Diagnostic Accuracy and Impact of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Preoperative Staging of Cutaneous Malignant Melanoma: Results of a Prospective Study in Indian Population

Piyush Chandra, Nilendu Purandare, Sneha Shah, Archi Agrawal, Ajay Puri, Ashish Gulia, Venkatesh Rangarajan

Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital, Department of Surgical Oncology, Bone and Soft Tissue Disease Management Group, Tata Memorial Hospital, Mumbai, Maharashtra, India

Abstract

The aim of the study was to evaluate the diagnostic accuracy of positron emission tomography/computed tomography (PET/CT) in staging patients with primary cutaneous malignant melanoma (CMM). We further compared the performance of PET/CT with conventional imaging (CT and ultrasonography [USG]) and assessed the impact of PET/CT on disease management. This was a single institution, prospective, double-blinded study, recruiting a total of 70 treatment naïve patients. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of PET/CT for N staging were 86%, 96%, 80%, and 97%, respectively. The sensitivity, specificity, NPV, and PPV of PET/CT for M staging were 87%, 100%, 93%, and 100%, respectively. The diagnostic accuracy of the PET/CT was superior to CT for N staging (90% vs. 84% for CT and 80% for USG) and M staging (95% vs. 90% for CT). No statistically significant difference was noted between PET/CT and CT for N staging (PET/CT vs. CT, \( P = 0.125 \); PET/CT vs. USG, \( P = 0.063 \)) or M staging (PET/CT vs. CT, \( P = 0.125 \)). PET/CT upstaged 23% of patients with clinically localized disease and 58% of patients with clinically palpable regional nodes. To conclude, fluorodeoxyglucose PET/CT is a highly sensitive and specific imaging modality for preoperative staging of primary CMMs. PET/CT impacts disease management in significant number of patients and should be especially recommended in all patients with clinically palpable regional nodes.

Keywords: Accuracy, cutaneous, diagnostic, Indian, malignant, melanoma, positron emission tomography/computed tomography, ultrasonography

Introduction

Cutaneous malignant melanoma (CMM) is the most aggressive form of skin cancer, the global incidence of which has increased in the past few decades, representing one of the fastest growing cancers in the Caucasian population. Identification of environmental risk factors, research in histopathology, identification of specific genetic mutations, technological advances in diagnostic imaging, and approval of targeted therapies (such as ipilimumab and vemurafenib) highlight the constant evolution of management of this disease.
efforts aimed at achieving control of this intractable cancer.\textsuperscript{[3]} 

There is growing evidence to suggest that disease in the non-White (Africans/Asians) population differs in its incidence, histopathology, and clinical course from that in the White population.\textsuperscript{[3]} The incidence of this disease in Asian population remains low. Acral lentiginous melanoma is the most common histological subtype in Southeast Asia, with the disease occurring in relatively older patients and with a longer delay in diagnosis.\textsuperscript{[4]} In India, the disease is fortunately rare with an incidence of 0.2% and 5-year prevalence of 0.3%.\textsuperscript{[3]} The disease is predominantly located in the lower extremities. Patients frequently present in advanced clinical stages attributed probably to lack of awareness or poor health infrastructure.

The prognosis of CMM heavily depends on the stage where patients with local disease have a 10-year tumor-specific survival of 80% and those with distal metastases surviving a median of 6 months.\textsuperscript{[5]} Multiple prospective studies done in Caucasian populations suggest positron emission tomography/computed tomography (PET/CT) to be the most accurate imaging modality for staging CMM, influencing disease management in up to 10-57% of the high-risk patients.\textsuperscript{[7-10]} There remains a paucity of such supportive evidence in non-White population.

Our primary aim was to prospectively evaluate the diagnostic accuracy of PET/CT in clinical staging of CMM in the Indian population. Secondarily, we compared the diagnostic performance of PET/CT and conventional imaging (CI) and also assessed the impact of staging PET/CT on disease management.

Patients and Methods

Patients

This was a single institution, prospective, double-blinded study done in accordance to the rules and regulations of the institutional review board. A total of 70 consecutive patients (mean age-58 years, males-45, and females-25) were recruited in this study from August 2013 to December 2015. All patients had a histopathological diagnosis of malignant melanoma which was obtained by either excision biopsy or wide local excision done prior to or within 2 weeks of staging PET/contrast-enhanced CT (CECT) study. Staging in addition to whole-body PET/CECT also included ultrasonography (USG) of the regional nodes. Prior informed consent was taken in all patients involved in the study. Patients with clinical N0 disease were followed up with serial clinical/imaging follow-up. Sentinel node biopsies (SNBs) for N0 disease were not done for any patient.

