Clinical Science

Routine restaging PET/CT and detection of initial recurrence in sentinel lymph node positive stage III melanoma

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Abstract

BACKGROUND: Follow-up of patients with sentinel lymph node–positive stage III melanoma uses history, physical exam, and cross-sectional imaging. The aim of this study was to evaluate positron emission tomographic (PET)/computed tomographic (CT) scans in the detection of recurrence.

METHODS: From 2003 to 2009, a single-institution prospective database of all cutaneous melanoma patients was used to identify sentinel lymph node–positive stage III patients with disease-free survival >1 year and 1 restaging PET/CT scan.

RESULTS: Thirty-eight patients were identified, with a median follow-up period of 27.5 months. Seven (18%) developed recurrence (median time to recurrence, 25 months). Recurrences were detected as follows: 3 by patients, 1 by physician, 1 by PET/CT scan and lactate dehydrogenase, 1 by PET/CT scan, and 1 by brain magnetic resonance imaging. One hundred eight follow-up PET/CT scans were performed. Two of 38 patients had asymptomatic metastases detected by routine restaging PET/CT scan, and there were 9 scans with false-positive results.

CONCLUSIONS: With short follow-up, the utility of routine PET/CT scans in identifying unsuspected recurrence in patients with sentinel lymph node–positive stage III melanoma appears minimal. © 2014 Elsevier Inc. All rights reserved.

The incidence of melanoma in the United States is among the fastest rising of all cancers. According to Surveillance, Epidemiology and End Results data from the National Cancer Institute, the incidence of melanoma increased from 15 per 100,000 in 1986 to ≥25 per 100,000 in 2006 for Caucasians. It has been estimated that in 2011, there were 70,230 new diagnoses of melanoma in the United States. Ten-year survival rates are dependent on a number of variables, with a positive sentinel lymph node (SLN) remaining a powerful predictor of recurrence and survival. In patients with SLN metastasis, depending on the total number of positive nodes, 5-year survival rates for stages IIIa to IIIc can range from 40% to 80%, meaning that a sizable proportion of patients will develop recurrences during that time period. Despite the significant risk for recurrence in these patients, there are no clear data to suggest how best to screen patients for detection of recurrence.
The recommended surveillance guidelines for patients with stage III melanoma differ significantly among countries, with broad variability in the timing of clinic visits, recommended radiologic imaging, and proposed laboratory testing. Although a majority of melanoma recurrences are regional and as such are detected by patients or clinicians, 25% to 45% of all initial recurrences will be distant stage IV metastases. Consequently, there is theoretical utility in using routine follow-up radiologic imaging tests to screen for distant recurrence. However, data as to the actual utility of this approach are lacking, particularly with regard to newer imaging modalities. In this study, we sought to examine the contribution of routine restaging positron emission tomographic (PET)/computed tomographic (CT) scans in detecting initial recurrence in routine follow-up of asymptomatic patients with SLN-positive stage III melanoma.

Methods

We performed a single-institution retrospective review of an institutional review board–approved prospectively collected cutaneous melanoma database. All patients undergoing surgical treatment from 2003 to 2009 were included in this study, 2003 being the 1st year that fusion PET/CT imaging was available at our institution. The study population included all patients in American Joint Commission on Cancer stages IIIa and IIIb (T1 to T4, N1 to N2a, M0) who were initially evaluated by SLN biopsy (clinically node negative) and underwent routine follow-up at our institution. Indications for SLN biopsy at our institution include any melanoma with Breslow depth \( \geq 0.75 \) mm and any melanoma <0.75 mm with ulceration, mitotic rate >1/mm\(^2\), regression, or extension to the deep margin of the biopsy specimen. Recurrences were identified from the medical record and classified as outlined below.

