lacks anatomical resolution and as a result [6], combined PET/CT is employed to provide anatomical and metabolic datasets in a single examination. This combined modality was found superior to either alone in evaluation of melanoma as well as other oncological diseases, including lung, esophageal, and colon carcinomas [7]. These studies support the use of PET and PET/CT to confirm clinical suspicion of metastases, evaluate patients for recurrent disease, and to stage patients with metastatic disease prior to changes in management.

The role of PET/CT in the initial staging of patients without signs or symptoms suggestive of metastasis is less conclusive. The inadequacy of PET/CT for detecting regional metastasis is highlighted by Yancovitz et al. [8] who demonstrated a 2% true positive and 12% false negative rate when compared to the gold standard of sentinel lymph node biopsy (SLNB). Similarly, in a study of 61 patients receiving PET/CT in clinical stage I and II melanoma with at least 1.0 mm thick lesions, PET/CT had only a 5.9% sensitivity for positive lymph nodes confirmed by SLNB [9].

As for distant metastasis in the asymptomatic patient, the evidence thus far supports restricting the use of PET/CT to a limited set of circumstances. However, these studies are limited by small sample size and inclusion of patients receiving single modality imaging with CT or PET in addition to those receiving dual PET/CT imaging [8–10]. The aim of this study is to further elucidate the utility of dual PET/CT imaging in initial staging of melanoma patients using a larger sample size. We focused on high-risk patients with primary lesions of at least 1 mm who were clinically asymptomatic and without exam findings suggestive of metastasis. We analyzed true and false positive rates and documented any changes made in the clinical management of patients based on PET/CT findings.

MATERIALS AND METHODS

This study is a retrospective analysis of all operative melanoma patients at Rhode Island Hospital. All patients enrolled between June 2005 and June 2011 with at least intermediate thickness melanoma (at least 1 mm) were included for analysis. Patients with lymph node enlargement on exam or symptoms suggestive of metastatic disease were not included.

Abbreviations: PET/CT, positron emission tomography/computed tomography; FDG, [F-18]-fluoro-2-deoxy-D-glucose; SLNB, sentinel lymph node biopsy.

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excluded. Relevant clinicopathologic, demographic, and survival data were recorded for all patients. Patients’ medical records were reviewed to obtain results from radiologic studies, biopsies, and surgical interventions. PET/CT examinations were obtained by either referring physicians or the surgeon. The accuracy of positive PET/CT findings was judged according to follow-up imaging, biopsy, and clinical information. Outcome measures included incidence of true and false positives, and any change in clinical management. A true positive was defined as a finding categorized as highly suspicious for melanoma that proved to be metastatic melanoma on further radiologic or histologic evaluation. A false positive was defined as an imaging finding that was read as highly suspicious for melanoma in a patient that had no further evidence of metastatic melanoma on imaging or clinical follow-up, or that required no further workup.

**PET/CT**

The PET/CT examination was performed in fasting patients 75 min after administration of 0.14 mCi/kg of fluorine-18 fluorodeoxyglucose on a PET-CT scanner. The biograph scanner consists of a combination of a dual-detector helical CT and a high-resolution PET scanner with a 15.8-cm axial field of view and an in-plane spatial resolution of 4.6 mm. Blood sugar level was checked before the scan and administration of radiopharmaceutical. CT imaging was performed directly after PET-imaging with the patient in precisely the same position. The acquisition parameters for dual-detector helical CT were 120kV, 120 mAs, 0.5 sec per CT rotation, 5 mm × 5 mm helical acquisition, 875 mm length. The CT was acquired in the craniocaudal direction ranging from cranial base to midfemur.

**SLN Biopsy**

Preoperatively, 1.0 mCi (18.5–37 MBq) of technetium Tc 99m–filtered sulfur colloid was injected intradermally around the primary tumor or biopsy site. In most cases, a lymphoscintigram was obtained to determine the draining lymph node basin. The area over the sentinel lymph node, as seen by the external gamma camera, was marked on the skin. SLNB was performed under local or general anesthesia. Perilesional intradermal injections of isosulfan blue were performed at surgery, followed by 5-min massages of the site. A gamma probe was used intraoperatively to detect sentinel lymph nodes. Lymph nodes were considered sentinel if they were blue and/or concentrated radiotracer. All nodes with radioactive counts greater than 10% of the hottest node recovered were also considered sentinel lymph nodes. Pathologic evaluation was performed on at least three sections through each sentinel node.

**RESULTS**

In this study, 902 patients who underwent surgery for melanoma were evaluated. The study included 442 (49%) females and 460 (51%) males. Seventy-six of 382 (42%) melanomas were located on the trunk, 364 (40%) were located on the extremities, and 156 (17%) were located on the head and neck. One hundred six (12%) were ulcerated, and 283 (31%) had at least one mitosis per 10 high power fields. With regard to Breslow tumor thickness, 654 patients had tumor depth of <1.0 mm (73%), 120 (13%) were 1.0–1.9 mm, 62 (7%) were 2.0–2.9 mm, 16 (1.8%) were 3–3.9 mm, and 50 patients had a depth of invasion greater than 4.0 mm (0.6%) (Table I). Three hundred twenty (35%) underwent SLNB, of which 73 (8%) were positive.