Positron emission tomography/computed tomography scans protocol

Prerequisite for fluorodeoxyglucose (FDG) PET/CT examination was 6 h fasting and optimum blood sugar (<180 mg/dl) and normal recent serum creatinine. FDG activity was administered intravenously 60 min before the study and at a dose of 3-5 MBq/kg. Water-based oral contrast was given for bowel distension. After obtaining a scout image, breath-hold CT was acquired followed by whole-body CT and then PET acquisition. CT parameters for breath-hold CT includes slice thickness 3 mm, pitch 1.08, field of view (FOV) 356 mm, voltage 120 kV with automated mA correction, image matrix 512 × 512. Body CT was acquired in caudocranial direction with parameters that included slice thickness 2 mm, pitch 0.83, voltage 120 kV, FOV 600 mm, rotation time 0.5 s, automated mA, image matrix 512 × 512. Eighty milliliters of low osmolar nonionic intravenous contrast was administered in all eligible patients at a rate of 1.8 ml/s and scan delay was 50 s. CECT was used for diagnostic purpose and attenuation correction of the PET data. PET parameters included an axial FOV of 576 mm, in-plane spatial resolution of 4 mm, and acquisition time of 45 s/bed position. Images were reconstructed iteratively using RAMLA algorithm.

Data analysis

PET/CT images were read independently by two experienced nuclear physicians. CECT of the thorax, abdomen, and pelvis (performed as a part of the whole-body PET/CT) was reviewed independently by experienced radiologists. CECT and USG together were termed as CI. The readers were blinded to the histopathology and clinical details. “PET/CT positive” was defined as lesions which were positive by either PET or CT criteria. PET-positive lesions were determined visually (positive if lesion uptake intensity more than liver/background). No standardized uptake value (SUV) threshold was used. In case of no uptake in lesions, CT criteria were used to determine PET/CT positive/negative status. “CT criteria” for positive metastatic node included rounded nodes, size more than 1 cm for noncervical and > 1.5 cm for cervical nodes, loss of fatty hilum, contrast enhancement, and central necrosis. “CT criteria” for positive visceral metastases were by detection of soft-tissue masses/lesions, focal cutaneous thickening, and/or contrast enhancement. For skeletal lesions, positive CT criteria were lytic lesion with a soft tissue component or sclerosis. “USG criteria” for positive node were enlarged rounded nodes, hypoechogenicity, and loss of fatty hilum.
Diagnostic performance of PET/CT and CI for nodal (N) and metastatic (M) staging was evaluated with histopathological correlation and clinical follow as the standard of reference. Patient with clinically N0 disease were followed with serial clinical examination/imaging of the regional nodes. Significance of differences between PET/CT and CI findings were analyzed using McNemar’s exact test.

Results

Patients
A total of 70 patients were recruited (mean age 58 years, range 29–85) [Table 1]. Site of primary melanoma was 87% in the lower extremity/foot (n = 61), followed by thumb (5%, n = 4), scalp (2%, n = 2), breast (1%, n = 1), trunk (1%, n = 1), and thigh (1%, n = 1). Breslow thickness was available in 61% (43/70) of patients (mean 6.5 mm, range 1–13 mm). Ulceration status was positive in 52% (37/70) of patients. Sixty-four percent (45/70) of patients had locoregional adenopathy with or without distant metastases, out of which 39 patients were detected at primary staging and 6 patients during follow-up. By clinical examination, 44.2% (31/70) of patients had palpable nodal disease and 55.7% regional nodes (39/70) were clinically nonpalpable. 28% (20/70) had distant metastases at initial staging and in 4% (3/70), distant metastases were identified on follow-up. 27% (19/70) patients died during follow-up. Mean follow-up time was 14.1 months (range 1–33 months). All patients tolerated the PET/CT well without any procedure-related adverse effect.

N staging
PET/CT correctly identified nodal metastases in 55% (39/70) of patients, with a sensitivity and specificity of 86% and 96%, respectively. Mean size of enlarged nodes was 3.5 cm (range 0.9–18 cm) and mean maximum SUV was 14.8 (range 3.5–52.7). The diagnostic performance of PET/CT and CI for N staging is summarized in Table 2. PET/CT was advantageous over CT/USG in identifying subcentimeter-sized nodal metastases [Figures 1 and 2]. Six patients who were PET/CT negative for nodal disease at primary staging had nodal recurrence on follow-up (mean 16.8 months, range 6–29 months) [Figure 3]. The difference between PET/CT and CI was not found to be statistically significant (PET/CT vs. CT, P = 0.125 and PET/CT vs. USG, P = 0.063). An additional benefit of PET/CT over CI was noted in detection of in-transit nodal metastases in ipsilateral popliteal nodes in 21% (13/61) patients with primary melanoma in the lower extremity.

