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Original Article

Diagnostic performance of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in anorectal melanoma

ABSTRACT

To evaluate the diagnostic role of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) in initial staging and restaging of anorectal melanoma. This was a single-institution, retrospective observational study; patients for initial staging and with clinical or radiological suspicion of disease recurrence referred for PET/CT between January 2006 and December 2015 were included in the study. Diagnostic performance of PET/CT was evaluated for baseline staging and disease recurrence. A total of 61 patients who were referred for initial staging were included. PET/CT correctly detected primary lesion in 57 (93.44%) cases, regional nodes in 46 (75.4%) cases, nonregional nodes in 22 (36%) cases, and distant metastases in 25 (41%) cases. The sensitivity (SN); specificity (SP); positive predictive value (PPV); negative predictive value (NPV); and accuracy for primary lesion, regional nodes, nonregional nodes, and distant metastases were 96.6%, 100%, 100%, 50%, and 96.7%; 97.9%, 100%, 100%, 93.3%, and 98.4%; 100%, 100%, 100%, 100%, and 100%; and 100%, 100%, 100%, 100%, and 100%, respectively. A total of 24 patients were included for suspected recurrence/restaging. All the patients were treated previously by surgery, radiotherapy, or chemotherapy. PET/CT detected disease recurrence in 20 (83.3%) patients. Ten patients had recurrence at the primary site, 8 of whom also had distant metastases and 2 had only locoregional metastatic nodes. In the remaining 10 patients, there was no primary site recurrence; however, 2 patients had locoregional nodal and distant metastases and 8 patients had only distant metastases. PET/CT was false negative in 1 patient, which missed liver metastasis. SN, SP, PPV, and NPV of PET/CT was found to be 95%, 100%, 100%, and 75%, respectively, with accuracy of 96%. PET/CT demonstrates overall high diagnostic accuracy in the initial staging and detection of recurrent disease in cases of anorectal melanoma.

Keywords: Accuracy, anorectal, diagnostic, melanoma, positron emission tomography/computed tomography

INTRODUCTION

Melanomas arise from melanocytes, which are derived from embryonic neural crest cells. Anorectal melanoma is a rare, aggressive malignancy and most arises from the dentate line.[1] They account for <1% of all malignant melanomas and fewer than 3% of all anal tumors.[1-3] The incidence of anorectal melanoma is about 1–2 cases per million population per year in the United States, with statistical estimates in similar range in Europe and Asia.[4] The incidence of anorectal melanoma is thought to be increasing.[4] Most of the patients present with nonspecific symptoms and as a result tend to have disease progression to advanced stage at initial presentation.[1] The overall risk factors for anorectal melanoma are also poorly

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known. The relationship between cutaneous melanoma and ultraviolet B light, which is a carcinogenic stimulus, is well documented.[5] However, it is not obvious what triggers the development of anal melanoma as anal mucosa is never exposed to sunlight. As with cutaneous melanomas, which are 20 times more common in whites than blacks, there is no such evidence for anal melanomas.[3] Tumor stage is an independent prognostic variable for overall survival. However, there are no well-established staging systems and treatment protocols due to its rarity. Siegal *et al*. reported that survival for Stage I patients (local disease) was 48 months, Stage II (local disease with regional nodes) was 12 months, and Stage III (distant metastases) was 10 months.[6] Thus, it is important to have accurate imaging modality for staging anorectal melanoma. The role of positron emission tomography/computed tomography (PET/CT) in staging and restaging of several cancers has already been established. The literature regarding the role of PET/CT in anorectal melanoma is sparse as it is a rare type of tumor. Only few case reports and case series are documented in literature. No studies or any guidelines establishing the role of PET/CT in anorectal melanoma are currently published. The aim of our retrospective audit was to report our experience in evaluating the diagnostic accuracy of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT in staging and restaging of anorectal melanoma.