PET/CT scans for initial staging were performed on 218 patients, including 69 with thin melanomas. In this report, we reviewed 149 PET/CT scans performed in our group of 248 patients with at least an intermediate thickness melanoma (Table II). Positive scans were identified in 28% (41/149) of patients. Specifically, increased FDG uptake was found in 9 local (near site of primary melanoma), 12 regional (lymph node), and 24 distant sites (metastasis) (Table III). An invasive subsequent procedure, such as a biopsy, to further aid in diagnosis was performed in 44% (18) of patients (Table IV). Six (15%) patients were diagnosed with metastatic cancer based on histologic findings. Each of these six patients with a true positive PET/CT had regional disease subsequently diagnosed by a SLNB that corresponded to the suspicious PET/CT finding. Therefore, none of the six true positive PET/CT scan patients had a change in initial surgical management based on preoperative imaging. The PET/CT scans of an additional 49 patients with positive SLNB did not predict the metastatic nodes later found on

**Table I. Patient Characteristics of All Operative Patients (n = 902)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>460</td>
</tr>
<tr>
<td>Female</td>
<td>442</td>
</tr>
<tr>
<td>Site of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>364</td>
</tr>
<tr>
<td>Trunk</td>
<td>382</td>
</tr>
<tr>
<td>Head and neck</td>
<td>156</td>
</tr>
<tr>
<td>Breslow tumor thickness</td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 mm</td>
<td>654</td>
</tr>
<tr>
<td>1.0–1.9 mm</td>
<td>120</td>
</tr>
<tr>
<td>2.0–2.9 mm</td>
<td>62</td>
</tr>
<tr>
<td>3–3.9 mm</td>
<td>16</td>
</tr>
<tr>
<td>&gt;4.0 mm or greater</td>
<td>50</td>
</tr>
<tr>
<td>Ulceration</td>
<td>106</td>
</tr>
<tr>
<td>Mitosis</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>616</td>
</tr>
<tr>
<td>1–5</td>
<td>179</td>
</tr>
<tr>
<td>6–10</td>
<td>54</td>
</tr>
<tr>
<td>&gt;10</td>
<td>53</td>
</tr>
</tbody>
</table>

**Table II. Patient Characteristics of Those Who Received a PET/CT (n = 218)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow tumor thickness</td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 mm</td>
<td>69</td>
</tr>
<tr>
<td>1.0–1.9 mm</td>
<td>52</td>
</tr>
<tr>
<td>2.0–2.9 mm</td>
<td>41</td>
</tr>
<tr>
<td>3–3.9 mm</td>
<td>16</td>
</tr>
<tr>
<td>&gt;4.0 mm or greater</td>
<td>40</td>
</tr>
<tr>
<td>Ulceration</td>
<td>72</td>
</tr>
<tr>
<td>Mitosis</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>72</td>
</tr>
<tr>
<td>1–5</td>
<td>62</td>
</tr>
<tr>
<td>6–10</td>
<td>31</td>
</tr>
<tr>
<td>&gt;10</td>
<td>43</td>
</tr>
</tbody>
</table>

**Table III. Incidence of True and False Positive Findings According to Location of Increased PET/CT FGD Uptake**

<table>
<thead>
<tr>
<th></th>
<th>True positive</th>
<th>False positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Regional</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Distant</td>
<td>0</td>
<td>24</td>
</tr>
</tbody>
</table>

Because tests can yield multiple results, total number of interpretations exceeds total number of studies.
TABLE IV. Clinical Follow Up of Patients With False Positive PET/CT Scans (n = 35)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy (SLNB; muscle, bone, lung biopsy; upper/lower endoscopy; thyroid fine needle aspirations)</td>
<td>18</td>
</tr>
<tr>
<td>Biopsy site changes</td>
<td>13</td>
</tr>
<tr>
<td>Additional imaging studies</td>
<td>10</td>
</tr>
</tbody>
</table>

Because multiple studies can be done on one patient, total number of interventions exceeds total number of patients.

operative intervention. Therefore, PET/CT did not reliably exclude regional metastasis.

The first patient with a true positive PET/CT had lymphadenopathy identified on PET/CT in the left inguinal region, and subsequently confirmed to have lymph node metastases by a positive SLNB and a completion lymph node dissection (CLND) revealing six positive nodes. A second patient had left axillary lymph node disease identified both on PET/CT and on SLNB, totaling five positive nodes removed. A third patient had seven positive lymph nodes removed on CLND following a positive PET/CT scan and SLNB. Patient 4 had a predictive PET/CT scan and SLNB of the supraclavicular nodes. The fifth and sixth patients had predictive right axillary node biopsy and PET/CT scan.