Our paradigm for managing SLN-positive patients is as follows: all patients undergo whole-body staging PET/CT scans and completion lymphadenectomy. If PET/CT imaging does not reveal distant stage IV disease, the recommended follow-up schedule includes a history and physical examination with a health care provider (surgical oncologist, dermatologist, or surgical nurse practitioner) every 3 months for the first 3 years, followed by every 6 months in years 3 to 5 and then at least annually to year 10. At these visits, we perform a full-body examination of the skin and lymph node basins and obtain annual routine blood work, including lactate dehydrogenase (LDH). We also recommend annual whole-body PET/CT imaging for at least the first 3 years. During a portion of the time period encompassed by this study, we also recommended annual brain magnetic resonance imaging (MRI), although that has not been our most recent paradigm.

Calculation of time to recurrence or death and follow-up time began from date of SLN biopsy and was expressed in terms of months. Recurrences were categorized into 1 of 4 groups: (1) local recurrence, defined as that occurring within 2 cm of the primary tumor; (2) in transit; (3) regional lymph node basin; and (4) distant soft tissue, distant lymph node basin, or visceral. We also categorized patients as symptomatic (eg, neurologic change, pain in regional lymph node basin) or otherwise asymptomatic with the exception of a physical finding such as an in-transit nodule, or an abnormal diagnostic study. This latter group included asymptomatic patients whose disease was detected by any adjunct diagnostic method, including laboratory studies, chest X-Ray, CT or PET/CT scans, and brain MRI.

For the purposes of analysis, we considered those patients who sought care from their physicians because of new symptoms (eg, neurologic deficit, decreased performance status) and who were subsequently diagnosed with recurrences as having been “patient detected” because it was a specific symptom that prompted the diagnostic evaluation and detection, even if a specific diagnostic study confirmed the recurrence. This was done in an attempt to group all of the patients who had self-detected interim findings, whether they were otherwise asymptomatic physical findings or symptoms that prompted their return to their physicians, into 1 group because these are the patients whose routine follow-up examinations and diagnostic studies were not useful in detecting recurrence.

Results

We identified 83 patients with SLN-positive stage IIIa or IIIb melanoma who were treated at our institution from 2003 to 2009. Of these patients, all had undergone initial staging PET/CT scans, 6 had false-positive findings, 1 had otherwise undetected in-transit disease, and 1 had a second primary (papillary thyroid cancer); all patients underwent completion regional nodal dissection. There were 28 patients who developed recurrences within 1 year, and 17 were lost to follow-up. Of the 28 patients who had early recurrences, 19 had local or regional recurrences, 8 detected by their physicians on routine follow-up and 11 detected by the patients. Five patients had distant metastases that were detected when they presented with symptoms that warranted further investigation with cross-sectional imaging that detected the recurrence. One patient had a distant metastasis that was detected asymptptomatically at the 6-month time point when PET/CT imaging was ordered because of a concerning finding on the initial PET/CT scan.

The remaining 38 patients had disease-free survival >1 year and \( \geq 1 \) routine restaging PET/CT scan. The cohort included 20 men (53%) with a median age of 50 years (range, 23 to 85 years) and 18 women (47%) with a median age of 47.5 years (range, 18 to 76 years) (Table 1). The primary tumor T stage distribution was as follows: 4 T1, 19 T2, 8 T3, and 7 T4 tumors. The mean Breslow depth was 2.4 ± 1.6 mm, with a median Breslow depth of 1.8 mm (range, 0.7 to 6.0 mm). Anatomic sites included 3 head and neck (8%), 18 trunk (47%), 7 upper extremity (19%), and
10 lower extremity (26%) lesions. The primary lesion was associated with ulceration in 13 patients (34%). The mitotic rate was <1/mm² in 16 patients (42%), ≥1/mm² in 19 (50%), and unknown in 3 (8%). There were 29 patients with only 1 positive lymph node, 8 patients with 2 or 3 positive nodes, and 1 patient with >3 positive lymph nodes. Only 2 patients (5%) had additional positive lymph nodes on completion lymph node dissection, both with only 1 positive node on SLN biopsy. The size of largest lymph node metastasis was <0.1 mm in 10 patients (26%), 0.1 to 1.0 mm in 18 patients (48%), and >1.0 mm in 10 patients (26%).