MATERIALS AND METHODS

This was an institutional review board-approved, single-institution, retrospective observational study. Consecutive patients were included. Inclusion criteria were biopsy-proven cases of anorectal melanoma referred for initial staging and for suspected recurrence/restaging who underwent a PET/CT between January 2006 and December 2015. Patients in whom biopsy report was not available or with synchronous malignancy at any other site were excluded from the study. Diagnostic performance of PET/CT was evaluated for baseline staging and restaging with clinical suspicion of recurrence. PET/CT studies were evaluated for the ability to detect the primary disease, nodal, and other sites of metastases. Histopathology was used as gold standard. When tissue diagnosis was not available, clinical or radiological follow-up was used as reference standard. The sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated at 95% confidence interval. At present, as there is no staging system specific to the disease, a clinical staging as suggested by several retrospective studies for mucosal melanomas was used, Stage I as localized disease only and Stage II as regional lymph node (LN) involvement. Nodes in the pelvis below the common iliac were considered locoregional nodes. Disease in nodes from common iliac and above and other organs was Stage III.

Patient preparation and positron emission tomography/computed tomography protocol

All patients were asked to fast for at least 6 h prior to the study and blood glucose levels checked and confirmed to be below 150 mg/dl (8.3 mmol/L). The studies were taken 60 ± 15 min following intravenous administration of 5 MBq/kg body weight of ^{18}F-FDG. Imaging was performed using Philips Gemini TF TOF 16/64 PET/CT scanners (PET crystal-LYSO). After obtaining a scout image, breath-hold CT was acquired followed by whole-body CT and the PET acquisition in the same anatomic location. Whole-body CT was acquired from skull base to midthigh region (slice thickness 2 mm, 120 kV voltage, automated mA, rotation time 0.5 s, pitch 0.83, image matrix 512 × 512, field of view (FOV) 600 mm) without any breath-hold instructions. Separate breath-hold CT was acquired (slice thickness 3 mm, 120 kV, automated mA, pitch 1.08, FOV 300 mm, image matrix 512 × 512) for the evaluation of the lungs. Eighty milliliters of oral contrast was administered in all eligible patients at a rate of 1.8 ml/s and scan delay of 50 s. Water-based oral contrast was given for bowel distension. Contrast-enhanced CT was used for diagnostic purpose as well as for attenuation correction of PET data. PET was acquired in three-dimensional mode in about 5–8 bed positions with an acquisition time of 60–90 s/bed position, axial FOV 576 mm, and in plane spatial resolution of 4 mm.

Image reconstruction and interpretation

The images were reconstructed iteratively using RAMLA algorithm. CT attenuation correction, dead time correction, and decay correction were applied. Images were viewed on Philips workstation having extended brilliance workspace version 4.5.3.40140, equipped with fusion viewer software that enables the display of PET, CT, and fusion PET/CT images.

The images were reviewed by two experienced nuclear medicine physicians. Any area with intensity greater than background that could not be identified as physiological activity on PET images or which on CT correlation did not fit into benign (infective/inflammatory/degenerative) was considered to be suggestive of tumor on PET/CT study. CT criteria for positive metastatic node included size more than or equal to 1 cm in short-axis measurement, rounded nodes, loss of fatty hilum, central necrosis, and/or contrast enhancement. Morphologic characteristics of pulmonary lesions on CT were taken positive even in the absence of ^{18}F-FDG uptake.

The diagnostic accuracy of ^{18}F-FDG PET/CT for the detection of primary tumor/recurrence and the metastatic lesions was correlated with either histopathology or subsequent clinical/follow-up imaging.

Statistical analysis

All the PET/CT studies were evaluated for the ability to detect the primary disease, nodal, and distant metastatic sites. The SN, SP, PPV, NPV, and accuracy were calculated at 95% confidence interval.

RESULTS

Initial staging

A total of 61 (45 males and 16 females) patients with an age range of 28–88 years were included for initial staging. Among the 61 patients, 13.1% had Stage I, 29.5% had Stage II, and 57.4% had Stage III at initial presentation. Primary tumor site was localized to anal canal, rectum, and anorectal region [Table 1]. The primary tumor/lesion was detected in 57 patients out of 61. In four patients in whom no lesions were detected, PET/CT was true negative in two and false negative [Figure 1] in the other two patients (SN, 96.6%; SP, 100%; PPV, 100%; NPV, 50%; and accuracy, 96.7%). Regional nodal involvement was correctly detected in 46 out of 61 patients with false negative in one patient (SN, 97.9%; SP, 100%; PPV, 100%; NPV, 93.3%; and accuracy, 98.4%). Histopathological correlation was available for primary and regional nodal disease in all patients [Figures 2]. Twenty-two patients had nonregional nodes positive on PET/CT, whereas distant metastases were detected in 25 patients with SN 100%, SP 100%, PPV 100%, and NPV 100% [Figure 3]. These were confirmed with subsequent follow-up imaging [Table 2].

