

Role of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography in restaging and prognosis of recurrent melanoma after curative surgery

ABSTRACT

Malignant melanoma is a highly aggressive tumor and surgical resection is the primary treatment. However, the chances of recurrence are quite high despite complete resection. The aim of study was to evaluate the ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography-computed tomography (PET/CT) in detection of recurrent melanoma after curative surgery and its prognostic value. Fifty-four melanoma patients (32 women) with prior primary lesion resection were evaluated with ¹⁸F-FDG PET/CT for clinically suspicious recurrent disease. The diagnostic accuracy of ¹⁸F-FDG PET/CT (visual interpretation as well as semi-quantitative parameter) was determined on the basis of subsequent imaging and clinical follow-up. Melanoma-specific survival and risk of progression (hazard ratio [HR]) were assessed using Kaplan–Meier method and Cox regression analysis. ¹⁸F-FDG PET/CT detected recurrent diseases in 36 (66%) patients including distant metastases in 13 patients and second synchronous malignancy in 2 patients. Overall, the sensitivity, specificity, positive predictive value, and negative predictive value of ¹⁸F-FDG PET/CT were 91.2%, 80.0%, 88.6%, and 84.2%, respectively, with area under the curve of 0.86 (95% confidence interval: 0.74–0.97; $P < 0.05$). Positive ¹⁸F-FDG PET/CT study was associated with a significantly shorter overall survival than negative study (30.8 ± 4.6 vs. 64.5 ± 6.9 months, $P < 0.05$). Apart from positive ¹⁸F-FDG PET/CT scan, maximum standardized uptake value (SUVmax) >2.7 and combination of both were independently associated with an increased risk of disease progression (HR = 7.72, 21.58, and 11.37, respectively; $P < 0.05$). ¹⁸F-FDG PET/CT showed enhanced diagnostic performance in patients with suspicious recurrent malignant melanoma leading to appropriate management. FDG positivity along with SUVmax >2.7 provides important prognostic value in predicting the survival outcomes and assessing the risk of disease progression.

Keywords: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography, malignant melanoma, prognostic factor, prognostic value, survival analysis

INTRODUCTION

Malignant melanoma is an uncommon malignancy (~1% of all malignancies), but this potentially lethal cutaneous malignancy results in approximately 80% of mortality related to skin cancers.^[1,2] The last four decades have seen dramatic increase in melanoma cases with rise in incidence by 15 times in the western population, and a similar trend but of significantly lower magnitude is being observed among Asian population.^[3,4] Complete surgical resection of the localized disease usually results in cure, whereas locoregional and metastatic disease requires systemic therapy. Survival in melanoma is closely associated with stage of the disease

which decreases with higher stage and it has been shown that 5-year survival rate declines from 78% to 40% from Stage IIIA to Stage IIIC, decreasing further in metastatic disease. The

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patients with Stage IV disease have the median survival rate of 8–18 months and only 5%–19% patients survive up to 5 years.^[5,6] High mortality in advanced stages has necessitated to detect the disease in initial stages, so the effective treatment can be employed. The malignant melanoma may involve any organ anywhere in the body (though the liver, bone, and brain are frequently involved) far from the primary lesion, so regional imaging may not be helpful in mapping the disease distribution. The risk of recurrence in the form of locoregional relapse or metastatic disease is seen in around one-third of the patients in postsurgical period.^[7] However, there is a lack of consensus for optimal follow-up, use of imaging, and blood tests in posttreatment melanoma patients.^[8] The patients with higher stage disease may be benefitted with early identification of regional or distant relapses with the use of ultrasonography for lymph nodes, positron emission tomography–computed tomography (PET/CT), or CT.^[9,10] Whole-body ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET/CT has demonstrated an added value over CT in diagnostic accuracy, prognosis, and impact on management during follow-up by detecting loco-regional recurrence and occult distant metastasis in melanoma patients.^[11–13] Although majority of melanoma lesions are FDG avid, few of them have shown tracer avidity similar to the background with contentious significance. Melanoma patients with faint tracer-avid lymph nodal metastases have shown a higher disease-free survival compared to intense tracer-avid lymph nodal metastasis.^[14] The patients undergoing surgical resection of FDG-avid metastatic disease picked on ¹⁸F-FDG PET/CT have also shown better survival.^[15]

The approach for early detection of recurrent disease in high-risk melanoma patients with imaging seems to be appropriate as shown in a retrospective meta-analysis of 74 studies comprising 10,528 patients where ¹⁸F-FDG PET/CT showed best diagnostic performance for detection of metastatic disease.^[13] However, a consensus is still lacking for the indications and timing of ¹⁸F-FDG PET/CT in the follow-up period. The aim of this study was to assess the utility of ¹⁸F-FDG PET/CT in detecting recurrence of malignant melanoma after primary surgical excision and its prognostic implication in patients' survival.