The median follow-up period was 27.5 months (range, 13 to 78 months). Of the 38 patients in the cohort, only 7 patients had developed recurrences of their disease. The median time to recurrence was 25 months (mean, 28.3 months; range, 13 to 42 months). The sites of initial recurrence were as follows. Two were in-transit disease, both detected by the patients. One patient had self-detected regional nodal recurrences (cervical). Four patients had distant recurrences, 1 (distant dermal metastasis) detected by physician exam, 1 (liver and lung metastasis) detected by both LDH drawn before the clinic visit and a positive PET/CT result before the clinic visit in an asymptomatic patient, 1 (contralateral axillary node) detected by routine restaging PET/CT imaging, and 1 (brain) detected on routine screening (restaging) brain MRI. For the patients with recurrences, the mean age was 57 years (range, 27 to 76 years). The mean Breslow depth was 3.5 ± 1.9 mm (median, 2.5 mm; range, 1.75 to 6 mm), and 4 patients had ulcerated primary tumors. Two patients had mitotic rates <1/mm², and 4 patients had only 1 positive lymph node. The clinical and pathologic characteristics of the patients with recurrence are listed in Table 2. Of those with recurrences not detected by routine PET/CT imaging, 2 of 5 (40%) had negative PET/CT results at the time of recurrence.

A total of 108 routine follow-up screening PET/CT scans were performed in these 38 patients (Table 3). The range was 1 to 7 scans per patient (mean, 2.86 ± 1.56; median, 2). A total of 11 scans were suspicious for recurrence, but only 2 were truly positive. One patient who had true-positive screening PET/CT results was found to have contralateral axillary nodal disease that was not otherwise detected on exam; the other true-positive screening PET/CT scan detected asymptomatic liver and lung metastasis. The other 9 suspicious results were proved to be benign after further imaging or surgical biopsy. In total, 12 additional imaging tests were performed (5 CT scans, 2 MRI scans, and 5 short-follow-up PET/CT scans), and 5 procedures were performed to either obtain tissue or further examine a specific area of concern. Procedures included a colonoscopy, a fine-needle aspiration (FNA) that was nondiagnostic and led to a subsequent surgical biopsy, a computed tomography-guided biopsy, and an ultrasound-guided biopsy.