Table 1: Patient demographics

Characteristics	*n*
Staging	61
Gender	
Male	45
Female	16
Age (years)	
Median	56
Range	28-88
Location of tumor	
Anal canal	25
Rectum	23
Anorectum	13
Stage	
I	8
II	18
III	35

Restaging

A total of 24 (15 males and 9 females) patients were included for suspected recurrence/restaging [Table 3]. All patients underwent surgery. 79.2% (19/24) of patients underwent surgery alone; 16.7% (4/24) of patients were treated with surgery followed by chemotherapy; and 4.2% (1/24) of patients underwent surgery followed by radiotherapy. PET/CT detected disease recurrence in 20 (83.3%) patients. Ten patients had recurrence at the primary site [Figure 4], 8 of whom also had distant metastases [Figure 4a] and 2 had only locoregional metastatic nodes. In the remaining 10 patients, there was no primary site recurrence; however, 2 patients had locoregional nodal and distant metastases and 8 patients had only distant metastases. Histopathological confirmation was available in 6 patients, whereas imaging and clinical follow-up confirmed recurrence in the remaining patients. Thus, primary site recurrence was noted in 10 (41.7%) cases, locoregional nodes in 10 (41.7%) cases, and distant metastases in 18 (75%) cases. Liver was the most common site of distant metastases in 45.8% (11/24) of patients, followed by lungs 37.5% (9/24). PET/CT was negative for recurrence in three patients. This was confirmed by follow-up imaging studies in two cases and short-term clinical follow-up in one case. PET/CT was false negative in one patient, which missed liver metastases [Figure 5]. Ultrasonography-guided fine-needle

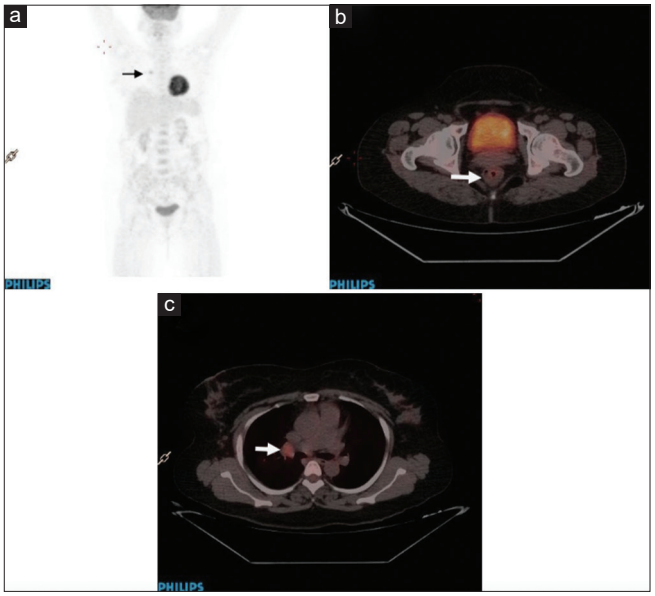

Figure 1: A 52-year-old patient presented with bleeding per rectum. Biopsy revealed features consistent with malignant melanoma. FDG PET/CT was done as baseline imaging. MIP image (a) shows no abnormal focal increased tracer uptake in the pelvic region. No focus of hypermetabolism or soft tissue lesion is seen in the anal canal region. Postsurgery histopathology results revealed submucosal malignant melanoma of rectum with reactive regional nodes. Thus, PET/CT showed false-negative results at the primary tumor site. MIP (b) and fused (c) images show focal uptake in the reactive right hilar node. FDG: Fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; MIP: Maximum Intensity Projection

