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Original article

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

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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 (CI) (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 CI 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 CI 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.[1] 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

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efforts aimed at achieving control of this intractable cancer.[2]

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.[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.[4] In India, the disease is fortunately rare with an incidence of 0.2% and 5-year prevalence of 0.3%.[5] 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.[6] 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.[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.

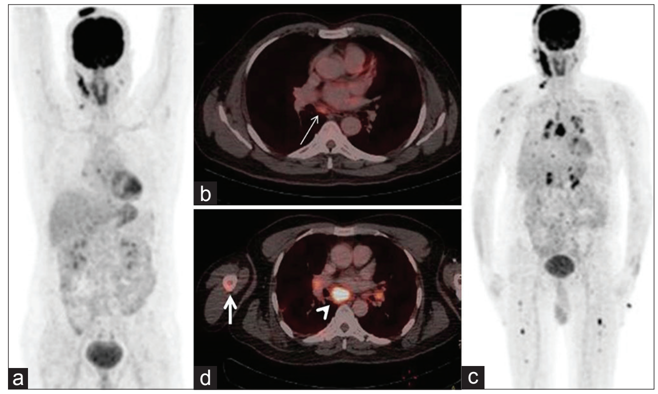

Figure 1: A 52-year-old male with primary cutaneous melanoma of scalp. (a) Maximum intensity projection image showing fluorodeoxyglucose avid lesion in the scalp and fluorodeoxyglucose avid cervical lymph nodes. Focal fluorodeoxyglucose uptake noted in subcarinal (thin white arrow) and right hilar nodes by positron emission tomography/computed tomography positive and computed tomography negative (<1 cm) for metastatic disease. (a and b) Metastatic disease was confirmed on 3 months follow-up, shown on maximum intensity projection (c) and fused transaxial positron emission tomography/computed tomography images (d) with increase in the size of fluorodeoxyglucose avid subcarinal nodes (arrowhead) and evidence of new metastatic lesions in the marrow (bold white arrow) and distal nodes. This case illustrates the higher sensitivity of positron emission tomography/computed tomography over computed tomography for identification of nodal and skeletal metastases

Table 1: Patient and tumor characteristics

	n=70
Age	
<60 years	39
>60 years	31
Gender	
Males	45
Females	25
Primary site	
Foot	61
Thumb	4
Scalp	2
Breast	1
Trunk	1
Thigh	1
Breslow's thickness	
1-4mm	17
>4mm	26
Unavailable	27
Tumor ulceration	
Present	37
Absent	17
Unavailable	16
Clinico-radiological stage	
Stage II	25
Stage III	23
Stage IV	22

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

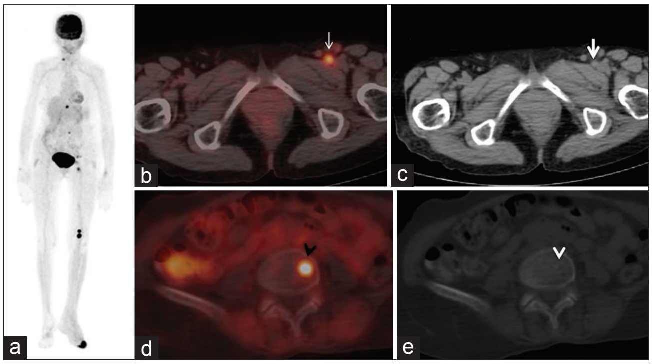

Figure 2: An 82-year-old female with cutaneous melanoma in the left foot. Maximum intensity projection image (a) shows focal fluorodeoxyglucose uptake in the primary disease in the foot, uptake in-transit nodes in the lower thigh, regional nodes in left groin, and focal uptake in multiple metastatic 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