### Comments

The follow-up of patients with stage III melanoma is controversial, and few data exist as to the most appropriate management paradigm. In theory, early detection of recurrence allows a greater number of therapeutic options, such as surgical metastasectomy and/or systemic therapy with novel agents with proven survival benefit. Data suggest that patients or their partners detect a majority (67% to 75%) of recurrences, and the role of imaging is not fully defined. One recent study showed that only 7% of asymptomatic recurrences were detected by routine imaging. In contrast, another demonstrated that in stage III patients with systemic recurrences, routine radiographic imaging discovered 51% of these recurrences.
<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Tumor site</th>
<th>Breslow depth (mm)</th>
<th>Ulceration</th>
<th>Mitotic rate</th>
<th>Positive lymph nodes</th>
<th>Months to recurrence</th>
<th>Months from negative PET/CT results to recurrence</th>
<th>Type</th>
<th>Detection method</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>M</td>
<td>Trunk/low back</td>
<td>6</td>
<td>Yes</td>
<td>10/mm²</td>
<td>1</td>
<td>14.01</td>
<td>0</td>
<td>Distant/cutaneous metastasis on left breast</td>
<td>Physician</td>
<td>PET/CT at time of recurrence negative</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>LE</td>
<td>5.5</td>
<td>Yes</td>
<td>2.4/mm²</td>
<td>6</td>
<td>25.58</td>
<td>12.23</td>
<td>Distant/brain</td>
<td>MRI</td>
<td>Asymptomatic, negative PET/CT at time of recurrence</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
<td>HN</td>
<td>1.8</td>
<td>Yes</td>
<td>NA</td>
<td>1</td>
<td>40.34</td>
<td>3.06</td>
<td>Regional/in transit</td>
<td>Patient</td>
<td>Patient detected in transit lesion, PET/CT at time of recurrence positive only at recurrence</td>
</tr>
<tr>
<td>53</td>
<td>M</td>
<td>LE</td>
<td>5.2</td>
<td>No</td>
<td>1/mm²</td>
<td>2</td>
<td>36.66</td>
<td>13.02</td>
<td>Regional/in transit</td>
<td>Patient</td>
<td>Patient detected in transit lesion, PET/CT at time of recurrence positive only at recurrence</td>
</tr>
<tr>
<td>58</td>
<td>M</td>
<td>HN</td>
<td>2.5</td>
<td>No</td>
<td>4.5/mm²</td>
<td>3</td>
<td>17.10</td>
<td>3.78</td>
<td>Regional/cervical lymph node</td>
<td>Patient</td>
<td>Patient detected lymphadenopathy, PET/CT at time of recurrence positive only at recurrence</td>
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<tr>
<td>54</td>
<td>M</td>
<td>Trunk</td>
<td>1.75</td>
<td>No</td>
<td>0.4/mm²</td>
<td>1</td>
<td>42.81</td>
<td>12.00</td>
<td>Distant/opposite lymph node basin</td>
<td>PET/CT</td>
<td>At yearly follow-up, PET/CT detected asymptomatic lymphadenopathy in opposite lymph node basin</td>
</tr>
<tr>
<td>76</td>
<td>F</td>
<td>LE</td>
<td>2.02</td>
<td>Yes</td>
<td>0/mm²</td>
<td>1</td>
<td>25.78</td>
<td>11.51</td>
<td>Distant/liver/lung</td>
<td>LDH and PET/CT</td>
<td>At yearly follow-up, LDH was positive and PET/CT detected asymptomatic metastasis</td>
</tr>
</tbody>
</table>

CT = computed tomography; F = female; HN = head and neck; LDH = lactate dehydrogenase; LE = lower extremity; M = male; MRI = magnetic resonance imaging; NA = not available; PET = positron emission tomography.
studies highlight the disparate nature of the literature, although historically, much of the literature suggests that routine radiographic surveillance adds very little to clinical exam for the detection of initial recurrence. This study was undertaken using the most sensitive radiologic imaging modality currently available to help unravel this controversy.

There are currently few data on the utility of PET/CT imaging in the surveillance of asymptomatic patients with stage III melanoma. Although PET/CT imaging appears useful in evaluating patients with known metastatic disease, its value in asymptomatic patients is not well characterized. To date, 3 small studies have evaluated the use of PET or PET/CT imaging in the routine staging of patients around the time of initial diagnosis. In 2 of these, the incidence of detecting clinically unsuspected disease with PET/CT imaging was <2%. The third study reported that 12% of patients (4 of 33) with American Joint Commission on Cancer stage III disease had positive PET/CT findings for otherwise undetected melanoma. However, interpretation of these data is difficult because 22 patients with the same stage of disease elected not to undergo PET/CT imaging, which adds an element of selection bias to these results. This suggests that in this subset of patients without macrometastatic disease in a lymph node, PET/CT imaging may not be helpful in finding distant disease. This could be related to an inability of PET/CT imaging to identify disease <1 cm in size. There are no published data that we are aware of reporting on the efficacy of routine PET/CT imaging in detecting recurrence in the follow-up of patients with stage III melanoma.