Table 2: Result of Initial staging

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Primary	96.6	100	100	50	96.7
Nodes					
Regional	97.9	100	100	93.3	98.4
Nonregional	100	100	100	100	100
Metastases	100	100	100	100	100
Overall	98.6	100	100	85.8	98.9

PPV: Positive predictive value, NPV: Negative predictive value

Table 3: Patient demographics

Characteristics	*n*
Restaging	24
Gender	
Male	15
Female	9
Age (years)	
Median	58
Range	43-89
Treatment received	
Surgery alone	19
Surgery+chemotherapy	4
Surgery+radiotherapy	1
Recurrence sites	
Local	10
Locoregional nodes	10
Distant metastases	18

aspiration cytology (FNAC) of the liver lesion was done prior to the PET/CT scan, which had revealed metastatic malignant melanoma consistent with known primary in anorectum.

SN, SP, PPV, and NPV of PET/CT was found to be 95%, 100%, 100%, and 75%, respectively, with accuracy of 96% [Table 4].

DISCUSSION

Mucosal melanoma of anorectum is very aggressive disease with extremely poor prognosis with overall 5-year survival rates of 3%–22%.[1-3] Most of the patients present late because of nonspecific symptoms. Furthermore, majority of the lesions lack obvious pigmentation.[7,8] Surgery with or without adjuvant radiotherapy is the mainstay of treatment for locoregional disease. Despite aggressive local surgical control even in early-stage disease, local and distant site recurrences occur frequently due to its multifocal nature and clinically occult lymphatic spread.

PET, a whole-body metabolic imaging modality, appears ideal for accurate disease status evaluation before undertaking curative resection. Malignant melanoma cells are extremely FDG avid because of the upregulation of glucose transporter proteins, which forms the basis of FDG PET imaging.

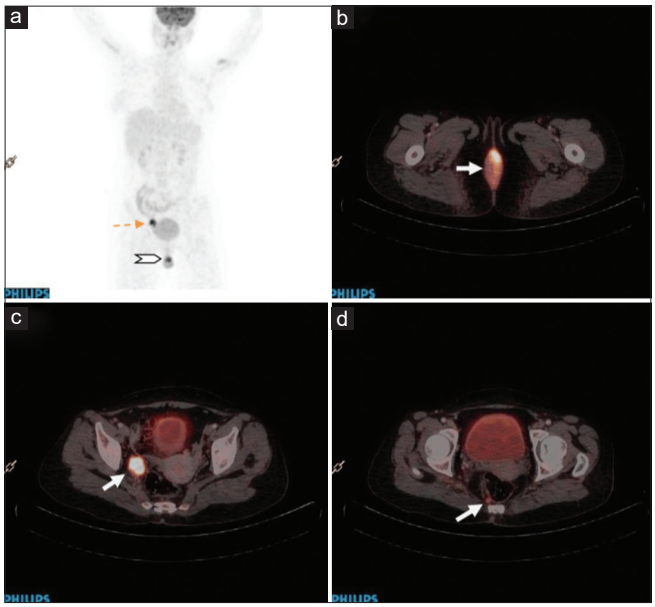

Figure 2: A 41-year-old patient presented with blood in stools, pain in perianal area, and weight loss. Biopsy revealed malignant tumor which had epithelioid and slightly spindle-shaped appearance. Immunohistochemistry was positive for HMB 45 and S100 proteins. MIP image (a) shows increased FDG tracer uptake in the pelvis and below it. Fused transaxial PET/CT images reveal FDG-avid growth in the anal canal (b) with metastatic right internal iliac node (c) and perirectal nodule (d). FDG: Fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; MIP: Maximum Intensity Projection

Combing anatomical imaging CT with metabolic imaging PET provides the added advantage of anatomical localization and also increases the SN and SP by differentiating pathological uptake from benign/physiological uptake.

Data about FDG PET/CT in anorectal malignant melanoma are sparse. Few case reports and case series are noted in literature.[9-13] Studies in primary cutaneous malignant melanoma have shown the superiority of PET and PET/CT over conventional imaging in initial staging and recurrent disease/restaging.[14-17]

This study was performed with an aim to calculate the diagnostic performance of PET/CT in initial staging and restaging with suspected recurrence in anorectal melanoma.

