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# Clinical Use of Positron Emission Tomography in the Management of Cutaneous Melanoma

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**Cutaneous melanoma is the seventh most common newly diagnosed cancer among Americans. It frequently metastasizes and is difficult to treat. Accurate disease staging is important for optimizing therapy and selecting appropriate patients for experimental trials. Positron emission computed tomography (PET) using $^{18}$F-fluorodeoxyglucose (FDG) has been studied extensively since 1991 and shows great promise in the detection of metastatic cutaneous melanoma. Cumulative data from the last 13 years is reviewed in this article and suggest that FDG-PET is the modality of choice for evaluating patients who fit into one of four categories: 1) individuals with a high risk for distant metastases based on extent of locoregional disease, 2) patients with findings that are suspicious for distant metastases, 3) individuals with known distant tumor deposits who still stand to benefit from customized therapies if new lesions are discovered or treated lesions regress, and 4) patients at high risk for systemic relapse who are considering aggressive medical therapy. Despite the overall superiority of FDG-PET in the detection of melanoma metastases, limitations exist with respect to detection of small lung nodules and brain metastases, which are better evaluated by computed tomography and magnetic resonance imaging, respectively.**
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In 2004, Cutaneous melanoma is estimated by the American Cancer Society to be the seventh most common newly diagnosed cancer among Americans. A projected 55,100 individuals will be diagnosed with the disease this year, and 7910 will die from systemic metastases.[1] Although the recent rise in incidence may be partially related to improved screening programs and detection of earlier, thin lesions with a more favorable prognosis,[2] even patients with thin melanomas (less than 1 mm) have a 15% chance of developing metastases, and many will die from the disease.[3]

Surgical excision is a successful treatment for primary melanoma that has not metastasized. Unfortunately, few therapies exist that have a significant impact on survival in patients with regional or distant tumor spread. Surgical resection of regional lymph node tumor foci is important for local disease control and staging, and removal of isolated organ metastases may be beneficial in some individuals.[4] Radical prophylactic surgery, isolated limb perfusion therapy, and chemotherapy, although of some utility, have met with relatively limited long-term success in cases of advanced melanoma. Tumor vaccines are a hopeful area of research and have shown some survival benefit in subpopulations of patients with melanoma.[5]

Despite the difficulty in treating patients with metastatic disease, there is an urgent need for accurate tumor staging. Appropriate identification of local or distant tumor deposits is critical to identify patients who may benefit from invasive procedures while avoiding unnecessary, potentially harmful surgical therapies that would yield no improvement in survival. Furthermore, accurate staging is necessary to properly select patients for experimental therapeutic trials. As new, increasingly effective therapies are developed, accurate staging will be important to triage appropriate patients into one of the various treatment options. Finally, the ability to provide patients with detailed information about prognosis, based on accurate disease staging, not only allows for appropriate life planning but can give patients a sense of control over their disease through better understanding of their situation and less fear of the unknown.

Positron emission tomography (PET) is a useful noninvasive imaging modality for the staging of melanoma and has a potential role in assessing response to therapy. This work will review the current literature regarding the use of PET in the diagnosis, initial staging, re-staging, and treatment response monitoring of patients with cutaneous melanoma. Particular attention will be paid to the use of fluorodeoxyglucose (FDG), with additional brief discussion of experimental PET radiotracers. A review of the current staging system and conventional diagnostic tests provides a framework for discussion of the integration of PET into diagnostic pathways.

## Staging Systems

In general, the thicker the primary melanoma, the worse the prognosis. However, there are numerous other prognostic factors that

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have a significant impact on survival and led to the development of melanoma staging systems. In 2001, the American Joint Committee on Cancer updated their staging system for cutaneous melanoma to better address the improved understanding of risk factors that affect survival.[6] Clark's levels of invasion were removed from staging criteria for all but the thinnest lesions (≤1 mm), tumor thickness staging thresholds were changed to reflect updated prognostic information (thresholds of 0.75, 1.50, and 4.0 mm were changed to 1.0, 2.0, and 4.0 mm), ulceration was added as an independent predictor of worse prognosis (regardless of stage), and thick melanomas (>4.0 mm) were changed from stage IIIA to IIC. Stage I disease is now defined as lesions that are less than 1 mm thick and ulcerated or less than 2.0 mm thick and not ulcerated. Stage II disease includes localized lesions greater than 1 mm thick that are ulcerated and all lesions greater than 2.0 mm thick. Stage III disease is now defined by the presence of any type of regional metastasis, including in-transit metastases, satellite cutaneous metastases, and any type of regional lymph node metastasis. The size of nodal metastases is no longer considered significant, but the total number of metastatic nodes now influences subcategorization within stage III. Macroscopic nodal metastases are recognized as carrying a worse prognosis compared with microscopic lymph node involvement, and lung metastases are considered to carry a more favorable prognosis compared with other distant visceral lesions (M1b versus M1c disease).[6]

An appraisal of the current literature concerning PET in the management of melanoma is complicated by the multiple staging systems used by different authors (Table 1). Older studies generally use the 1997 American Joint Committee on Cancer (AJCC) staging system, whereas more recent publications use the revised AJCC criteria adopted in 2001.[7] Others make use of the M.D. Anderson staging system[8] and, thus, the resulting patient subpopulations used in these studies are all slightly different. To avoid confusion regarding variable application of the different staging systems, this review attempts, whenever possible, to organize findings based on the strict biological stage of the tumor.

**Table 1 Melanoma Staging Systems**

| | |
|---|---|
| **1997 AJCC Melanoma Staging System** | |
| Stage Ia | Primary tumor ≤0.75 mm |
| Stage Ib | Primary tumor 0.76-1.49 mm |
| Stage II | Primary tumor 1.5-4.0 mm |
| Stage IIIa | Primary tumor >4.0 mm |
| Stage IIIb/c | In-transit metastases, regional lymph node metastases |
| Stage IV | Distant spread |
| **2001 AJCC Melanoma Staging System** | |
| Stage Ia | Primary nonulcerated tumor ≤1.0 mm |
| Stage Ib | Primary nonulcerated tumor 1.01-2.0 mm or primary ulcerated tumor ≤1.0 mm |
| Stage IIa | Primary nonulcerated tumor 2.01-4.0 mm or primary ulcerated tumor 1.01-2.0 mm |
| Stage IIb | Primary nonulcerated tumor >4.0 mm or primary ulcerated tumor 2.01-4.0 mm |
| Stage IIc | Primary ulcerated tumor >4.0 mm |
| Stage IIIa | Primary nonulcerated tumor any thickness and 1 to 3 micrometastatic lymph nodes |
| Stage IIIb | Primary nonulcerated tumor any thickness and 1 to 3 macrometastatic lymph nodes<br>Primary ulcerated tumor any thickness and 1 to 3 micrometastatic lymph nodes<br>Any primary tumor and in transit or satellite metastases |
| Stage IIIc | Any primary ulcerated tumor and 1 to 3 macrometastatic lymph nodes<br>Any primary tumor and 4 or more metastatic nodes<br>Matted nodes<br>In transit or satellite metastases with any metastatic nodes |
| Stage IV | Any distant metastases |
| **M.D. Anderson Melanoma Staging System** | |
| Stage I | Primary cutaneous melanoma (any thickness) |
| Stage II | Focal recurrence or satellites |
| Stage IIIa | In-transit metastases |
| Stage IIIb | Regional lymph node metastases |
| Stage IV | Distant spread |