MATERIALS AND METHODS

Patient population

This study analyzed the data sets of 54 patients with histopathology-proven malignant melanoma that underwent ¹⁸F-FDG PET/CT imaging for suspicion of recurrence. All the included patients had ¹⁸F-FDG PET/CT studies done after a minimum of 6-month postsurgery. Information on age, sex,

characteristics of primary lesion, and current disease status in affected patients was retrieved and reviewed. Subsequently, the patients were on follow-up for clinical examination, imaging, and treatment as required at every 3 months with a mean follow-up period of 23.8 ± 18.1 months. The follow-up period in the patients was defined as the period from ¹⁸F-FDG PET/CT imaging to the last clinical review, and each patient had minimum follow-up of 6 months. Melanoma-specific survival (MSS) was defined as the time from ¹⁸F-FDG PET/CT imaging to death. For alive patients at the data cutoff date, MSS was censored at the last date of follow-up. The study was duly approved by the Institute Ethics Committee vide letter no. INT/IEC/2017/1305.

Fluorodeoxyglucose positron emission tomography/computed tomography acquisition

¹⁸F-FDG PET/CT studies were done in all the patients after minimum fasting for 6 h with blood glucose <150 mg/dl (8.3 mmol/l) and without any strenuous activity on or the day before the examination. Acquisition was performed at 45–60 min postintravenous injection of 370 MBq (~10 mCi) of ¹⁸F-FDG on dedicated hybrid scanners (Discovery 710 or Discovery STE-16; GE Healthcare, Milwaukee, Wisconsin, USA). A low-dose scout CT (120 kV, 10 mA) was acquired from vertex to toe. Contrast enhancement CT followed by 3D-PET acquisition was done in caudocranial direction with an acquisition period of 2 min per bed position using time-of-flight technique. The reconstructed attenuation-corrected PET, CT, and fused images were reviewed in three planes (the axial, sagittal, and coronal) along with maximum intensity projections.

¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography image analysis

Two qualified nuclear medicine physicians retrospectively evaluated the studies in agreement without being aware of clinical/imaging findings. Any positive findings in the form of focal tracer uptake on ¹⁸F-FDG PET were anatomically localized on contrast-enhanced CT images. Maximum standardized uptake value (SUV_{max}) for semi-quantitative analysis was obtained by assigning a region of interest over the lesion with highest tracer uptake.^[16] The histopathological examination wherever available and clinical and imaging follow-up for the past 6 months were taken as the reference standard in the patients. Any suspicious lesion with increase or decrease in size (posttreatment) at follow-up imaging was considered as true positive for recurrent disease.

Statistical analysis

All statistical computations were performed using the Statistical Package for the Social Sciences software (SPSS

Version 22.0; IBM Corp., Armonk, NY). Continuous data are communicated as the mean ± standard deviation. Descriptive analyses are used for the calculation of sensitivity and specificity of ¹⁸F-FDG PET/CT for detection of recurrent disease. Receiver operating characteristic (ROC) curve analyses were performed to determine the diagnostic accuracy of ¹⁸F-FDG PET/CT and optimal cutoff value of SUVmax for the prediction of death. Cox proportional hazard model was used to determine prognostic factor. Survival curves and mean survival with relative 95% confidence intervals (95% CI) for MSS were constructed using Kaplan–Meier method. Statistical significance was accepted at *P* < 0.05.

RESULTS

Patient characteristics

The demographic and clinical features of all 54 eligible patients (22 women and 32 men, age: 51.3 ± 16 years; range: 10–79) in the study are presented in Table 1. The extremities, trunk, and head were the primary sites for disease in 22, 21, and 11 patients, respectively. The patients during initial staging did not undergo sentinel node localization. All the patients had surgical excision of lesions at primary sites and ten patients also received either chemotherapy or combination of chemotherapy and radiotherapy in addition to the surgical treatment before ¹⁸F-FDG PET/CT study.

