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# PET/CT in restaging, prognosis, and recurrence in patients with malignant melanoma

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## Abstract

**Background:** Cutaneous malignant melanoma (CMM) is a highly aggressive tumor with high tendency of return despite complete surgical removal. It has a high risk of dissemination to regional lymph nodes and visceral organs. The prognosis is highly dependent on lymph node involvement and distant metastases. Positron Emission Tomography with Computed Tomography (PET/CT) is a valuable non-invasive tool for the diagnosis and staging of patients with MM. The purpose of the present study was to evaluate the role of integrated (PET/CT) in staging, restaging, prognosis, and prediction of recurrence in patients with malignant melanoma.

**Results:** Fifty malignant melanoma patients with age ranged from 28 to 74 years (mean age 55.94 + 13.40 years) were 28 males (mean age 56.71 + 12.82) and 22 females (mean age 54.95 + 14.34). All our patients were histopathologically proven to have malignant melanoma. Twenty-one patients came for initial staging by 18F-FDG PET/CT. Their findings were compared with the reference standards and showed the sensitivity of 93.33%, specificity of 60%, and accuracy of 85.71% for primary staging. 18F-FDG PET/CT scan in 11 clinical suspicion patients of relapse after treatment showed the sensitivity of 100%, specificity of 66.66%, positive predictive value of 88.88%; negative predictive value of 100%; and accuracy of 90.90%. FDG-PET/CT of whole body scan in 18 cases of stage IV melanoma showed sensitivity of 100%, specificity of 66.66%, and overall accuracy of 94.44% for detection of distant metastases. SUVmean and SUVmax in all studied groups were significantly higher in true positive more than true negative or false-positive patients diagnosed by PET/CT with high sensitivity (82.88–100%).

**Conclusion:** PET/CT imaging enhanced diagnostic performance in detection of the primary malignancy, in follow-up of high-risk patients and patients with suspected or known local or distant recurrence, and in restaging of patients with known distant metastatic disease to assess tumor response.

**Keywords:** FDG-PET/CT, Malignant melanoma, Imaging, Metastases, Staging, Follow-up high-risk patients

## Background

Melanoma, also known as malignant melanoma (MM), is a type of cancer that develops from the pigment-containing cells known as melanocytes. Melanomas typically occur in the skin but may rarely occur in the mouth, intestines, or eye [1].

Melanoma is an aggressive tumor with early tendency to metastasis to regional lymph nodes followed by distant metastasis. Although almost all organs can be involved, the most frequent target sites are the liver, bone, and brain. Despite recent advances in the understanding of oncogenic mechanisms and therapeutic interventions, the median survival in patients with metastatic disease does not go beyond 12 months [2].

Staging system for cutaneous melanoma is based on data from The American Joint Committee on Cancer

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(AJCC) which based on Tumor Nodal Metastases (TNM); stages include I, II, III, and IV. This staging was last revised in 2009 [3].

MM's mortality rate varies greatly depending on the stage of the disease at diagnosis. In the early stages of MM, the 5-year survival rates are quite high, 97 and 92% for stages IA and IB, respectively. This survival rate, however, falls drastically in the later stages of MM to between 10 and 30% for stage IV patients [4].

High mortality rate in terminal stages required early detection of initial stages, so effective treatment applied. MM tended to occur at any organ far from the primary one, so regional imaging was not effective in mapping of distribution of disease. Risk of post-operative recurrence and distant metastasis is seen in around one third of cases, with lack of unity of post-operative imaging tool [5].

PET/CT is a technique used to reduce false-positive findings by combining two imaging modalities. It combines the advantages of the metabolic imaging and anatomic localization in one session. PET/CT with its inherent whole-body capability is arguably the best imaging option to search for melanoma metastases with the potential to change treatment plan in as high as 49% [6].

It was found that among sonography, CT, PET, and PET/CT, PET/CT had the highest sensitivity (86%) and specificity (91%) for detecting metastases as deep soft tissue, lymph node, and visceral metastases [7].

In advanced stages of MM (i.e., III–IV), FDG-PET/CT can be of great value by locating distant metastases, thereby influencing treatment decisions [8–10].