Patients for initial staging were treatment naïve and for recurrence had previously undergone surgical resection, chemotherapy, or radiotherapy.

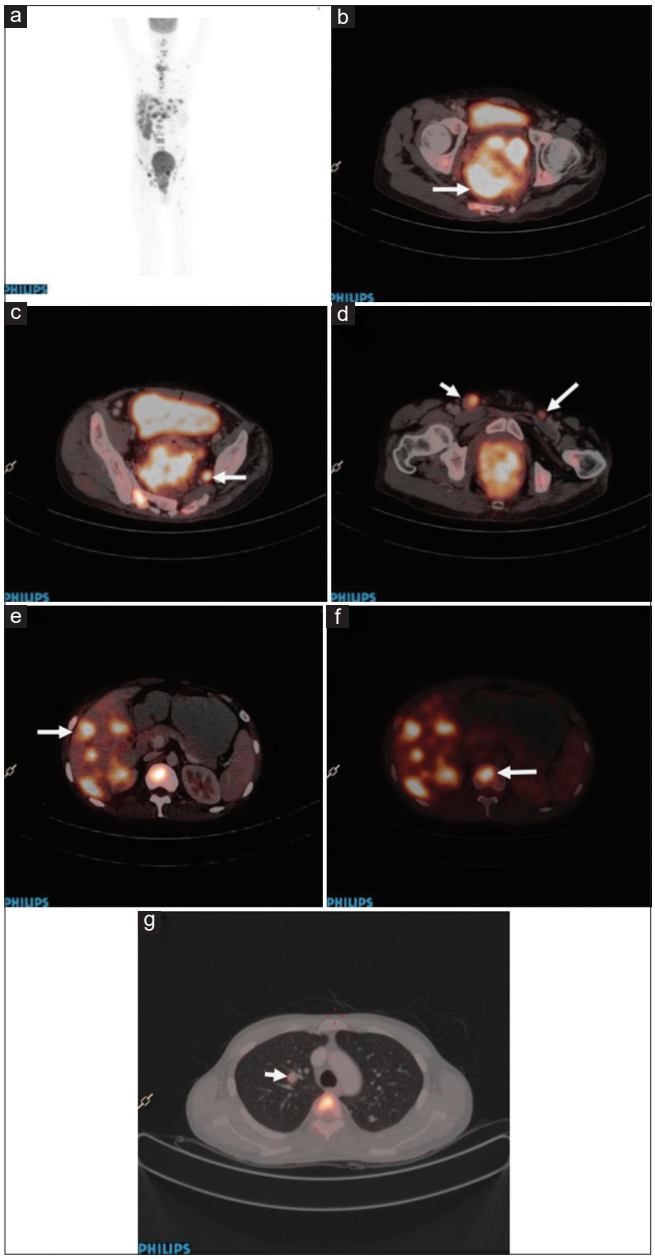

Figure 3: A 33-year-old patient presented with bleeding per rectum. Rectal growth biopsy is suggestive of malignant melanoma. Immunohistochemistry revealed tumor positive for HMB 45 and S100 protein. FDG PET/CT scan was done for initial staging. MIP images (a) show increased tracer uptake at multiple sites in the pelvis, liver, and multiple vertebrae. Fused transaxial PET/CT images show large anorectal mass (b), metastatic left internal iliac node (c), bilateral inguinal nodes (d), metastatic liver lesions (e), skeletal lesions (f), and lung nodules(g). The patient was considered for palliative chemoradiotherapy. FDG: Fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; MIP: Maximum Intensity Projection

In the initial staging group, primary lesion was correctly identified in 57 patients out of 61. In two patients, primary lesion was not evident on the scan of whom the surgical specimen was positive. In both cases, the thickness of the primary lesion was of about less than one centimeter size. This shows that small submucosal lesions may be missed on FDG PET. Regional nodal metastases were correctly identified