Outcome of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography

¹⁸F-FDG PET/CT findings are summarized in flowchart in Figure 1. Thirty-six (66%) out of 54 patients were positive on ¹⁸F-FDG PET/CT; locoregional disease was detected in 23 (42%) and distant metastases in 13 (24%) patients with or without locoregional disease. In addition, occult second primary malignancy (lung and pancreas) was also found in two patients subsequently proven by histopathology. Thirteen patients had metastatic disease in different organs (lung in nine, bones in six, liver in three, and brain in two patients, respectively) [Table 2 and Figure 2].

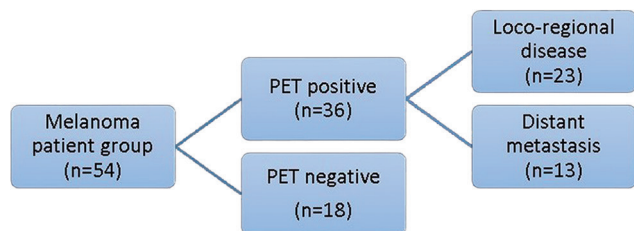


Figure 1: Flowchart showing the result of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography in suspicious recurrent disease

¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography performance parameters

¹⁸F-FDG PET/CT findings were compared with the reference standards (clinical examination, histopathology, and imaging) in all 54 patients, and ¹⁸F-FDG PET/CT was true positive in 31, true negative in 16, false positive in 4 patients, and false negative in 3 patients. PET/CT showed the sensitivity of 91.2% and specificity of 80% for detection of recurrent disease in melanoma patients [Table 3]. ROC curve taking visually interpreted FDG-avid lesions gave the best sensitivity and specificity of 91.2% and 80% respectively with reference standard as treatment received, clinical and imaging follow-up. The area under the curve (AUC) was 0.86 (95% CI; 0.74-0.97, *P* value <0.01) [Figure 3].

Table 1: Demographic and clinical characteristics of patients

Variables	Number (%)
Age (years)	
Mean±SD	51.3±16.4
Sex (%)	
Male	22 (41)
Female	32 (59)
Primary site (%)	
Head	11 (20)
Trunk	21 (39)
Extremity	22 (41)
Pre-PET/CT treatment (%)	
Surgery	44 (81)
Surgery + CT	6 (11)
Surgery + CT + RT	4 (8)

PET: Positron emission tomography; CT: Computed tomography; RT: Radiotherapy; SD: Standard deviation

Table 2: Characteristics of melanoma patients with distant metastases

Sex	Age (years)	Primary site	Distant metastases	SUVmax of recurrent lesion	MSS (months)
Male	30	Left sole	Bone, liver, spleen	35.4	11
Female	45	Left orbit	Lung	12.7	41
Male	50	Left inguinal	Lung, brain	13.8	13
Female	30	Anal canal	Lung	6.1	28
Male	28	Dorsal spine	Bone	29.7	20
Female	52	Urethra	Lung, bone	16.8	6
Male	63	Scalp	Brain	9.2	7
Female	36	Right great toe	Lung, liver	20.4	9
Female	70	Anal canal	Lung, bone	24.7	6
Female	65	Left foot	Lung, muscle	18.5	8
Male	45	Left great toe	Lung, liver	20.2	7
Male	53	Nasal cavity	Bone	15.1	7
Female	65	Anal canal	Lung, bone	12.1	10