The main indication of PET/CT in cutaneous melanoma is to detect recurrence or to restage disease following the detection of recurrence, particularly in patients with high-risk melanoma who are candidates for resection with curative intent. As patients therapy that showed no response could be changed, saving the patients from ineffective therapy and associated toxicities. There is still lack of agreement on the indications of post-therapy follow-up scans by PET/CT for MM patients.

The objective of this work is to evaluate the role of integrated Positron Emission Tomography/Computed Tomography (PET/CT) in staging, restaging, prognosis, and prediction of recurrence in patients with malignant melanoma.

## Methods

### Patient's population

This prospective interventional study was carried out following the approval of the Research Ethical Committee, from November 2017 to September 2019, on fifty (50) patients, age range 28–74 years with blood glucose levels below 150 mg/dL, histopathologically proven to

have malignant melanoma. The exclusion criteria were patients who were unable to remain supine for 30 min and those who were unable to put his or her arms overhead and patients with uncontrolled hyperglycemia (blood glucose level > 250 mg/dL), and pregnant patients were excluded from our study. Also, patients with vital sign instability, severe diabetes, severe illness, active infection renal disease who had serum creatinine level above 2.0 mg/dL were excluded from our study as in Fig. 1.

Informed written consent was obtained from all participants prior to use of PET/CT after full explanation of the benefits and risks of the procedure given to Research Ethical Committee. The patients' medical records were reviewed for the basic information comprising age and sex as well as primary tumor characteristics (location, histological type, ulceration, TNM stage, and FDG-PET/CT findings).

### Methods

Examined patients were categorized into 3 groups according to various referable causes: G1, including 21 patients for initial staging; G2, 11 patients with clinical suspicion of relapse; and G3, 18 patients in stage IV for suspicion and detection of metastatic deposits.

### Preparation

The patient was asked to fast for 6 h prior to the scan. All metallic items were removed from the patient, including dentures, pants with zipper, bra, belts, and bracelets. An 18-gauge cannula was inserted in the patient's anti-cubital fossa for administration of 18F-FDG.