M staging
PET/CT correctly identified distant metastases in 28% of patients (n = 20/70), with a sensitivity and specificity of 87% and 100%, respectively. The diagnostic performance of PET/CT and CI for M staging is summarized in Table 2. PET/CT was
An 82-year-old female with cutaneous melanoma in the left groin, uptake in-transit nodes in the lower thigh, regional nodes in left groin, and focal uptake in multiple metastatic skeletal lesions. Fused positron emission tomography/computed tomography transaxial images (b) show positron emission tomography/computed tomography positive subcentimeter left inguinal nodes (thin white arrow), which are negative by computed tomography criteria (short thick white arrow), (c) and fused positron emission tomography/computed tomography images showing positron emission tomography/computed tomography positive marrow lesion in body of L5 vertebra (black arrowhead) with no visible/subtle change (white arrowhead) on corresponding trans-axial computed tomography image (d), thereby re-illustrating the higher sensitivity of positron emission tomography/computed tomography over computed tomography for N and M staging.

The difference between PET/CT and CT was not found to be statistically significant (P<0.125).

**Discussion**

As per the National Comprehensive Cancer Network, cross-sectional imaging is recommended in the form of CT, PET/CT, or MRI in Stage IV and should be considered in Stage III melanoma where treatment with curative intent is planned. It does not recommend imaging in asymptomatic Stage I and II melanoma.[11] Inefficacy of PET for nodal and metastatic staging in clinically localized disease has been proved in many studies. One of the first such studies was the prospective study done by Wagner et al. in 1999 in 70 patients with primary thick melanomas, where the sensitivity and specificity of PET for diagnosing nodal metastases were 11% and 100%, respectively. The authors concluded that sentinel lymph node biopsies (SNB) had a higher sensitivity than PET for diagnosis of clinically occult nodal metastases.[13] Lower sensitivity of PET for identification of nodal disease was demonstrated in another study done by Acland et al., where PET did not detect metastases in about 14 sentinel nodes in 50 patients with thick cutaneous melanomas.[13]

Our results with localized disease show relatively higher sensitivity of PET/CT for identification of nodal metastasis [Table 3]. 55% (39/70) of patients in our study had clinically nonpalpable regional nodes. In this subset of patients, PET/CT correctly identified clinically occult nodal metastasis in 23% (9/39) of patients. This relatively higher detection rate could be probably attributed to higher T stage in most of our patients, where incidence of lymph node metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of nodal metastasis increases. The mean Breslow thickness in our patients with localized disease was 6.5 mm. In addition, accuracy of PET/CT for N staging increases if the size of suspected metastatic node is more than > 6 mm.[14] In 9 patients, where PET/CT detected clinically occult nodal disease, mean size of
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Figure 4: A 59-year-old male with primary melanoma in the left foot with clinically palpable regional nodes in the left groin. Maximum intensity projection image (a) shows increased fluorodeoxyglucose uptake in the enlarged left inguinofemoral nodes (thin black arrow) and left popliteal fossa. (b) Fused positron emission tomography/computed tomography images show solitary focus of increased fluorodeoxyglucose uptake involving a nodule in the left adrenal gland (thin white arrow), which was equivocal for disease by computed tomography criteria (arrowhead). Positive metastatic disease was proven by computed tomography-guided biopsy of the adrenal node. This case supports the recommendation of using positron emission tomography/computed tomography in patients with clinically palpable regional nodal disease (i.e., Stage III B/C) with high incidence of clinically occult metastatic disease.

Table 2: Overall performance of PET/CT and conventional imaging for initial staging

| Imaging modality | Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) | Accuracy |
|------------------|----------------------|----------------------|------------------------------------|-----------------------------------|----------|
| N staging        |                      |                      |                                    |                                   |          |
| PET/CECT         | 86 (72-94)           | 96 (77-99)           | 97 (85-99)                         | 80 (60-91)                        | 90%      |
| CECT             | 77 (62-88)           | 96 (77-99)           | 97 (83-99)                         | 70 (52-84)                        | 84%      |
| USG              | 75 (60-86)           | 88 (67-96)           | 91 (76-97)                         | 66 (48-81)                        | 80%      |
| M staging        |                      |                      |                                    |                                   |          |
| PET/CECT         | 87 (66-96)           | 100 (90-100)         | 100 (81-100)                       | 93 (82-98)                        | 95%      |
| CECT             | 70 (47-85)           | 100 (90-100)         | 100 (76-100)                       | 87 (74-94)                        | 90%      |

Table 3: Sites and frequency of distant metastasis on PET/CT

| Sites of distant metastases | No. of patients |
|-----------------------------|-----------------|
| Distal nodes                | 14              |
| Lungs                       | 9               |
| Skeleton/marrow             | 8               |
| Liver                       | 7               |
| Adrenal                     | 3               |
| Distant Skin                | 3               |
| Brain                       | 2               |
| Miscellaneous soft tissue   | 4               |