## Conventional Staging Techniques

Conventional staging of cutaneous melanoma relies on multiple surgical, histopathological, imaging, and biochemical modalities. Sentinel lymph node (SLN) localization and biopsy are now a mainstay of initial melanoma staging for patients with intermediate-risk primary lesions (thickness 1.0 to 4.0 mm) and clinically negative lymph nodes.[9] Histopathological evaluation of the sentinel node allows selection of patients who may benefit from regional nodal dissection (those with positive SLNs) and spares others (those with negative SLNs) from surgery when the risk of local spread is sufficiently low. The histological status of regional lymph nodes is the most significant predictor of recurrence.[10]

Chest radiography is a commonly employed modality for screening newly diagnosed patients for lung metastases. The low cost and minimal patient discomfort combined with knowledge that approximately 20% of patients with melanoma develop recurrent disease motivates clinicians to perform this test despite little rigorous evidence to support its utility. Terhune and coworkers demonstrated that although chest radiography identified abnormal findings necessitating further evaluation in 15% of 876 patients newly diagnosed with melanoma, only 1 (0.1%) was found to have a true positive chest x-ray demonstrating pulmonary metastases.[11]

Ultrasound imaging and fine-needle aspiration of abnormal regional lymph nodes may be useful in identifying a small number of patients with local metastases. This technique has the potential to spare patients from the additional surgical risk of sentinel node biopsy before regional nodal dissection.[12] However, this methodology is not in widespread use in the United States and there is little evidence supporting the role of ultrasound in the evaluation patients with melanoma.

Computed tomography (CT) imaging is not particularly helpful in the initial evaluation of patients with stage I or II disease because of its high false-positive rate and the overall low frequency of patients with anatomically identifiable metastases.[13] Despite extensive clinical use in patients with suspected or known stage III melanoma, only a limited and somewhat controversial literature supports its routine use. It may be most useful in patients with cervical or groin adenopathy.[14]

The role of CT in suspected or known stage IV disease is most significant in the evaluation of pulmonary metastases, but sensitivity

in the evaluation of intraabdominal, head and neck, and distant nodal metastases is not well defined.[15-17]

In patients with cutaneous melanoma, magnetic resonance imaging (MRI) typically is reserved for the evaluation of suspected brain metastases in symptomatic patients. There are few studies systematically evaluating its role in imaging other regions of the body, although it has been proven useful in characterization of suspected or known liver metastases.[18]

The most commonly tested biochemical marker for metastatic melanoma is the serum lactic dehydrogenase level. It is an inexpensive, reasonably sensitive method for alerting the physician to the possibility of liver metastases, but it can be elevated for other reasons. Lactic dehydrogenase and other serum tumor markers, including S100 protein, are of limited benefit in detecting extrahepatic metastases.

# Improving Staging of Melanona with FDG-PET

As demonstrated above, no single modality is highly sensitive and specific for the detection of all types of local or distant lesions of metastatic melanoma. An all-inclusive, accurate staging technique would greatly simplify the complexity of modalities in use today, reduce costs, and ease the strain on patients requiring numerous imaging studies, biopsies, and laboratory tests.

In 1991, Wahl and coworkers[19] and Kern[20] independently demonstrated that radiolabeled glucose analogs were preferentially taken up in murine melanomas and human melanoma xenografts, setting forth the rationale for the potential use of FDG in patients with melanoma. In 1993, Gritters and coworkers imaged 12 patients with FDG-PET and found a sensitivity and specificity of 100% for detecting visceral and lymph node metastases.[21] Numerous investigators have subsequently examined the utility of PET for identification of local and distant metastatic disease by means of molecular imaging with FDG. This paradigm is in theory, an elegant solution.

## Initial Diagnosis

The relatively easy detection of atypical pigmented lesions on physical examination has led to little research in the use of FDG-PET for initial diagnosis of cutaneous melanoma. Anecdotal reports describe the ability of PET to detect occult cutaneous metastases, but unlike in other malignancies, including lung cancer, there is no defined role for PET in the initial diagnosis of melanoma. The inherent spatial resolution of PET reduces sensitivity for detection of lesions less than 80 $mm^3$,[22] and it is unlikely that this technique (as currently performed) will ever be effective in the initial diagnosis of small, surgically curable, melanoma in situ.

## Initial Staging of Clinically Localized Disease

Once the diagnosis of cutaneous melanoma has been made by biopsy of a suspicious lesion, determination of the potential utility of FDG-PET becomes more complicated. Assessment of the SLN draining the tumor site becomes of paramount importance, in particular for intermediate and high-risk lesions greater than 1 mm in thickness where the probability of malignant spread is increased.

In 1997, Wagner and coworkers studied 11 patients with both palpable and nonpalpable regional lymph nodes who underwent elective or therapeutic lymphadenectomy on 14 regional nodal basins and found that FDG-PET correctly predicted nodal metastases in 7 of 7 histologically positive nodal basins and correctly excluded nodal disease in 7 of 7 histologically negative nodal basins (sensitivity 100%, specificity 100%). However, all seven patients undergoing elective lymph node dissection for nonpalpable disease had histologically negative lymph nodes and, as expected, negative PET scans. It was therefore impossible to assess the ability of FDG-PET to detect subclinical (nonpalpable) lymph node metastases because none of the patients had occult metastases.[23]

Rinne and coworkers included 52 patients with primary melanoma greater than 1.5 mm in depth and no evidence of local or distant metastases in a larger study examining the ability of FDG-PET to detect melanoma metastases. Among this subgroup of individuals, the accuracy of PET for identification of regional or distant metastases was reported to be 94.9% per lesion and 94.2% per patient and was clearly superior to conventional anatomic imaging (67.8% per lesion, 76.9% per patient).[24]

In 1998, Macfarlane and coworkers found that PET accurately predicted regional nodal status in 88% of 23 patients with primary melanomas that were greater than 1.5 mm thick.[25] This patient population was also mixed and consisted of patients with both clinically normal and abnormal regional lymph nodes. Among nine patients undergoing elective lymph node dissection for removal of clinically benign regional lymph nodes, eight of nine nodal basins were histologically negative, and all but one had no increased FDG uptake. In one patient with one histologically positive lymph node from a total seven resected, there was no increased FDG uptake. It was noted that this patient's lymph node had only minimal tumor involvement. Again, the very small number of patients with occult metastases in this patient population precludes drawing any conclusions about the ability of FDG-PET to routinely detect occult regional metastases. One might surmise from these experiments that the false-positive rate is low, but little can be said about the sensitivity.