MSS: Melanoma-specific survival; SUVmax: Maximum standardized uptake value

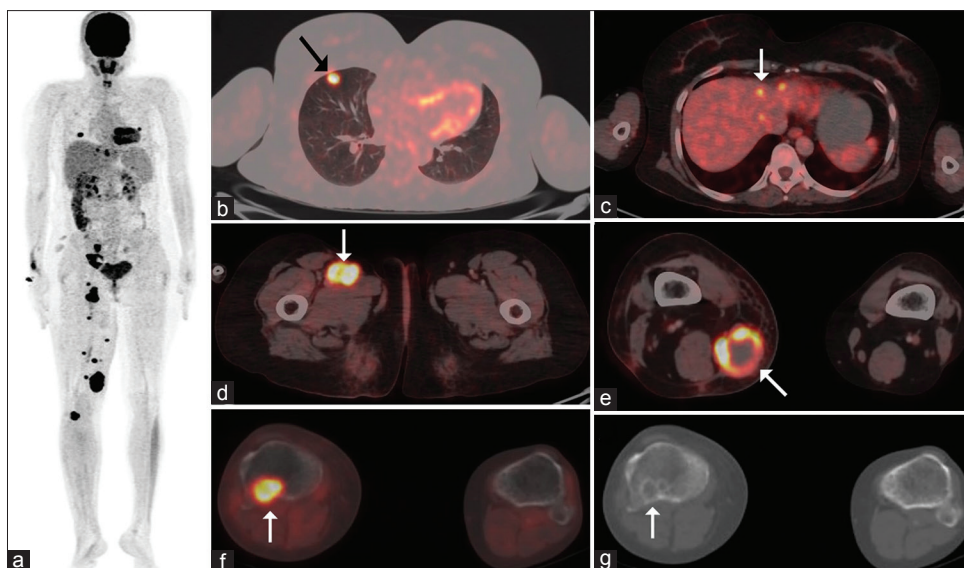


Figure 2: A 36-year-old woman with postcurative wide local excision of acral lentiginous melanoma of the right great toe presented with swelling in the right popliteal fossa. ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography maximal intensity projection image reveals widespread abnormal foci of fluorodeoxyglucose-avid lesions (a) tracer-avid lung lesion – black arrow (b), liver lesion – white arrow (c), intermuscular lesions – white arrow (d), pelvic and femoral lymph nodes (e), skeletal lesions (f and g), lytic lesion at the posterolateral end of the right tibial condyle on transaxial computed tomography – white arrow suggestive of metastatic disease confirmed by histopathology

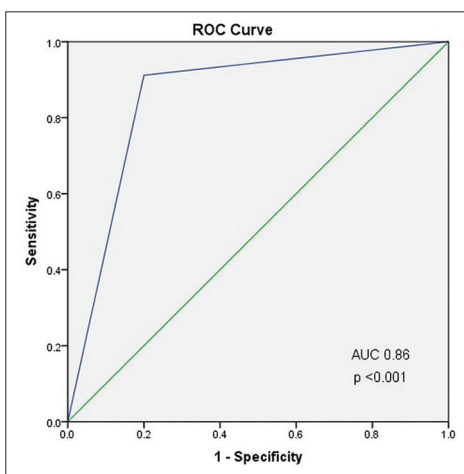


Figure 3: Receiver operating characteristic curve of visually interpreted ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography derived using histopathology, treatment received and clinical follow-up of patients as reference standard revealed area under the curve of 0.86 (95% confidence interval: 0.74–0.97, *P* < 0.01)

Survival analysis

A total of 21 patients (39%) died during mean follow-up of 23.8 ± 18.1 months. Among deceased, positive ¹⁸F-FDG PET/CT was observed in 20 patients (13 with distant metastasis, 5 with locoregional recurrence, and 2 with second primary malignancy). Kaplan–Meier survival plots were derived using visually interpreted ¹⁸F-FDG PET/CT result and SUVmax value as prognostic factors. Survival analysis showed that positive ¹⁸F-FDG PET/CT study was associated with a significantly shorter MSS than the negative study (30.8 ± 4.6 vs. 64.5 ± 6.9 months, *P* = 0.001). The ROC

Table 3: Diagnostic performance of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (*n* = 54)

Parameter	<i>n</i>	Diagnostic values	Percentage	95% CI
True positive	31	Sensitivity	91.2	76.3-98.1
False positive	4	Positive predictive value	88.6	73.3-96.8
True negative	16	Specificity	80.0	56.4-94.3
False negative	3	Negative predictive value	84.2	60.4-96.6

CI: Confidence interval

curve demonstrated that optimum SUVmax cutoff value for MSS was >2.7 (sensitivity 91% and specificity 85%). Using this cutoff threshold, SUVmax was dichotomized to generate Kaplan–Meier survival plot, which revealed SUVmax >2.7 as significant prognostic factor for MSS (26.2 ± 3.6 vs. 68.1 ± 4.1 months, *P* < 0.001). Survival analysis done by combining both positive ¹⁸F-FDG PET/CT result and SUVmax >2.7 also revealed similar results [Figure 4]. Cox proportional hazard model used to determine ¹⁸F-FDG PET/CT, SUVmax, and both combined as prognostic factors revealed hazard ratio (HR) of 7.72 (95% CI: 1.8–33.0; *P* = 0.006), 21.58 (95% CI: 2.8–168.6; *P* = 0.003), and 11.37 (95% CI: 2.5–50.6; *P* = 0.001), respectively [Table 4].