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in these patients would be an SNB for patients at risk of harboring nodal metastasis. [11]

Patients with clinically palpable regional node metastasis have higher incidence of harboring a clinically occult distal metastasis. PET/CT appears to be an ideal imaging modality in this clinical setting and impacts treatment decisions in a significant proportion of patients. Bastiaannet et al. in a prospective study on 251 patients showed that PET and CT upstaged about 27% of patients with palpable nodal metastases and recommended that PET and CT were done in patients with Stage III disease.[8] Aukema et al.’s prospective study done in 70 patients with palpable regional node involvement showed that sensitivity and specificity of PET/CT in detection of other sites of metastasis were 87% and 98%, respectively.[16] The authors showed that PET/CT changed management in 38% of the patients in addition to having a prognostic value in terms of overall survival. In our study, 44% (31/70) of patients had clinically palpable nodes. In this group of patients, PET/CT correctly identified distant metastasis in 64% (20/31) of patients. Out of these 20 patients, 2 patients had Stage IV disease by clinical examination. Hence, PET/CT upstaged 58% (18/31) of patients from Stage III to Stage IV by identifying clinically occult disease. The most common site of metastasis was distal nodes, followed by liver and lungs [Table 4].

Although comparable in localized disease, PET/CT appears to have a higher impact than CT in Stage III/IV. Reinhardt et al. analyzed 75 patients for primary staging,
out of which 42 patients were Stage III/IV. They showed that PET/CT detected higher number of visceral and nonvisceral metastases than PET or CT alone and changing treatment decisions in about 42.4% patients. Bastiannet in 2009 showed that PET had an additional value over CT in 14% of patients, by identifying higher number of subcutaneous and marrow lesions. Diagnostic superiority of PET/CT over CI was validated by Bronstein et al. in 32 patients with oligometastatic Stage III and IV disease, where PET/CT detected lesions which were not seen/or not included in CI, thereby causing change in the management in 14% of the patients. In our study too, PET/CT had a higher diagnostic accuracy than CECT for identification of distant metastasis. In 5% of patients (4/70), PET/CT identified distant sites of metastasis which were negative on CECT. PET/CT detected lesions which were not included in imaging extent of CT (i.e., thorax to pelvis). PET/CT was particularly more sensitive than CT in identification of marrow and subcentimeter nodal metastasis. CT alone was better than PET/CT for identification of lung metastases. Although PET/CT performed better than CI, our initial results do not reveal any statistically significant difference between the two in either M or N staging.

One interesting observation in our study was identification of popliteal nodal metastases in a significant proportion of patients with melanoma of foot. A study done by Thompson et al. reported an extremely low incidence of popliteal node metastases of 0.31%. Incidence of popliteal nodes in our study (21%) was similar to the study done by Menes et al., which showed that popliteal basin is the first drainage site in about 9% with 30% of patients harboring distant metastases. Isolated metastatic involvement of popliteal involvement with enlarged groin nodes can also be rarely seen, in which case, a full popliteal nodal clearance is usually warranted. Popliteal nodes are usually not included on routine USG/CECT protocol for staging foot melanomas and are usually seen with whole-body imaging such as PET/CT. In our series, all the cases of popliteal nodal metastases also had synchronous groin and distal metastasis, so there was no significant impact of its identification on disease management. However, we still recommend popliteal nodes be evaluated clinically or by imaging, in addition to groin nodes for all cases of lower extremity melanomas, as it could potentially alter the surgical procedure.

One of the limitations of our study was observation and follow-up with serial clinical examination of groin with or without diagnostic imaging, in patients with clinically N0 disease. Ideally, these patients are candidates for SNB. One of the reasons for this approach was because most patients had undergone excision biopsy of the primary lesion elsewhere before they were referred to our hospital for further management. Sensitivity of SNB in post wide excision cases is understandably less accurate and is usually not recommended. Another limitation of the study was the short duration of follow-up. Longer follow-up leads to higher number of false negatives. Both these factors could well explain the apparently higher accuracy of PET/CT in localized disease in our study. We hence recommend SNB and close follow-up of patients with thick primary melanomas (T1b and beyond) with negative imaging for nodal disease.

**Conclusion**

To the best of our knowledge, this is the first prospective study in Indian population to evaluate the diagnostic performance of PET/CT in staging primary cutaneous melanoma. PET/CT was found to be a highly sensitive and specific imaging modality for nodal and distant metastatic staging, with comparable results to the multiple prospective studies done in the White population.

Overall, PET/CT changes management in a significant number of patients referred for primary staging and should be especially recommended in all patients with clinically palpable regional nodal metastases, where it changes management in significantly higher proportion of patients (58%) than in patients with clinically localized disease (23%).

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**Conflicts of interest**

There are no conflicts of interest.

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