Malignancy was excluded with additional imaging studies (CT, MRI) in 10 patients with positive PET/CT scans. An additional 13 PET/CT positive scans were attributed to biopsy site changes at the primary site such as focal inflammation/injury or had no follow-up management of the false positive finding. Importantly, aside from SLNB, six patients had additional invasive follow-up tests including upper and lower endoscopy, muscle biopsy, bone biopsy, lung biopsy, and two thyroid fine needle aspirations. None of these were positive for metastatic melanoma. Altogether there were a total of 35 falsely positive PET/CT studies (Table IV).

Although PET/CT scans changed initial treatment approach in 68% of patients, mostly with invasive procedures, 85% of the findings on the PET/CT scan were false positives. No distant metastatic disease was identified at initial evaluation, and all regional metastatic disease identified by PET/CT was also identified by SLNB. No patient was upstaged due to preoperative PET/CT. Two distant positive PET/CT scans identified unrelated disease (recurring prostate adenocarcinoma, and sarcoma). These incidental findings were more common than diagnosing actual distant metastatic melanoma disease, of which there were no findings. Figure 1 summarizes PET/CT findings and clinical follow-up of all patients.

DISCUSSION

In this study, we evaluated PET/CT findings in 149 patients with at least intermediate thickness melanoma to determine the accuracy of this imaging modality and its impact on clinical management. With respect to detection of regional metastasis, our findings echo those of previous studies [8,9]. SLNB revealed nodal disease in 94% (49/55) of patients testing negative by imaging and an additional six patients had false positive imaging studies, indicating the predictive value of PET/CT is not sufficient to take the place of SLNB. We did observe six instances of true positive nodal disease diagnosed on PET/CT (confirmed by SLNB in all cases). While some groups have successfully used preoperative imaging to proceed directly to complete regional lymphadenectomy on the basis of a positive fine needle aspiration biopsy (FNAB) [11] the low sensitivity of PET/CT for positive regional disease seen in our study and the low sensitivity of ultrasound guided fine needle biopsy published in other reports [12,13] argue that there is little utility in the use of PET/CT in selecting patients for preoperative FNAB.

In the case of distant metastases, PET/CT is useful when evaluating patients for recurrent disease and when restaging patients with metastatic disease prior to changes in management [5]. As for its role in the initial staging of patients, the data thus far does not support the use of PET/CT in asymptomatic patients. Two previous studies—one of 64 patients with T2 to T4 lesions and another of 42 patients with T1b-T3b disease—did not uncover any clinically silent distant metastases [8]. Our findings support these two previous studies and overcome some of their limitations. First, the sample size was larger in the present study and second, the patients included were uniformly imaged with dual modality PET/CT imaging. We conclude that PET/CT should not play a role during initial staging at time of melanoma diagnosis in patients with at least intermediate thickness primary lesions who otherwise are clinically negative for metastatic disease. In fact, the false positive rate of 85% adds morbidity in the form of invasive procedures (occurring in 6 out of 35 false positive cases), can cause psychosocial distress, and adds to health care costs without the benefit of change in staging or definitive surgical management. Our findings stress the importance of the history and physical examination so that PET/CT is limited to patients with signs or symptoms of metastatic disease.

The National Comprehensive Cancer Network (NCCN) guidelines reflect our findings, advocating for restraint in obtaining an extensive metastatic workup [14]. These guidelines argue for limiting PET/CT to patients with clinical suspicion of metastasis, those with confirmed regional metastasis on SLNB, and potentially patients with intermediate thickness lesions with high-risk features (ulceration, increased mitotic activity defined as greater than one mitotic figure per high power field) [14]. In our study, 69 (10%) of patients with thin melanomas underwent PET/CT (Table II), highlighting the overuse of medical imaging despite continued evidence of its futility and existing recommendations made by experts in the field. There remains a need

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for more adequate education of health care practitioners in the proper workup of melanoma patients at the time of initial diagnosis.

CONCLUSION

We recommend excluding PET/CT imaging preoperatively for asymptomatic patients with a negative physical exam, even in the case of higher risk patients who have at least intermediate thickness lesions. The absence of systemic disease even in the 50 patients with T4 lesions who are typically considered to be at an especially high risk for distant metastasis [15,16] underscores the need to limit the use of PET/CT imaging at initial diagnosis. Whether PET/CT imaging may be more effective for patients with a positive sentinel lymph node biopsy remains an avenue for further exploration. One study imaged 33 patients with positive SLNB using PET and found 4 true positives (12%) [17] and another study evaluated 69 patients with positive SLNB and diagnosed 3 patients with distant metastasis [18]. Furthermore, Gersenwald et al. [16] found that patients with thick melanomas represent a heterogeneous population, and survival varies considerably based on primary tumor ulceration and sentinel lymph node status. Therefore, the use of dual imaging modality for patients with positive SLNB, perhaps limited to patients with other high-risk features such as thick melanoma, ulcerative primary lesions, and macrometastases on SLNB, may increase true negative and true positive rates.

REFERENCES