Wagner and coworkers reported data from a large prospective trial containing 70 patients with primary thick melanomas (>1.0 mm) and 4 patients with recurrent melanoma in or adjacent to the surgical scar who underwent PET and SLN biopsy. Using the biopsy results as a gold standard for regional lymph node metastases, PET imaging found 2 true positives, 71 true negatives, 0 false positives, and 16 false negatives for a sensitivity of 11% and specificity of 100%.[26] This is one of the first articles to suggest that PET is not sensitive for staging of regional nodes in patients with newly diagnosed thick melanoma.

Acland and coworkers found that FDG-PET failed to identify all 14 positive SLNs found in 50 patients who underwent sentinel node biopsy for primary melanomas that were histopathologically greater than 1 mm in thickness or invading lymphatics.[27] Similarly, in another study of 6 histologically positive SLNs in patients with clinically localized disease, PET identified only one metastatic focus in a sentinel node that was >1 cm.[28] Fink and coworkers also found that among eight histologically positive SLNs in 48 patients with stage I or II disease, FDG-PET identified only one metastatic node and concluded that this phenomenon was likely "due to the small size of metastatic deposits in sentinel nodes".[29]

Wagner and coworkers determined that FDG-PET cannot reliably diagnose lymph node metastases in tumor deposits smaller than 80 $mm^3$.[22] Despite the early reports of success in this patient population, these latter findings have been confirmed by numerous other investigators,[30-34] and there is now strong evidence that FDG-PET is not useful in the initial staging of primary cutaneous melanoma, when there is no clinical evidence of local or distant metastatic spread (Table 2). The small size of most nodal metastases combined with the low prevalence of nodal disease in patients with

**Table 2** Detection of Regional Lymph Node Metastases in Primary Melanoma Using FDG-PET*

| Enlarged Nodes† | Author | Year of Publication | Number of Patients | Histologically Malignant/Benign Lymph Node Basins | Sensitivity of PET (%) | Specificity of PET (%) |
|---|---|---|---|---|---|---|
| Mixed group | Wagner et al[23] | 1997 | 11 | 7/7 | 100 | 100 |
| Mixed group | Macfarlane et al[25] | 1998 | 23 | 13/11 | 85 | 92 |
| No | Rinne et al[24] | 1998 | 52 | 15/37 | 100 | 94 |
| No | Wagner et al[26] | 1999 | 74‡ | 18/71 | 11-17§ | 94-100§ |
| No | Macfarlane et al[25] | 1998 | 9 | 1/8 | 0 | 88 |
| No | Belhocine et al[28] | 2002 | 21 | 6/15 | 14 | 93 |
| No | Havengna[34] | 2003 | 53 | 13/40 | 15 | 88 |
| Not defined | Acland et al[27] | 2001 | 50 | 14/36 | 0 | ‖ |
| Not defined | Schafer et al[30] | 2003 | 40 | 6/74 | 0 | ‖ |
| Not defined | Longo et al[32] | 2003 | 25 | 9/16 | 22 | ‖ |
| Not defined | Hafner et al[33] | 2004 | 100 | 26/74 | 8 | 100 |

*All patients were recently diagnosed with cutaneous melanoma and had no histopathologic evidence of regional lymph node metastases.
†Enlarged lymph nodes by either clinical exam, ultrasonography or computed tomography.
‡Four of 74 patients had recurrence at or adjacent to the surgical site and 70 had primary thick melanoma. No patients had enlarged nodes.
§Variable range depending on ROC threshold.
‖Cannot be determined from presented data.

primary melanoma argues strongly against a role for FDG-PET in primary staging of regional lymph nodes.[26,35] For this reason, the Center for Medicare Sciences in the United States does not reimburse for this indication.[36]

## Local Recurrence, Satellite, or In-Transit Metastases

There are no studies that specifically examine the efficacy of FDG-PET in the evaluation of patients with locally recurrent primary tumor (in contrast to adjacent satellite metastases or more distant in-transit lesions). However, two studies of the overall utility of FDG-PET in recurrent melanoma present data allowing a review of patients with satellite or in-transit metastases.

In a study of numerous patient types, Acland and coworkers examined nine individuals with satellite metastases adjacent to the primary tumor excision site. FDG-PET identified three abnormal foci; one true positive lung metastasis and two false positives.[8] Known regional lymph node metastases or in-transit metastases in 16 patients were considered together as a group (as a result of using the M.D. Anderson melanoma staging system) and generated a sensitivity of 93% and a specificity of 50% for the ability of FDG-PET to detect locoregional metastatic disease. The data presented do not allow analysis of the in-transit metastases alone and therefore little can be said about the utility of FDG-PET in patients with in-transit lesions and no evidence of regional nodal disease or distant spread. The low specificity in this article demonstrates the potential for false positives with FDG-PET and emphasizes the importance of obtaining a detailed clinical history (Fig. 1).

In a study by Stas and coworkers including patients with varying types of recurrent melanoma, one of seven patients with local primary tumor recurrence underwent a change of therapy because of downstaging of a suspicious lymph node discovered by conventional staging procedures. The patient reportedly had no disease at 26 months. Three of 18 cases with adjacent satellite metastases or distant in-transit lesions underwent a change of management due to FDG-PET results: two by means of an extended surgical field for additional in-transit lesions and one for discovery of a distant metastatic lymph node that led to cancellation of surgery and treatment instead with chemotherapy.[37]

Wagner and coworkers included four patients with in-transit metastases in a study of 70 patients designed to examine the ability of FDG-PET to detect occult regional lymph node metastases.[26] Sensitivity was 50% and specificity was 100% with one true-positive, one false-negative, and three true-negative lesions. The implications of these findings are uncertain given the small size of the subgroup with in-transit disease only.

Overall, there are scant data available to accurately judge the utility of FDG-PET in patients with known or suspected local recurrence, satellite lesions, or in-transit metastases. Acland's upstaging of one patient with an occult lung metastases and Stas' discovery of additional lesions in two patients suggests a possible role for PET in this population, but further studies are required. Certainly, it is expected that very small tumor volume disease will not be detected.

## Suspected Regional Lymph Node Metastases

Little is known about the utility of FDG-PET in patients with suspected regional metastases to adjacent lymph node basins, either at initial diagnosis or with follow-up monitoring for recurrent disease. The preceding evidence suggests that the sensitivity of FDG-PET may be low in patients with small metastases in adjacent lymph nodes. However, patients with suspected regional metastases based on physical examination or other imaging modalities may have a greater prevalence of larger, detectable metastases on PET compared with the majority of patients with clinically localized tumors who never develop distant disease (80% or greater).

Blessing and coworkers found a sensitivity of 74% and a specificity of 93% for the evaluation of 20 clinically suspicious lymph node basins by FDG-PET.[38] Crippa and coworkers found an accuracy of 91% for FDG-PET in the detection of metastases in 56 lymph node basins in 38 patients with clinically or radiographically enlarged lymph nodes. Sensitivity dropped off rapidly for lymph nodes less than 5 mm in largest diameter but was 100% and 83% for nodes that were greater than or equal to 10 mm and 6 to 10 mm, respectively.[39] Presumably, a greater prevalence of larger nodal metastases coupled with a higher incidence of any type of metastatic lymph nodes in this patient population led to the high accuracy of FDG-PET.