DISCUSSION

This retrospective study was intended to evaluate the utility of ¹⁸F-FDG PET/CT in detecting the recurrence in patients with malignant melanoma after primary treatment and its

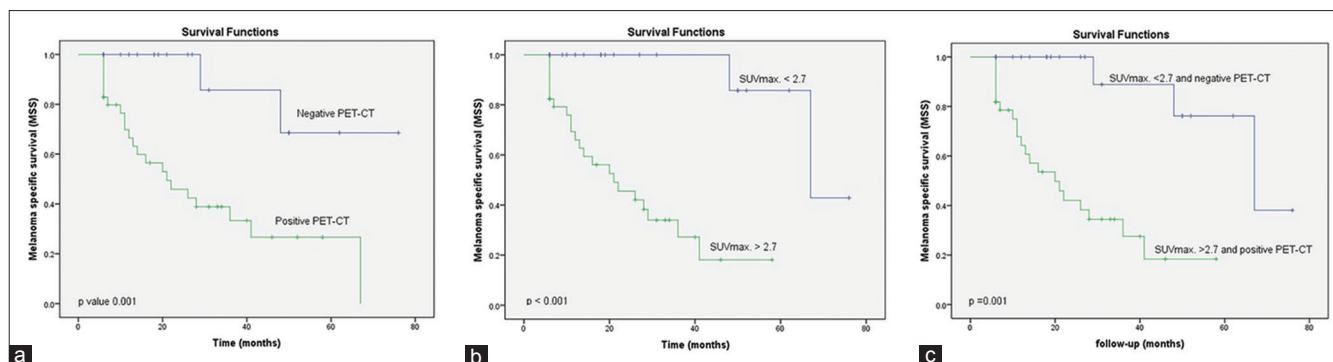


Figure 4: Kaplan–Meier analysis of melanoma-specific survival with respect to visually interpreted ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography result (a), maximum standardized uptake value values (b), and combined ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography result and SUVmax values (c)

Table 4: Melanoma-specific survival of patients with ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography result and maximum standardized uptake value

Prognostic factor	Variables	MSS (months), mean ± SD	P	HR	P
18F-FDG PET/CT results	Negative	64.5 ± 7.0	0.001	7.72	0.006
	Positive	30.9 ± 4.6			
SUVmax	<2.7	68.1 ± 4.1	<0.001	21.58	0.003
	>2.7	26.3 ± 3.6			
SUVmax >2.7 and positive PET/CT	Absent	63.8 ± 5.5	0.001	11.37	0.001
	Present	25.8 ± 3.7			

MSS: Melanoma-specific survival; ¹⁸F-FDG PET/CT: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; SD: Standard deviation; HR: Hazard ratio; SUVmax: Maximum standardized uptake value

impact in predicting the survival. ¹⁸F-FDG PET/CT in this study showed the sensitivity, specificity, positive predictive value, and negative predictive value of 91.2%, 80%, 88.6%, and 84.2%, respectively, for detection of recurrence. The positive ¹⁸F-FDG PET/CT study was associated with a significantly shorter MSS than the negative study (30.8 ± 4.6 vs. 64.5 ± 6.9 months, P = 0.001), and SUVmax >2.7 was significant prognostic factor for shorter MSS (26.2 ± 3.6 vs. 68.1 ± 4.1 months, P < 0.001). Survival analysis after combining both FDG positivity and SUVmax >2.7 demonstrated significantly shorter MSS.

The current recommendation of follow-up in patients of malignant melanoma includes regular clinical examination with emphasis for locoregional disease recurrence and systemic metastatic disease every 3 months during the first 2 years and at every 6 months for the next 3 years.^[13] The diagnostic imaging is still not the part of current recommendations in routine follow-up though specific imaging modalities may be valuable supplement.^[8] Among the imaging modalities, whole-body ¹⁸F-FDG PET/CT has the potential in detecting metastasis from malignant

melanoma with high sensitivity and specificity, and a meta-analysis of 14 studies with 753 higher stage melanoma patients having nearly 2000 lesions revealed sensitivity of 88% and specificity of 82%, respectively, for metastatic disease on ¹⁸F-FDG PET/CT.^[17] The diagnostic performance (sensitivity, specificity, positive predictive value, and negative predictive value) of ¹⁸F-FDG PET and ¹⁸F-FDG PET/CT in the pooled data on follow-up of patients with malignant melanoma had been reported 96%, 92%, 92%, and 95%, respectively.^[18] Although our study showed high diagnostic performance of FDG PET/CT in follow-up of melanoma patients for recurrent disease, it was somewhat lower than observed by other investigators.