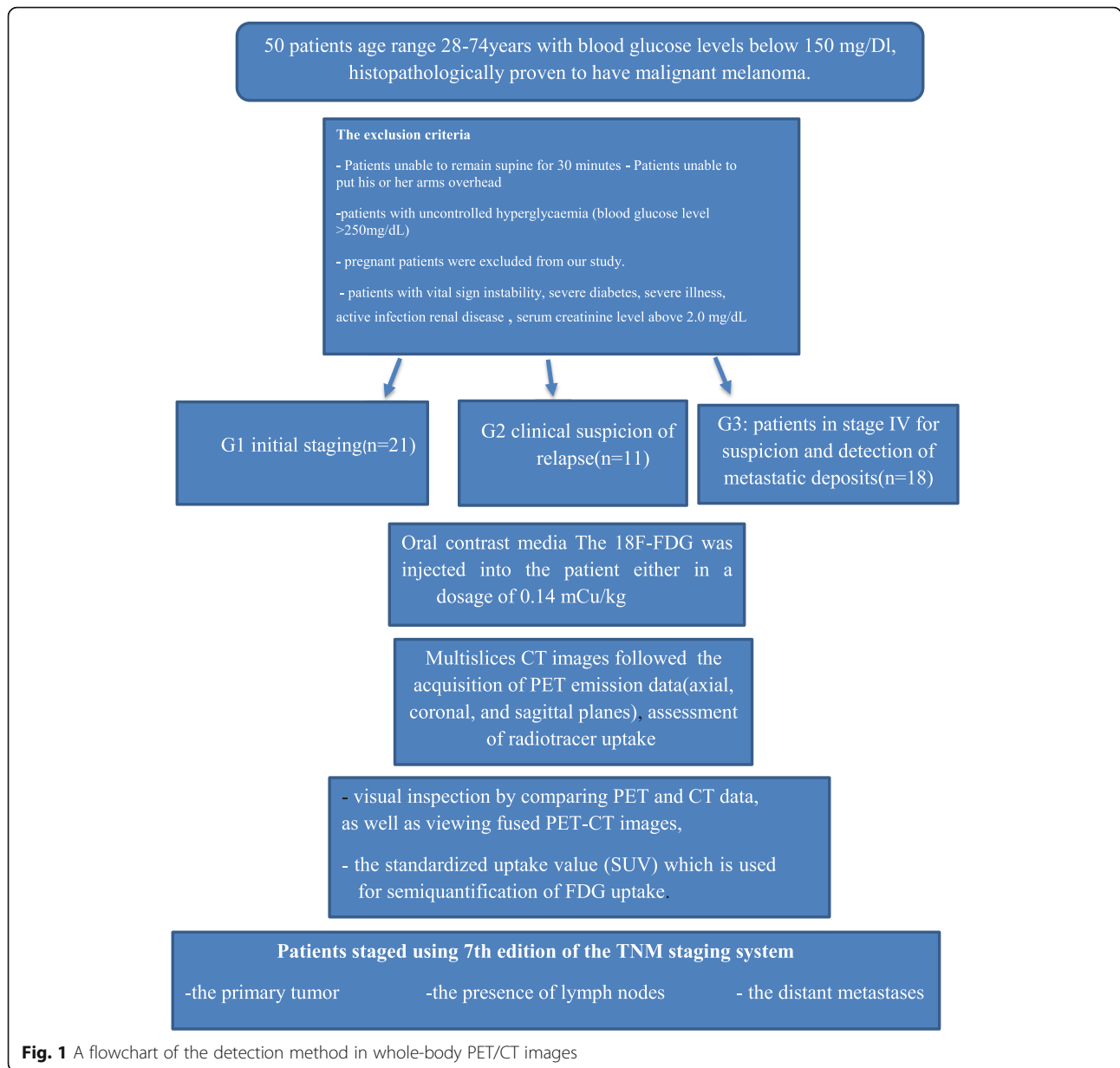
Patients were instructed to avoid caffeinated or alcoholic beverages and avoid any kind of strenuous activity; only water was allowed to prior to the examination and following the injection of the radioisotope to avoid physiologic muscle uptake of FDG.

For the diabetic patients, good control of blood glucose is essential because the uptake of FDG into cells is competitively inhibited by glucose, as they use a common transport mechanism (glucose transporters [GLUT]) for facilitated transport into both normal and tumor cells.

Serum glucose was routinely measured prior to 18F-FDG injection, and it should be below 150 mg/dL. Diabetic patients should not have regular insulin administered subcutaneously within 4 h from FDG administration.

Oral contrast media was used for all patients to distend the bowel wall and help to distinguish between bowel loops and any lymph nodes or masses in the abdomen and pelvic region.

The 18F-FDG was injected into the patient either in a dosage of 0.14 mCi/kg or as prescribed by the physician.



**Fig. 1** A flowchart of the detection method in whole-body PET/CT images

The patient waited for 45 to 60 min after FDG administration. This period is referred to as the uptake phase and is the necessary amount of time for the FDG to be adequately bio-distributed and transported into the patient’s cells.

Patients were asked to rest in a quiet room, devoid of distractions, and they were also asked to keep their movements, including talking, at an absolute minimum. This minimizes physiologic uptake of FDG into skeletal muscle, which can confound interpretation of the scan.

**PET/CT image interpretation**

Multi-slices CT images were performed immediately preceding the acquisition of PET emission data. The patients were asked for quiet breathing to avoid motion

artifacts and to match co-registration of CT and PET images in the area of the diaphragm.

The images were displayed in the axial, coronal, and sagittal planes. We assessed the images by both visual inspection and quantitative analysis of the area of abnormal uptake that was done followed by measuring of SUVmax by putting the region of interest (ROI). PET-CT images were evaluated regarding the primary tumor and the presence of lymph nodes and distant metastases. Patients were staged using 7th edition of the TNM staging system.