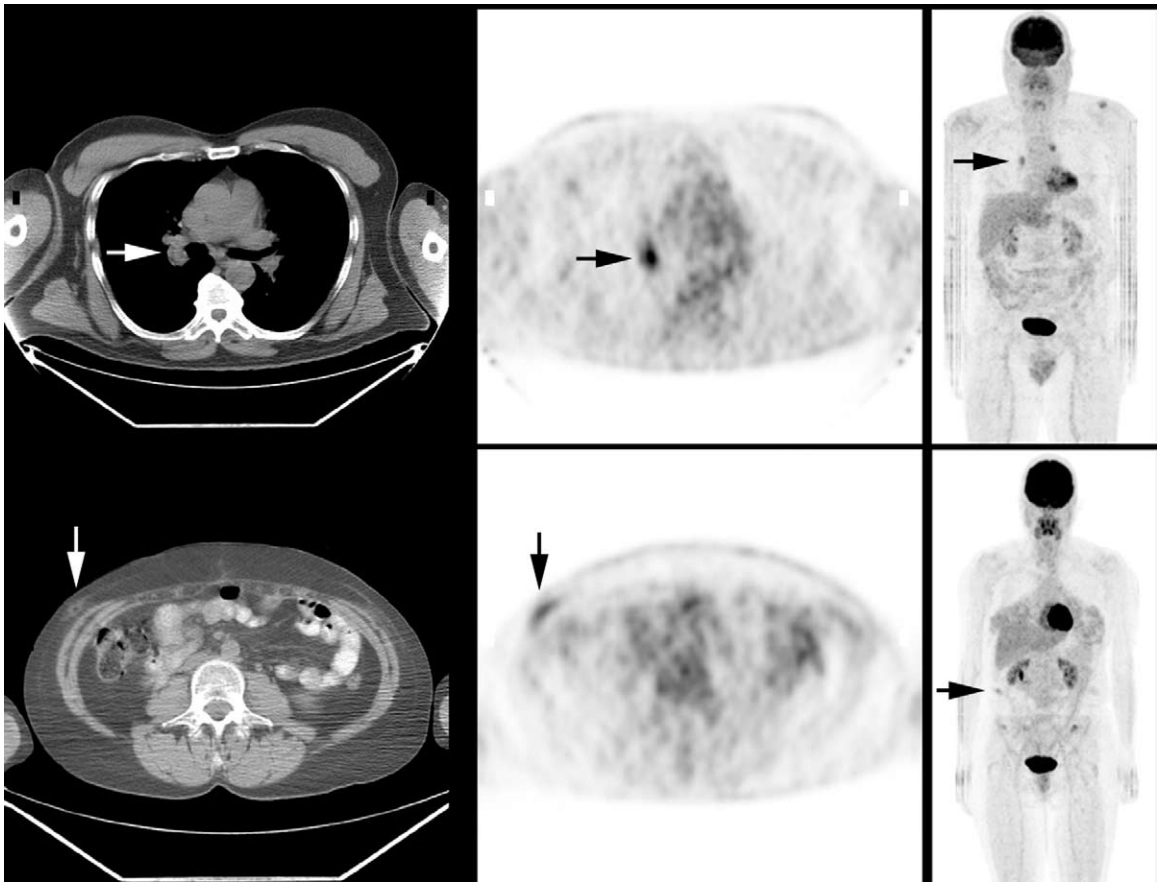

**Figure 1** False-positive PET scans. Upper row shows a 61-year-old male with a history of melanoma on the back that was resected 5 years ago. The patient underwent FDG-PET to evaluate a 0.5-cm nodule in the lingula as well as hilar and mediastinal lymphadenopathy. There was no FDG uptake in the lung nodule, but prevascular and right hilar lymph nodes demonstrated intense FDG uptake (arrows). An endobronchial biopsy confirmed sarcoidosis. Benign FDG uptake in the left shoulder caused by joint inflammation is noted. Lower row shows a 49-year-old female with melanoma, after resection of lung and brain metastases. The patient was receiving melanoma vaccine therapy. FDG-PET demonstrates multiple soft tissue foci in the abdomen (arrows) corresponding to vaccination sites.

Despite these encouraging findings, the clinical applicability of this information is not completely clear. If locoregional lymph nodes are palpable or enlarged on CT or ultrasound, is there any need for additional metabolic imaging or would it be easier to proceed directly to biopsy? Despite Crippa's negative predictive value of 89%, would a patient want to pass up a chance for improved survival or possible cure if they knew that a negative FDG-PET scan meant they still had an 11% chance that their palpable or enlarged lymph nodes were harboring metastatic disease that likely would grow unfettered without surgery? It is possible that a negative PET at diagnosis with a negative scan on follow-up would address the issue of lower than 100% initial sensitivity.

Another question the patient and clinician face when presented with suspected local metastases concerns the presence of distant metastatic disease. Although many studies confirm the superiority of FDG-PET compared with other imaging modalities for the detection of occult distant disease, none directly address the patient population with suspected but not confirmed regional metastases. Crippa's work demonstrated that 19 of 56 enlarged local lymph nodes were benign on biopsy, suggesting that a large proportion of patients with primary disease and suspected local metastases might in fact have no metastases at all. The performance of unnecessary surgery in this group is obviously undesirable. A majority of the studies documenting the accuracy of FDG-PET for detecting distant disease were performed on patients with already confirmed or at least suspected stage IV disease (see below for further discussion).[40,41] These individuals are likely to have larger and more numerous distant metastases and it is therefore difficult to apply the data to patients who only have suspected local metastases.

A study by Tyler and coworkers attempted to resolve the question of the utility of FDG-PET in the evaluation of suspected regional nodal metastases. Among 95 patients with palpable lymph node disease, in-transit metastases alone or both palpable local lymph nodes and in-transit metastases, FDG-PET identified 144 of 165 pathologically confirmed areas of melanoma (sensitivity 87.3%). There was a high false-positive rate that yielded a specificity of only 43.5%. More importantly, 36 unknown metastases were discovered that led to a change in clinical management for 16 of 106 (15%) patients.[42] These findings argue that FDG-PET has a useful role in the patient with suspected regional lymph node metastases.

## Confirmed Metastasis in a SLN

Several studies address the utility of FDG-PET in patients with various types of regional lymph node metastases (see below), but none directly assess its value in the subset of patients with clinically or

anatomically negative nodes and a positive SLN biopsy. Patients with histopathologically positive SLNs may have a lower tumor burden compared with those with metastatic lymph nodes detected by clinical palpation or radiologic exams. Studies investigating the efficacy of FDG-PET in this important subgroup are desperately needed before recommendations can be made. These individuals may represent a spectrum of patients who have either microscopic solitary lymph node metastases, diffuse nodal metastases, or possibly distant occult disease. Improved staging is critical to advance the treatment of these individuals. It is quite possible, but not yet proven, that PET could be useful in this high-risk population to exclude systemic metastases.