The investigators have also tried serum S-100B estimation in melanoma patients with recurrent disease. The rising serum S-100B has shown a higher specificity than lactate dehydrogenase for disease progression in follow-up, but the evidence is still not sufficient for recurrent disease.^[19] In a fair quality study (n = 90) by Wieder et al., ¹⁸F-FDG PET/CT was associated with sensitivity and specificity of 87% and 93%, respectively, for detection of melanoma recurrence, whereas serum S-100B monitoring alone was not enough to detect disease progression, though serum S-100B measurements along with whole-body ¹⁸F-FDG PET/CT increased its utility.^[20]

¹⁸F-FDG PET/CT had also been used in predicting the survival in patients after treatment. It had shown its utility in predicting the survival in a study of 252 Stage III melanoma patients with clinical suspicion of recurrence where the 5-year survival rate was significantly higher in patients with negative ¹⁸F-FDG PET/CT study compared to patients with positive study (47.6% vs. 16.9%, P < 0.001).^[21] The present study also supports this association as negative ¹⁸F-FDG PET/CT findings were related with significantly longer MSS than the positive findings (64.5 ± 6.9 vs. 30.8 ± 4.6 months, P = 0.001). Similarly, Mena et al.^[22] in their study demonstrated that overall survival differed significantly between patients with at least one of the

fourth or subsequent positive ^{18}F -FDG PET/CT scans and those with all negative fourth or subsequent ^{18}F -FDG PET/CT scans (median OS, 28 ± 25.6 vs. 44.3 ± 24.9 months). However, multivariate analysis in their study revealed that a positive ^{18}F -FDG PET/CT scans did not remain statistically significant after adjustment for clinical suspicion ($P = 0.954$).

The semi-quantitative metabolic parameter (SUVmax) evaluated previously to predict the recurrence in patients with malignant melanoma observed the sensitivity of 88.9% and specificity of 67.9% at SUVmax cutoff value of 2.2.^[23] Recently, Son *et al.* in their study of 41 patients with primary cutaneous malignant melanoma showed that pretreatment SUVmax and total lesion glycolysis were significantly higher in patients with recurrence versus without recurrence and nonsurvivor versus survivor. SUVmax value of 1.8 was a significant predictor of disease-free survival, and the optimal cutoff value for evaluation of MSS was 2.2.^[24] However, all the patients in the present study had surgical excision of the primary disease before ^{18}F -FDG PET/CT, and SUVmax of the highest tracer-avid recurrent lesions was obtained. The somewhat higher SUVmax value (2.7) obtained in our study might be due to the evaluation of recurrent disease rather than the primary disease as done in a study by Son *et al.*^[24] PET parameter like SUVmax represents more correctly about the metabolic activity in the lesion rather than stratifying the PET data as tracer-avid or nonavid lesions in dichotomous manner. The present study showed that the SUVmax >2.7 with 91.2% sensitivity and 85% specificity was an independent prognostic predictor of MSS (HR: 21.58, $P = 0.003$) and patients with higher SUVmax had poor survival. Previous studies did not explore the prognostic value of SUVmax in recurrent disease after primary surgical excision. The present study supports that SUVmax parameter serves as a significant prognostic marker for recurrence risk assessment and predicting the survival in malignant melanoma patients during restaging. This study has limitations including its retrospective nature, limited sample size, and exclusion of other patient-related factors. The patient cohort was only from single hospital (a referral tertiary care hospital), which might have influenced the results.

CONCLUSION

This study showed that there was enhanced diagnostic performance and predictive value in survival outcomes in malignant melanoma patients with suspicious recurrence using ^{18}F -FDG PET/CT. The SUVmax value >2.7 serves as a significant prognostic marker for recurrence risk assessment and predicting the survival in malignant melanoma patients during restaging.

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Conflicts of interest

There are no conflicts of interest.

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