**Statistical analysis**

All the PET/CT finding results recorded and analysis using mean, standard deviation, minimum, median, and

**Table 1** The staging of patients with the TNM system and AJCC stage

Total stage grouping		
Stage grouping	No. of patients	Percentage
IA	0	0%
IIA	2	4%
IIB	4	8%
IIC	5	10%
IIIA	7	14%
IIIB	4	8%
IIIC	10	20%
IV	18	54%
<b>Total</b>	<b>50</b>	<b>100%</b>

maximum in quantitative data by using count (frequency) and relative frequency (percentage) for analysis the data. Correlations between quantitative variables were done using chi-square test, sensitivity, specificity, and accuracy with positive predictive values, and negative predictive values were calculated; *P* values less than 0.05 were considered significant. The calculations were done by using a statistical software package (SPSS for Windows, SPSS Inc, Chicago, IL).

**Results**

Fifty MM patients with age ranged from 28 to 74 years (mean age 55.94 + 13.40 years) were eligible for this study. They were 28 males (mean age 56.71 + 12.82) and 22 females (mean age 54.95 + 14.34). All our patients were histopathologically proven to have malignant melanoma and demonstrated blood glucose levels below 150 mg/dL.

The most common age for MM ranged between 66 and 74 years. Furthermore, our results revealed that males are more affected than females with MM, in which 28 (56%) of our patients were males and 22 patients (44%) were females.

The most common site for the primary melanoma was on the head/neck (36%), followed by the trunk (30%), followed by the lower extremities (16%), and upper extremities (14%). The common histological type is nodular (84%), followed by acral lentiginous (10%), and finally superficial spreading (6%).

The AJCC stage at initial diagnosis of 50 MM patients was as follows: no patients had stage I disease, 11 patients (22%) had stage II disease, 21 patients (42%) had stage III disease, and 18 patients (36%) had stage IV disease (Table 1).

Twenty-one (G1) out of 50 MM patients in our study had done 18F-FDG PET/CT imaging for initial staging. Their findings were compared with the reference standards (clinical examination, histopathology, and imaging CT). 18F-FDG PET/CT was true positive (TP) in 15, true negative (TN) in 3, false positive (FP) in 2, and false negative (FN) in 1 patient. PET/CT showed the sensitivity of 93.75%, specificity of 60%, and accuracy of 84.21% for detection of MM (Table 2).

The diagnostic values of PET/CT, SUVmean, and SUVmax in G1, *n* = 21 patients, of MM are shown in Table 3. SUVmean and SUVmax in all the 21 patients of initial staging were significantly higher in true positive than true negative or false-positive patients diagnosed by PET/CT.

An example for primary staging was a male patient aged 61 years, who complain of multiple left chest wall pigmented skin lesions proved to be malignant melanoma, nodular type, after surgical excision of one of them. Patient came for primary staging by PET/CT (Figs. 2, 3, and 4).

Our retrospective study evaluated besides the initial staging of primary tumor the utility of 18F-FDG PET/CT in detecting the recurrence in patients with malignant melanoma after primary surgical treatment. 18F-FDG PET/CT findings in G2, *n* = 11 patients, with suspicious of recurrent locoregional disease were true positive in 8 (72.72%) locoregional disease, true negative in 3 (18.18%), false positive in 1 (9.09%) patient, and false negative in 0 (0%) patients. PET/CT showed the sensitivity of 100%, specificity of 66.66%, positive

**Table 2** Sensitivity (Sens), specificity (Spec), accuracy, PPV, and NPV of PET/CT in initial staging in 21 malignant melanoma cases

		Malignant melanoma					Chi-square	
		TP	TN	FP	FN	Total	$\chi^2$	FE <i>P</i> value
PET/CT	<i>n</i>	15	3	2	1	21	5.915*	0.041*
	%	71.42	14.38	9.52	4.78	100		
ROC	PET/CT	<b>Sens</b>	<b>Spec</b>	<b>PPV</b>	<b>NPV</b>	<b>Accuracy</b>		
		<b>93.33</b>	60	88.23	75	85.71		

TP true +ve, FN false -ve, TN true -ve, FP false +ve, PPV positive predictive value, NPV negative predictive value,  $\chi^2$  chi-square test, FE Fisher Exact, *P* *P* value for comparing between the two studied groups