## Confirmed Lymph Node Metastases Beyond the SLN

Until effective medical treatment of metastatic melanoma is developed, surgical resection of local nodal metastases will remain the primary method for obtaining local tumor control and potentially preventing distant metastases in some patients. The value of FDG-PET in this patient population is not to identify already confirmed regional lymph node metastases but to localize occult distant metastases that might be amenable to surgical resection. Another possible use of FDG-PET in this subgroup is to exclude metastatic disease in patients with equivocal findings on conventional anatomic images.

In 1997, Wagner evaluated the utility of FDG-PET in a mixed population of patients undergoing elective lymph node dissection (based on tumor depth with no evidence of local or distant metastases) or therapeutic lymph node dissection for biopsy or fine-needle aspiration confirmed local lymph node metastases. In seven FDG-PET scans for patients with confirmed regional lymph node metastases, PET identified five of the local lymph node metastases. Four occult metastases were found in three patients in the form of a left adrenal lesion, a subcutaneous nodule, a mediastinal focus and an in-transit metastasis. Although the numbers are small, this article suggests that FDG-PET can up-stage a significant number of patients who would otherwise have been considered to harbor only local lymph node metastases.[23]

Acland and coworkers grouped all patients with in-transit metastases and regional lymph node metastases into one stage using the M.D. Anderson staging system. They found a sensitivity of 93% and a specificity of 50% for detection of all metastases. More importantly, 28% patients in this group were found to have previously unknown distant metastases that may have altered patient management.[8] Applying these findings to patients with nodal metastases and no other tumor foci is somewhat problematic because of the inclusion of patients with biologically different in-transit metastases but suggests that patients with varying types of local metastases have a high chance of being up-staged by FDG-PET.

## FDG-PET in the Identification of Distant Metastases

Evaluating the precise utility of FDG-PET in patients with suspected or known distant metastases is difficult because of the diversity of clinical scenarios, but this is a setting in which PET is frequently applied. Patients recently diagnosed with melanoma can have clinical, laboratory, or radiologic evidence of distant metastases. Patients with previously resected melanoma can present with findings that are suspicious for recurrent disease in the form of distant metastases. Finally, patients with previously treated distant metastases require accurate re-staging to plan future surgical or medical management. Further complicating the situation is that all of these patient subgroups may have differing degrees of tumor burden (both in terms of size and number of lesions) and therefore FDG-PET may prove effective and justified in some scenarios and not in others.

In 1993, Gritters and coworkers reported on the utility of FDG-PET to detect metastatic disease in 12 patients of varying stage, including patients with thick primary tumors, palpable lymph nodes, subcutaneous nodules or presumed metastases on CT imaging. FDG-PET identified 15/15 intraabdominal visceral and lymph node metastases that were 0.5 to 8.0 cm in diameter. Five of these lesions were not seen on initial CT imaging, although retrospective review found three, and follow-up CT identified the lesions within 2 to 6 months. PET also identified two biopsy-proven skin metastases and two soft-tissue lesions in the musculature of the back that were only seen on retrospective review of the CT. FDG-PET was less successful for pulmonary metastases and identified only 4 of 27 lesions. All but one of these 27 lesions was smaller than 1.0 cm.[21] The authors' main conclusion was that FDG-PET appeared to be sensitive for the detection of metastases, and postulated that it might play an important role in patient management.

Steinert and coworkers examined a mixed group of 33 patients with known metastatic melanoma or high-risk primary melanoma (lesions thicker than 1.5 mm). PET identified 37/40 metastases for a sensitivity of 92%. Six patients were found to have seven new lesions not identified by conventional staging modalities, including five lymph node metastases, one local recurrence, and one muscle metastasis.[43] It is difficult to determine whether PET would have altered patient management because the data are not clear regarding which patients with new lesions already had known metastases.

In addition to evaluating patients with thick primary lesions, Rinne and coworkers also examined 48 individuals with clinical or CT findings suggesting local or distant metastatic disease. In this patient population, a sensitivity, specificity and accuracy for FDG-PET was found to be 91.8%, 94.4%, and 92.1%, respectively, compared with 57.6%, 45%, and 55.7% for conventional imaging modalities.[24] It is unclear how many of these patients had locoregional metastases versus distant metastases, but these data suggest that FDG-PET is superior to conventional imaging, except perhaps in the lungs and brain, for all patients with any type of metastatic disease. These data can probably be fairly applied to patients with known distant metastases because their average tumor burdens should be at least as large as those with local metastases.

Holder and coworkers confirmed the superiority of FDG-PET for the detection of melanoma metastases compared with CT. In a study of 76 patients with varying stages of melanoma, FDG-PET had an overall sensitivity and specificity of 94.2% and 83.3%, respectively compared with 55.3% and 84.4% for CT in the detection of melanoma metastases, particularly in the liver, lymph nodes, and soft tissues. These authors also noted that the accuracy of detection of lung metastases was comparable when comparing CT to PET,[44] but others have not substantiated this finding.

Eigtved and coworkers also confirmed the superiority of FDG-PET over conventional staging methods in a mixed population of 38 patients with either local recurrence, in-transit recurrence, regional lymph node metastases, or distant metastases. The authors found a sensitivity and specificity of 97% and 56%, respectively, for all metastatic foci using PET, compared with 62% and 22% using conventional techniques. They concluded that FDG-PET would be useful in excluding patients from mutilating surgery that would be of no benefit and found that 34% of patients were re-staged after PET.[45] As is the case in many other studies, these findings do not easily apply to individual patients because the subjects involved were heterogeneous with respect to stage. Nevertheless, these studies all suggest that PET is indeed superior for localization of distant

**Table 3** Detection of Melanoma Metastases Using FDG-PET

| Author | Year of Publication | Location of Metastases | Sensitivity of PET (%) | Specificity of PET (%) |
|---|---|---|---|---|
| Gritters et al[21] | 1993 | Abdominal | 100 | * |
| | | Lymph nodes | 100 | 100 |
| | | Pulmonary | 15 | * |
| | | Skin and muscle | 80 | * |
| Steinert et al[43] | 1995 | All foci | 92 | 100 |
| Rinne et al[24] | 1998 | Neck and abdominal lymph nodes | 100 | 100 |
| | | Mediastinum | 71 | 100 |
| | | Liver | 100 | 100 |
| | | Abdomen | 100 | 94 |
| | | Peripheral lymph nodes | 97 | 100 |
| | | Bones | 100 | 100 |
| | | Skin | 100 | 100 |
| Holder et al[44] | 1998 | All foci | 94 | 83 |
| Eigtved et al[45] | 2000 | All foci | 97 | 56 |
| | | Abdomen | 100 | 100 |
| | | Pulmonary/intrathoracic | 100 | * |
| Swetter et al[46] | 2002 | All foci | 84 | 97 |
| Gulec et al[40] | 2003 | >1-cm lesions | 100 | 75 |
| | | <1-cm lesions | 13 | 33 |

*Cannot be determined from presented data.

metastases outside of the lungs and brain, independent of the particular stage of the high-risk patient.