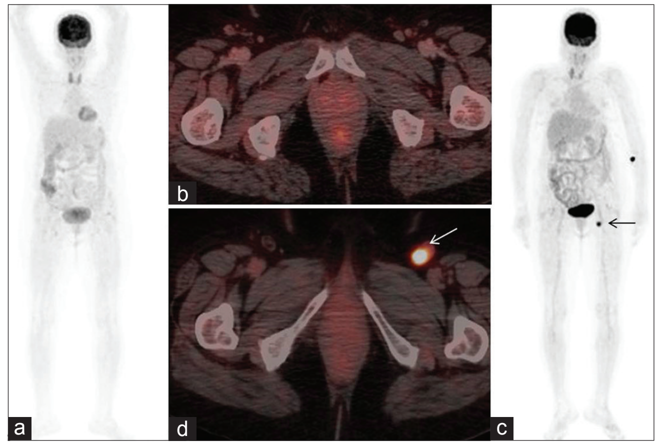

Figure 3: A 61-year-old female post wide local excision of left foot melanoma for staging. Maximum intensity projection (a) and transaxial image fused positron emission tomography/computed tomography images of the left groin (b) do not show any evidence active metabolic disease. Patient was followed up and diagnosed with clinically palpable positive metastatic left inguinal nodes seen here on (c) follow-up maximum intensity projection (thin black arrow) and (d) fused transaxial positron emission tomography/computed tomography of groin (thin white arrow), post 8 months of a negative whole body positron emission tomography/computed tomography. This case illustrates the high false negativity/low sensitivity of positron emission tomography/computed tomography in identification of microscopic nodal disease in early stage of disease

clearly advantageous over CT for M staging in 4 patients. In one patient, PET/CT identified a solitary adrenal metastasis (confirmed by CT-guided biopsy) which was equivocal on CT [Figure 4]. In the rest of 3 patients, PET/CT identified marrow and distal subcentimeter-sized nodal metastases which was negative on CT criteria [Figures 1 and 2]. PET/CT was falsely negative for M staging in 3 patients where distant metastasis was detected at 3, 4, and 6 months, respectively. The difference between PET/CT and CT was not found to be statistically significant (*P*-0.125).

Impact of positron emission tomography/ computed tomography on disease management

In localized disease, PET/CT upstaged 23% (9/39) patients by additionally identifying clinically occult nodal metastasis. In these same nine patients, PET/CT also identified distal metastasis in 3 patients. In patients with clinically palpable nodes, PET/CT identified clinically occult distant metastasis in about 58% (18/31) of patients, thereby changing treatment decision from curative intent to palliative intent. Overall, PET/CT led to change in the management in about 38% (27/70) of patients who were referred for primary staging.

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 that SNB had a higher sensitivity than PET for diagnosis of clinically occult nodal metastases.[12] 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

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%

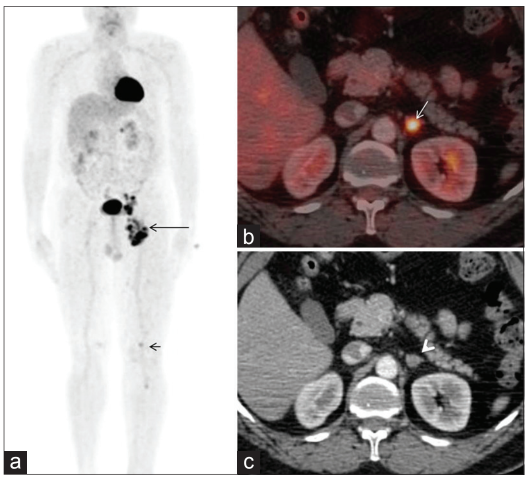

Figure 4: A 59-year-old male with primary melanoma in the left foot with clinically palpable regional nodes in the left groin. Maximum intensity projection image (a) shows increased fluorodeoxyglucose uptake in the enlarged left inguinofemoral nodes (thin black arrow)and left popliteal fossa. (b) Fused 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

the nodes was 1.9 cm (range-0.9–2.1 cm). This highlights the importance of imaging over clinical examination alone for evaluation of nodal disease. Although PET/CT showed better accuracy over CI, the sensitivities of all imaging modalities were relatively low [Table 3]. This accuracy would be probably lower with longer follow-up. A study done by Veit-Haibach *et al*. in 2009 showed that incidence of false negative results increases with follow-up duration and decreases the sensitivity of PET/CT for detection of nodal disease.[15] In our study too, we considered metastases which occurred at follow-up after normal initial PET/CT as a false negative result. 20% (6/30) of patients in our study, who had no nodal disease identified on initial PET/CT, had nodal metastases identified on follow-up (mean duration 16.8 months). Hence, we recommend close follow-up of Stage II patients where PET/CT or CI was negative for the nodal disease. A more appropriate recommendation

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

#PET/CT was more sensitive than CT for detection, *CT alone was more sensitive than PET/CT for detection

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 CI in Stage III/IV. Reinhardt *et al*. analyzed 75 patients for primary staging,

Table 4: PET/CT and conventional imaging in clinically localized disease (clinically no palpable nodal disease)

Imaging modality	Nodal metastasis detection rate	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %	Accuracy %
PET/CECT	23%	60	95	90	79.3	82
CECT	15%	38	95	85	71	74
USG	12%	33	87	63	67	66

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.[7] 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.[9] 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*.[17] 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.[18] 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.[19] 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.[11] Another limitation of the study was the short duration of follow-up. Longer follow-up leads to higher number of false negatives.[15] 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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