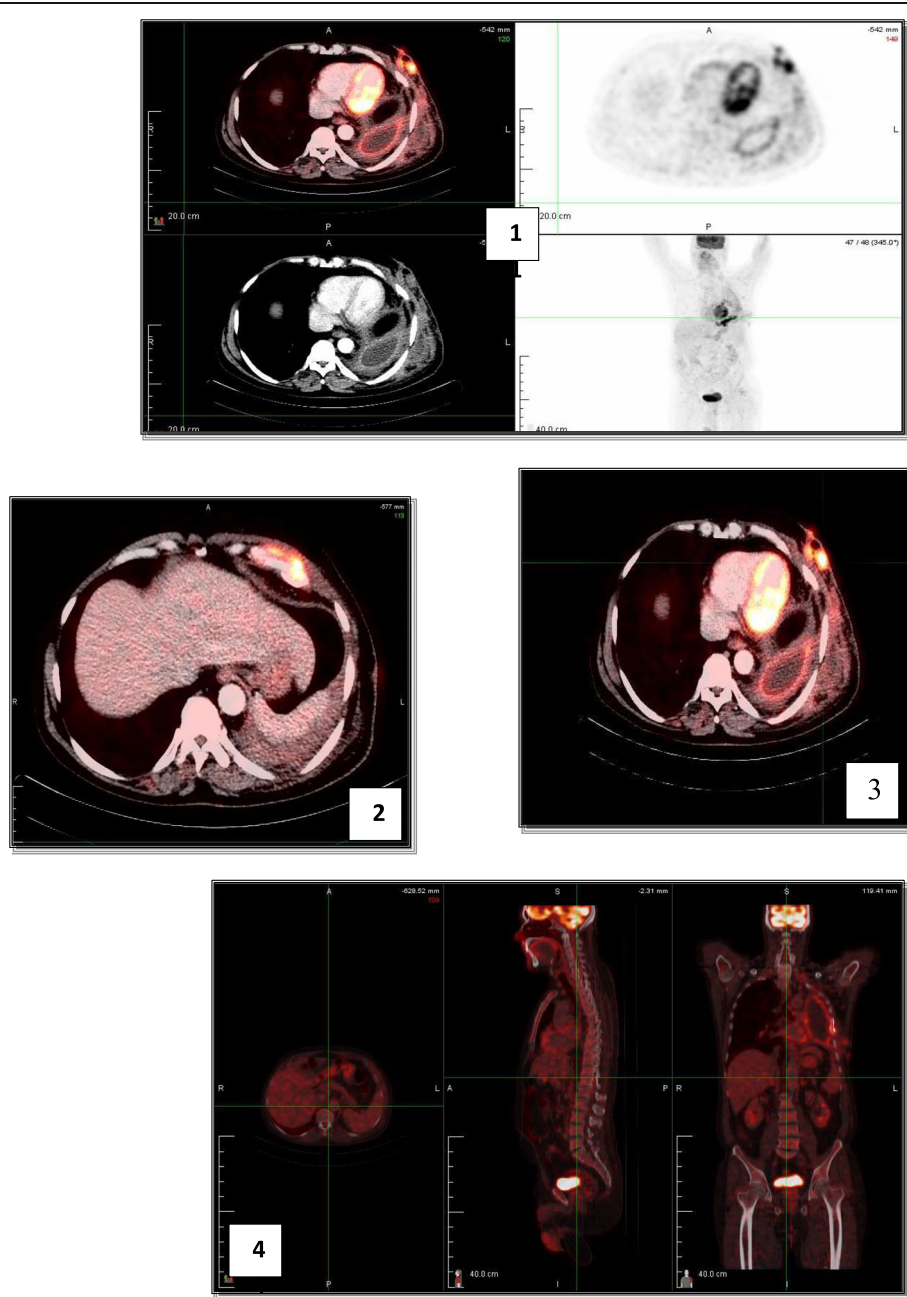
\*Significant

**Table 3** The diagnostic value of SUVmean and SUVmax for initial staging in G1, n = 21 malignant melanoma cases