Several other studies confirm the increased accuracy of FDG-PET compared with conventional staging of melanoma metastases. Swetter and coworkers reported in a study of 66 consecutive PET and CT scans a sensitivity and specificity of 84% and 97% for PET in the detection of metastatic disease compared with 58% and 70% for CT.[46] Other investigators demonstrated improved 3- and 5-year overall survival among patients undergoing resection of pulmonary metastases when FDG-PET excluded extrapulmonary metastases before surgery. Unfortunately, no survival benefit was noted at 7 years.[47]

Gulec and coworkers studied 49 patients with known or suspected metastatic melanoma by comparing the findings of CT of the chest, abdomen, and pelvis; MRI of the brain; and whole-body FDG-PET. In 27 patients (55%), PET identified more metastatic sites compared with CT and MRI. In 6 of the 27 patients, FDG-PET identified metastases outside of the fields of view of the CT and MRI. Forty-four lesions were pathologically confirmed to be melanoma and the FDG-PET findings led to a change in management for 24 (49%) patients, 18 of which involved canceling or planning new surgery.[40]

Although most data suggest that FDG-PET is superior to conventional imaging modalities for the assessment of metastatic melanoma, not all authors confirm this finding. Dietlein and coworkers retrospectively reviewed 68 patients who underwent FDG-PET imaging in addition to conventional staging methods and found that PET detected fewer pulmonary, hepatic and cerebral metastases, but more lymph node and bone foci.[41] However, this study had numerous methodological weaknesses, including a nonstandardized PET acquisition protocol, use of retrospective data from multiple institutions, variance with respect to the conventional imaging modalities employed for each patient, frequent lack of histological follow-up, heterogeneous indications for testing, and a high prevalence of anatomically detectable metastases in the patient population. These factors precluded an accurate evaluation of the ability of PET to detect occult disease. Similarly, Krug and coworkers found that FDG-PET detected fewer lung and liver metastases compared with conventional imaging in 24 patients, but admits that "no reliable estimation of sensitivity, specificity, and accuracy could be obtained owing to the small number of confirmed findings in the study. . .".[48] Additional studies are required to determine whether MRI of the brain and/or liver and CT of the chest should be regularly used for the detection of brain, liver and lung metastases. When using PET/CT, we certainly will sometimes detect small lung metastases on CT that are occult on PET.

Overall, the vast majority of the available literature suggests that FDG-PET is the most accurate imaging modality for identifying distant metastases in patients at high risk for harboring malignant lesions (Table 3). Data presented in previous sections suggest that this modality identifies a significant number of distant metastases in patients with locoregional disease (Figs. 2 and 3), and subsequent articles reviewed just above suggest that patients with distant metastases also benefit from the identification of additional distant lesions and subsequent changes in management (Fig. 4). The available studies are limited by incorporation of mixed patient populations, and additional trials with better-defined patient populations are needed to advance the literature regarding the efficacy of PET. The two articles suggesting no benefit to using FDG-PET had significant methodological limitations as outline above and the overall evidence of the utility of PET in staging distant metastases is now strong. Although scant literature exists on changes in morbidity and mortality, the relatively recent advent of PET and the associated initial studies suggest that PET plays an important role in the management of patients with more advanced disease, primarily through changes in management. PET or PET/CT also may be very useful for sequential re-staging in follow-up, but little specific data exist. Our opinion is that brain metastases and small lung metastases may be missed by PET but detected by anatomic imaging. Before a definitive answer to the question of the optimal utilization of FDG-PET in patients with local and distant metastases can be made, outcome studies that take the analysis a step beyond change in management are required. If such studies confirm the utility of FDG-PET, then final cost-benefit analyses can be accurately performed and a more