Given the lack of available evidence as to the utility of routine radiographic imaging in patients with melanoma, it is not surprising that guidelines for the follow-up of patients with melanoma differ around the globe, and there is no international consensus. According to the National Comprehensive Cancer Network in the United States, it is recommended that for stage III melanoma, follow-up should occur every 3 to 6 months for the first 2 years, with a comprehensive history and physical focusing on skin and nodal basins. For years 3 to 5, follow-up should occur every 3 to 12 months and then annually after year 5. In these guidelines, chest x-ray, CT imaging, or PET/CT imaging is to be considered every 6 to 12 months to survey for metastatic disease. In addition, brain MRI should be considered annually. There is no specific recommendation for routine screening blood tests. British guidelines recommend only history and physical exams every 3 months for the first 3 years and then every 6 months for the next 2 years, followed by yearly after that. They state that screening ultrasound, CT imaging, and PET imaging are not useful in screening asymptomatic patients. German guidelines include a history and physical exam every 3 months for the first 5 years and then every 6 months for the next 5 years. They include lymph node ultrasound every 3 to 6 months for the first 5 years as well as serum S100 levels every 3 to 6 months for the first 5 years. Also recommended are other imaging studies, such as abdominal ultrasound, chest x-ray, CT imaging, MRI, and PET imaging as warranted every 6 months. Clearly, from the above variation in recommended surveillance, there is no international consensus.

In this data set, to date, routine restaging PET/CT imaging in the follow-up of SLN-positive stage III melanoma was not helpful in identifying occult recurrence. Of the 38 patients in the study, 2 patients had true-positive PET/CT findings for disease that was not otherwise appreciated by the patients or clinicians, although 1 patient also had an elevated LDH level before the clinic visit. Importantly, an additional 9 scans (8%) had false-positive results. We included any abnormal finding that resulted in additional testing or procedures, including short-follow-up scans. These false-positive results increase the costs associated with routine screening and increase the anxiety and emotional distress of patients. The cost associated with routine screening is certainly quite high and may become prohibitive in the future considering recent attempts at cost containment.

Of the 83 patients in our database with SLN-positive stage III melanoma, 28 had recurrences within 1 year. Clearly, this limited the utility of routine imaging in detecting recurrence when performed annually as per our paradigm. Identifying a subset of patients at greatest risk not only for recurrence but also early recurrence may be the key to developing follow-up guidelines that incorporate routine imaging in a meaningful way and in whom these studies are more likely to be beneficial.

We acknowledge several limitations of our study. Most important, the sample size was ultimately quite small, with only 38 patients. Second, the incidence of recurrence among those with ≥1 routine PET/CT scan was low; perhaps this will change with greater follow-up time. There were also a number of patients who were lost to follow-up, likely because of significant distances many patients travel within our catchment area. Last, the small numbers of patients and recurrences did not allow for analysis of clinical and pathologic characteristics that may be associated with the radiographic detection of initial recurrence. With these limitations, it is difficult to draw definitive conclusions that should alter practice, but instead, we

### Table 3 Results of 108 routine follow-up PET/CT scans

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>n</th>
<th>Negative (90%)</th>
<th>Suspicious (10%)</th>
<th>True-positive (2%)</th>
<th>False-positive (8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT Imaging</td>
<td>108</td>
<td>97</td>
<td>1</td>
<td>2/11</td>
<td>9/11</td>
</tr>
</tbody>
</table>

CT = computed tomographic; PET = positron emission tomographic.
would encourage these results to be used as preliminary data and for hypothesis generation.

Conclusions

Clearly, there is much controversy and few data surrounding the correct use of PET/CT imaging in patients with melanoma. There is no defined role for its routine use in staging or in surveillance. There is also no international consensus on the best way to follow patients with SLN-positive stage III melanoma once they are surgically rendered disease free. This study brings up the question as to how to effectively follow patients after surgical resection of melanoma and how to thoughtfully incorporate radiographic imaging in the evaluation of these patients. Future work should be targeted at identifying clinical and pathologic risk factors that increase the likelihood of recurrences of various types and stratifying patient follow-up on the basis of these patterns, as opposed to a “one-size-fits-all” approach. For stage III patients alone, given the broad spectrum of recurrence risk for stages IIIa to IIIc, it is likely that strategies for follow-up evaluation should be different. Larger data sets and perhaps quality of care initiatives such as those undertaken by the Agency for Healthcare Research and Quality may greatly improve our understanding of this question.

References