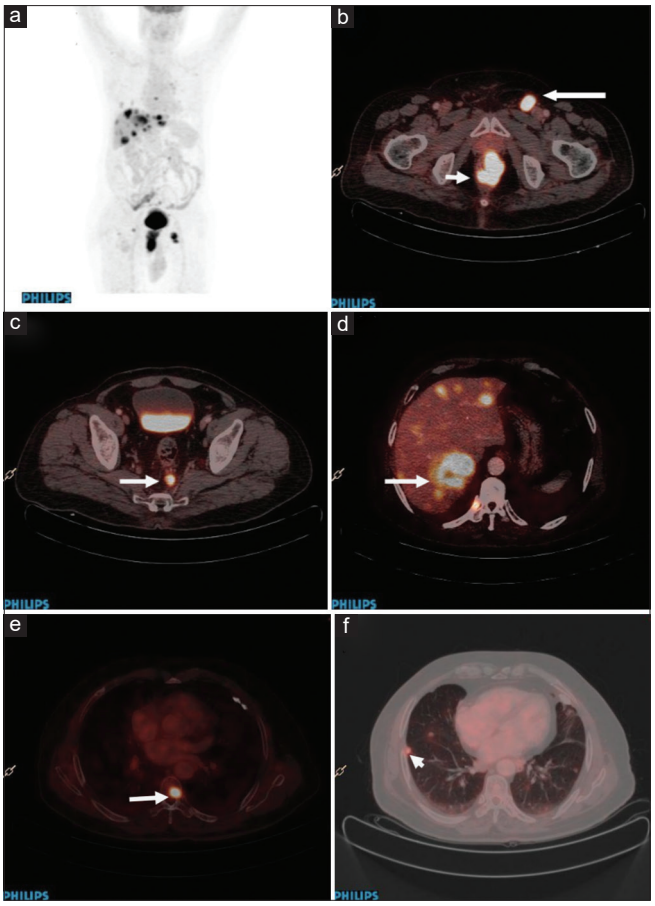

Figure 4: A 89-year-old patient presented with biopsy proven anal malignant melanoma. PET/CT scan was for restaging in the view of growth detected on per rectal examination. MIP image (a) shows focal increased tracer uptake in the pelvis, liver, right lung, and dorsal vertebra. Fused transaxial FDG PET/CT images show anorectal soft tissue mass (short arrow) and left inguinal node (long arrow) (b); pararectal nodule (c); liver metastases (d), metastatic dorsal vertebral lesion (e); and lung nodules (f). The patient was considered for palliative chemotherapy. FDG: Fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; MIP: Maximum Intensity Projection

in 46 (75.5%) patients. PET/CT was true negative in 14 (23%) patients and false negative in one patient. Postsurgery histopathology was positive for nodal metastases. Although PET is the best modality to detect metastases in subcentimeter size nodes, no imaging modality has yet proven accurate for the detection of micrometastases. This remains a drawback of imaging. However, of all imaging modalities, FDG PET/CT has still the best results.

Thus, in our study, PET/CT demonstrated high SN, SP, and accuracy for the detection of primary tumor and locoregional nodes. The primary lesions and nodes which were missed on PET/CT were of cm and subcentimeter size. It is known that PET may limit the detection of lesions less than centimeter size due to finite spatial resolution of the imaging system and due to partial volume effects.

Table 4: Result of Restaging

n	PET/CT			
	Positive		Negative	False negative
24	20		3	1
Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
95	100	100	75	96

PPV: Positive predictive value, NPV: Negative predictive value, PET: Positron emission tomography, CT: Computed tomography