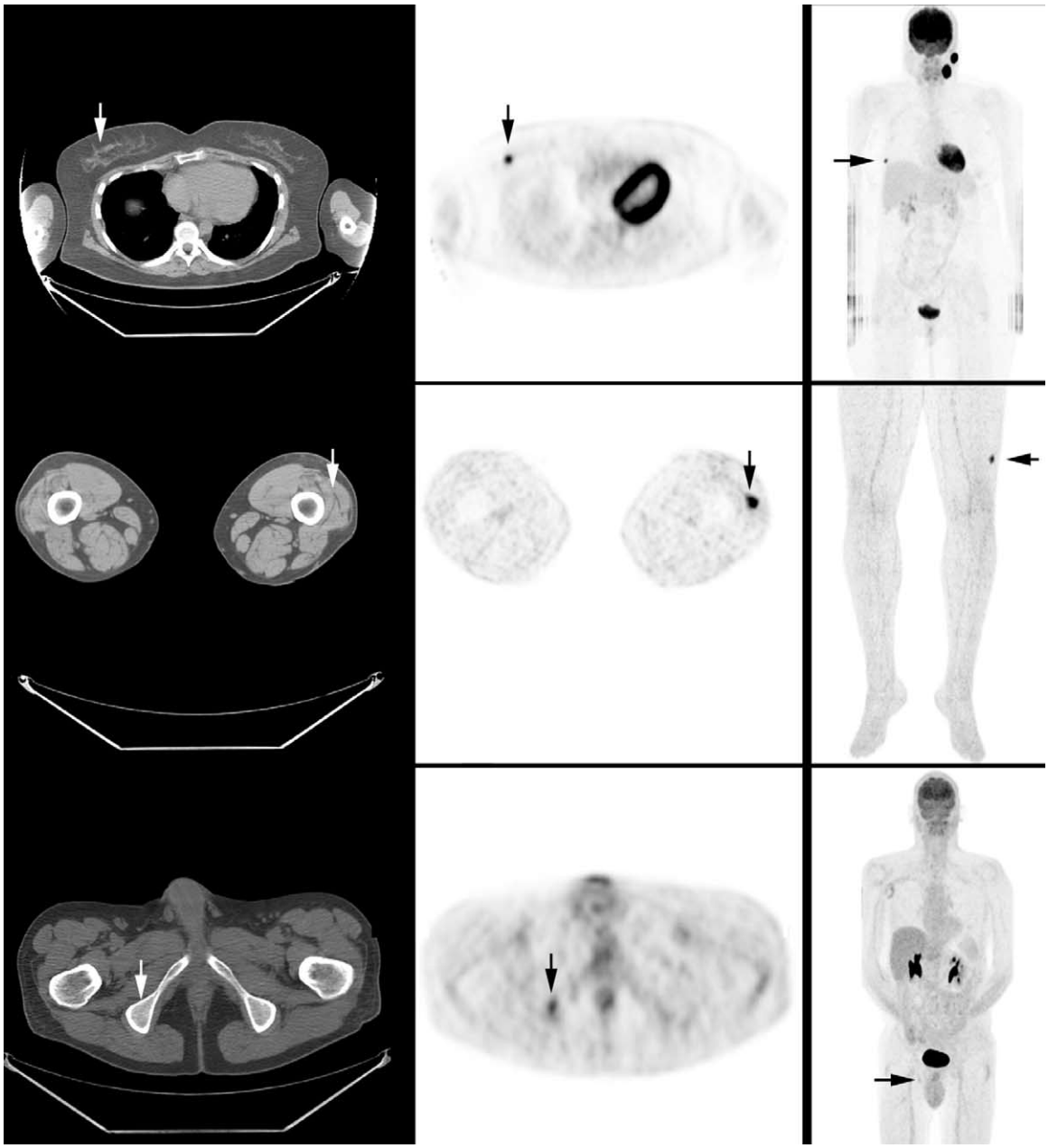

**Figure 2** Occult metastases in three patients with no previous evidence of distant disease. The top row depicts a 42-year-old female with a history of melanoma on the scalp resected 7 years ago. The patient developed local recurrence in the left parotid. FDG-PET demonstrates local recurrence and a distant right breast focus (arrows) that was biopsied and confirmed to be metastatic melanoma. The middle row depicts a 52-year-old male with melanoma and a recently diagnosed lung metastasis. In addition to lung metastases, FDG-PET demonstrated an occult distant focus in the soft tissues of the left thigh (see arrows). Biopsy confirmed metastatic melanoma. The lower row depicts a 56-year-old female with melanoma on the right shoulder and previously resected right maxillary metastases. In addition to identifying recurrence in the right shoulder, FDG-PET demonstrated an occult focus in the right ischium (arrows). Metastatic disease was confirmed by MRI.

standard consensus for the use of FDG-PET in all stages of melanoma can be developed.

## Response to Therapy

Little is known about the value of FDG-PET in evaluating response to therapy in patients with melanoma. In a study examining the utility of FDG-PET in the staging of patients planning to undergo isolated limb perfusion therapy with melphalan with or without tumor necrosis factor, three patients underwent imaging before and 1 month after treatment. The authors noted a reduction in the number of visualized limb lesions in all three patients and diffuse FDG uptake throughout the perfused limb, likely because of post-treatment inflammation.[49] These findings suggest that PET may be useful in evaluating response to experimental therapies, but further studies evaluating the ability of FDG-PET to predict patient outcomes are needed before any definitive recommendation can be

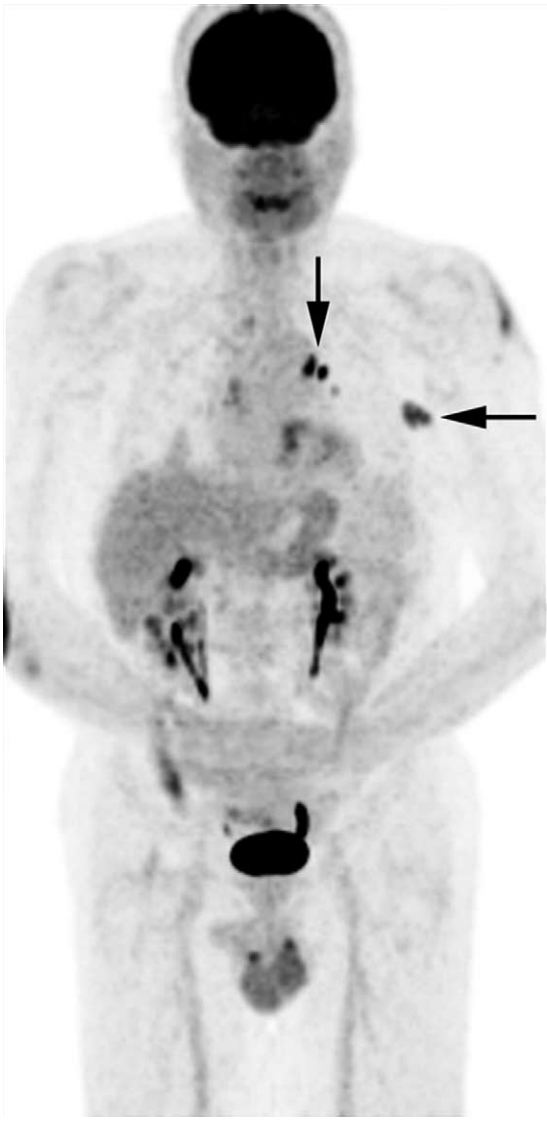

**Figure 3** Shown is a 56-year-old male with a history of melanoma on the left shoulder with new satellite metastases and left axillary lymphadenopathy. The patient underwent CT imaging, which revealed an equivocal 6-mm nodule in the left lung base. FDG-PET confirmed metastatic disease in the axilla (horizontal arrow) and identified unknown pulmonary, mediastinal and hilar metastases (vertical arrow).

made. In patients undergoing melanoma vaccination, careful attention must be paid to false positive findings due to inflammation at the injection sites and associated local draining lymph nodes (Fig. 1).

## Other PET Tracers

Numerous PET radiopharmaceuticals have been developed in an attempt to better image melanoma metastases, but few have approached the success of FDG. In 1995, Lindholm and coworkers demonstrated that $^{11}$C-methionine PET detected all melanoma lesions greater than 1.5 cm in diameter, but missed 5 smaller pulmonary lesions in ten patients.[50] In 1997, Boni and coworkers evaluated radioiodinated tyrosine, a precursor of melanin synthesis, and found that melanoma cell cultures preferentially accumulated $^{125}$I-alpha-methyl-tyrosine (AMT) compared with fibroblasts. If proven effective, the positron emitting $^{124}$I form of AMT might have been useful in PET imaging of humans. However, in human single photon emission computed tomography studies, $^{123}$I-AMT detected only 37% (10/27) of melanoma metastases identified by FDG-PET, suggesting that a positron emitting form of iodinated AMT may not be successful.

Also in 1997, Mishima and coworkers demonstrated the utility of an $^{18}$F-DOPA (3,4-dihydroxyphenylalanine) analog in PET imaging of melanoma.[51] $^{18}$F-DOPA has demonstrated increased uptake in selected FDG-negative melanoma metastasis[52] and has been studied in the evaluation of response to therapy.[53]