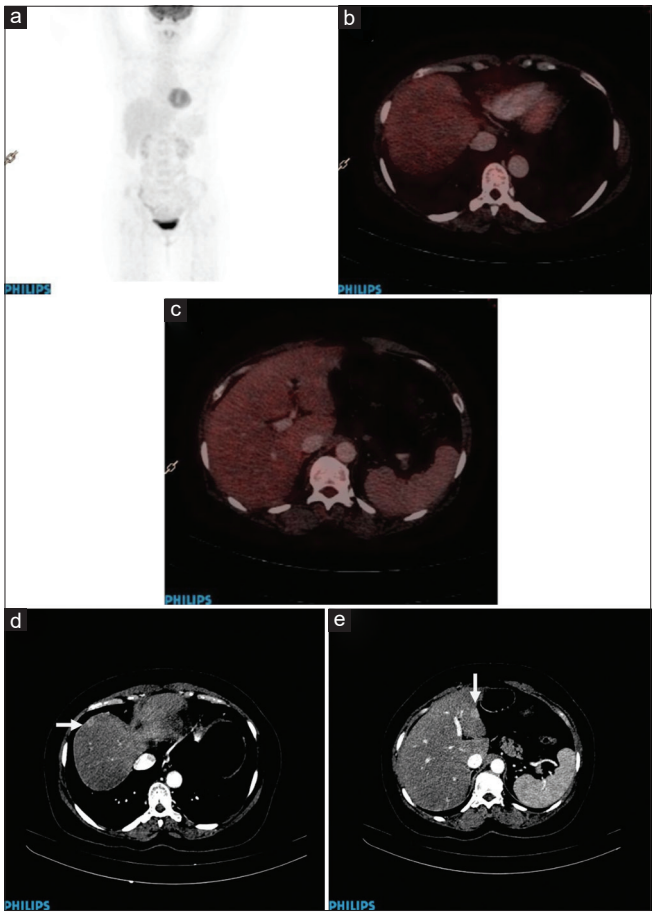

Figure 5: A 53-year-old patient initially presented with pain in abdomen and underwent anal polypectomy. Biopsy report revealed anorectal melanoma with immunohistochemistry results positive for HMB 45 and S100 protein. Follow-up USG done revealed left liver lobe hypoechoic suspicious lesion. USG done six months later showed increase in the size of suspicious left liver lobe lesion. FNAC revealed metastatic malignant melanoma consistent with known primary in the anorectum. FDG PET/CT done for restaging showed no abnormal focus of increased tracer uptake in the scan as seen in MIP (a) and fused transaxial images (b and c); triphasic diagnostic CT scan done a week after shows subcentimeter size enhancing liver lesions in segment VIII and III (d and e), best appreciated in portovenous phase. Thus, PET/CT did not detect the subcentimeter size metastatic liver lesions. FDG: Fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; USG: Ultrasonography; FNAC: Fine-needle aspiration cytology

The main strength of PET/CT, being a whole-body imaging, lies in the detection of distant metastases. This was supported by our study, which showed a SN, SP, and diagnostic accuracy of 100% for distant metastases.

The results of our study for the detection of regional nodes and distant metastases in anorectal melanoma were similar to that of the results of case series by Falch *et al*.,[9] who also found that PET/CT is superior for LN and distant metastases.

In our restaging cohort of 24 patients, PET/CT detected recurrence in 20 patients. PET/CT was true negative in three patients and false negative in one patient in whom liver metastases were missed.

The patient in whom PET/CT did not detect liver lesions was a FNAC-proven case of metastatic liver lesion consistent with primary from anorectum prior to PET scan. The patient was referred for PET/CT to rule out other sites of distant metastases. No other lesions were found on PET/CT. Subsequently done diagnostic triple-phase CT showed subcentimeter size enhancing liver lesions. The reason for false-negative results of PET/CT may be due to subcentimeter size of the lesion and a contrast-enhanced low-dose CT was done and not a diagnostic triple-phase CT scan.

Similar studies done in cutaneous melanoma for recurrent disease/restaging showed that PET was superior for the detection of locoregional recurrence and distant metastases with high SN and SP as compared to conventional imaging.[18-20]

Our study also revealed similar results with overall high SN, SP, PPV, and diagnostic accuracy for the detection of recurrent disease. To our knowledge, this is the first study in literature which looked at the role of FDG PET/CT in initial staging and restaging of the mucosal melanomas of anorectum.

The limitations of our study include it was a retrospective analysis and the number of patients included were small. However, considering the rarity of the disease and lack of data on it, such studies are reported to strengthen the sparse existing literature. Histopathological examination of all metastatic sites was not available as this is not always feasible nor ethical in clinical practice.

CONCLUSION

PET/CT demonstrates a high diagnostic accuracy in the initial staging and detection of recurrent disease in cases of anorectal

melanoma. The aggressive nature and propensity to metastasize needs a whole-body evaluation making FDG PET/CT the preferred modality and one-stop imaging for anorectal melanomas.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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