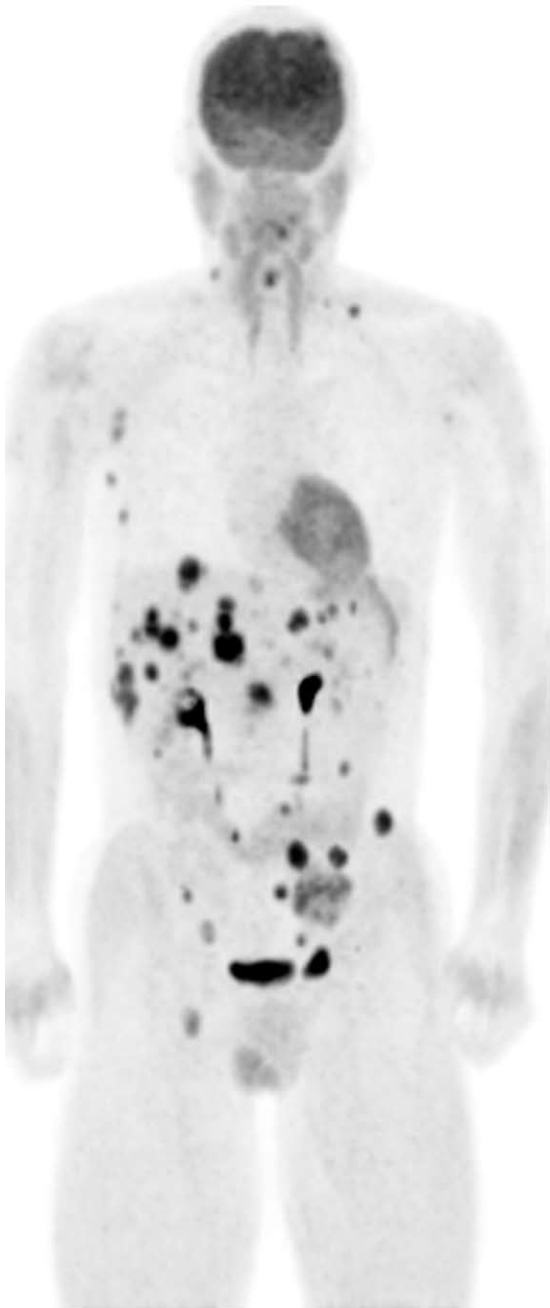

**Figure 4** Shown is a 46-year-old male with known diffuse metastatic melanoma. Follow-up FDG-PET (pictured) demonstrated progressive disease, which led to a change in medical therapy.

Other tracers include $^{18}$F-labeled thymidine, which has been reported to have a sensitivity of 88% for the detection of regional lymph node metastases.[54] Sadzot and coworkers found $^{11}$C-N-methylspiperone uptake in a patient with ocular melanoma,[55] and Froidevaux at al are developing radiolabeled alpha-melanocyte stimulating hormone analogs that show promise by binding to the cell membrane of melanomas.[56] Clearly, there is diverse and intensive research in the field of melanoma-binding tracers, many of which can be compounded with PET radiopharmaceuticals and are aimed at overcoming specificity problems associated with FDG.

## Medicare Reimbursed Indications

On July 1, 1999, Medicare began coverage for the use of FDG-PET in the evaluation of recurrent melanoma before surgery. Two years later, FDG-PET became a reimbursable test for the diagnosis, staging, and restaging of malignant melanoma. FDG-PET is not covered for the evaluation of regional nodes on initial diagnosis of primary melanoma. For initial diagnosis, PET is only covered "in clinical situations in which the PET results may assist in avoiding an invasive diagnostic procedure, or in which the PET results may assist in determining the optimal anatomical location to perform an invasive diagnostic procedure." It is expected that this indication will be rare. More commonly, PET is expected to be used primarily for staging or restaging, especially when "the stage of the cancer remains in doubt" or PET is expected to provide additional necessary information not available by conventional imaging modalities. Furthermore, PET is approved if treatment will "differ depending on the stage of the cancer identified." It is covered for restaging, suspected recurrence, or individuals requiring additional information regarding the "extent of known recurrence."[36]

# Conclusions

We can conclude that FDG-PET is a very potent, noninvasive imaging tool for detecting distant metastatic melanoma, although it has certain limitations. There are no data suggesting the utility of FDG-PET in the initial diagnosis of melanoma, or in patients with thin primary lesions less than 1 mm and no evidence of metastases.

In patients with thick primary lesions, satellite metastases, and in-transit tumor deposits, there is scant literature suggesting the ability of PET to detect occult distant disease. Prospective trials with clearly defined patient subgroups and rigorous verification methods are needed to determine how many patients might benefit from additional staging with FDG-PET. A broad recommendation cannot be made for this subgroup, but clinicians are encouraged to consider FDG-PET in individual patients where the presence of satellite metastases and in-transit lesions raises questions about the possibility of advanced distant disease.

In patients with positive SLN biopsies and no other evidence of local or distant metastases, there also is minimal literature supporting the routine use of FDG-PET in additional staging. Most patients in the subgroup will undergo regional nodal dissection and will benefit from the prognostic power of this well-established technique. Prospective studies examining the utility of FDG-PET in patients with positive sentinel node biopsies should be done to generate data sufficient for the development of guidelines for the use of FDG-PET. Certainly, in the highest risk patients, whole-body PET may play an important role.

Studies by Wagner and coworkers[23] and Acland and coworkers[8] suggest that FDG PET may upstage a significant number of patients with confirmed regional lymph node metastases and argue that FDG-PET should be strongly considered in this patient population. Again, well-designed prospective trials may ultimately answer the question of the utility of PET in these patients, but for now, the evidence presented by these authors combined with the data supporting the sensitivity of PET for detection of metastases in mixed subgroups suggests that FDG-PET should be strongly considered for such patients to identify distant metastases that might, if resected, lead to a survival benefit.

Numerous investigators have demonstrated the superiority of FDG-PET compared with CT for the detection of distant metastases in many locations within the body among various populations of patients with melanoma. Staging or re-staging of patients with suspected or known distant metastases is likely to be most accurate if FDG-PET is included in the diagnostic regimen. Studies evaluating changes on FDG-PET scans in response to treatment will also hopefully better define its role in patients with advanced disease. The recent advent of PET-CT fusion technology and its application to patients with melanoma[57] will likely influence the accuracy of this modality as well. For these reasons, FDG-PET is recommended in the routine management of patients with distant metastases who still have the opportunity to benefit from localization of new lesions by means of additional surgical resection or avoidance of unnecessary procedures. For now, PET may provide disease burden information in patients with diffusely metastatic disease, but advances in therapy might eventually lead to the increased use of PET as a means for monitoring response to treatment.

A systematic review of the PET literature by Mijhnout and coworkers concluded that guidelines for the effective use of PET in melanoma cannot be generated because of the poor methodological quality of available studies.[58] More recently, Prichard and coworkers concluded that FDG-PET was most useful in patients with regional metastases who would benefit from upstaging that might alter clinical management.[59] We agree that some of the data presented above is limited by problems related to heterogeneous, small patient populations, high pretest disease probability, and verification bias. However, until the necessary studies become available, some consensus is necessary to guide patients and clinicians facing the question of whether or not to order a PET scan. Medicare has approved PET for the diagnosis, staging, and restaging of melanoma (excluding regional lymph nodes), and its use is now justified and reimbursable for patients with clinical questions that cannot be accurately answered by any other means. Under the appropriate circumstances outlined above, we feel that FDG-PET is the modality of choice for evaluating patients who fit in to one of four categories: 1) individuals with a high risk for distant metastases based on extent of locoregional disease, 2) patients with findings that are suspicious for distant metastases, 3) individuals with known distant tumor deposits who still stand to benefit from customized therapies if new lesions are discovered or treated lesions regress, and 4) patients at high risk for systemic relapse who are considering aggressive medical therapy.

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