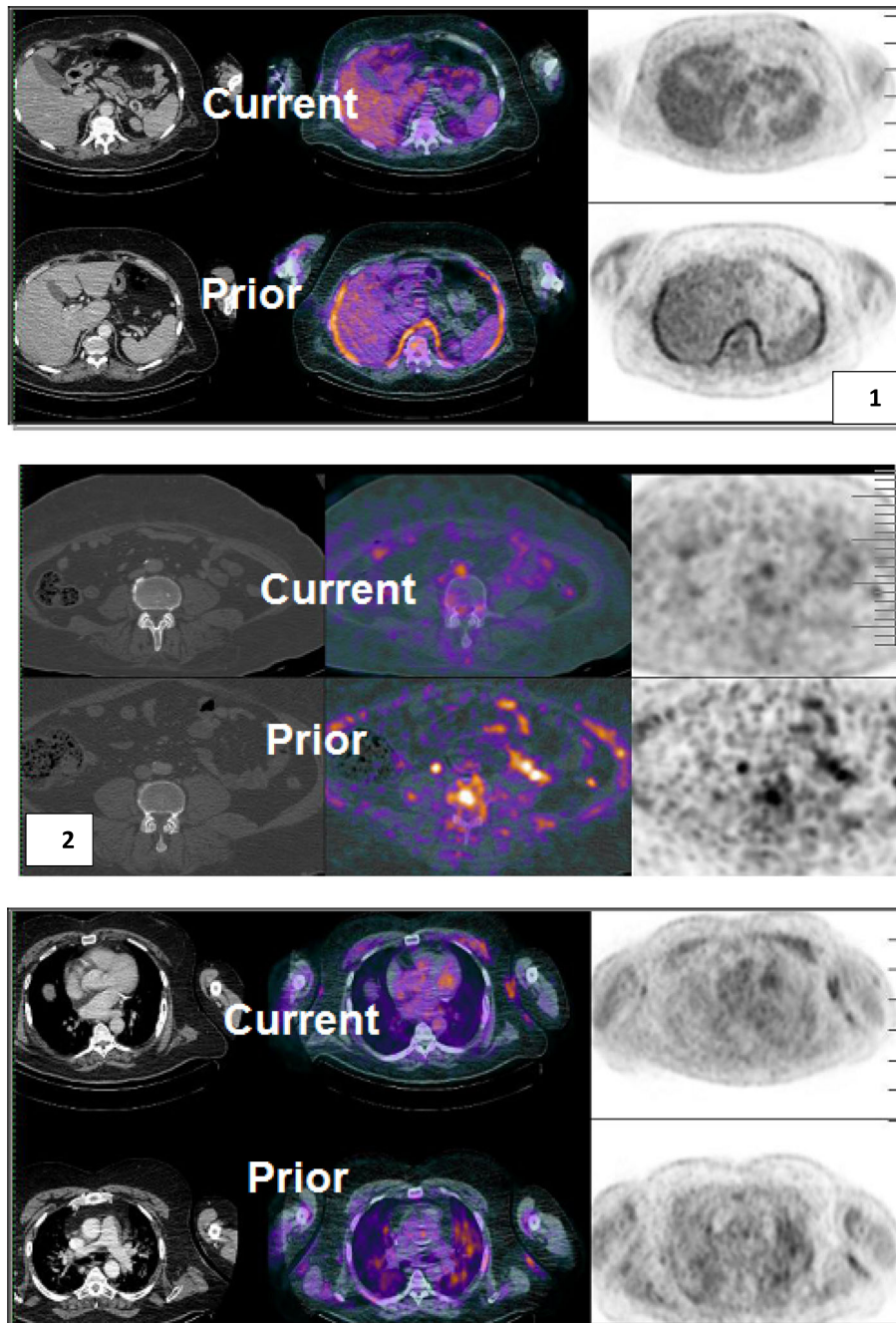
Prognostic factor	TP (n = 15)	TN (n = 3)	FP (n = 2)	FN (n = 1)	Sen	P value
SUVmean ± SD	8.4 ± 2.04	1.2 ± 0.5	4.4 ± 1.12	2.23 ± 04	79.02	0.044*
SUVmax	10.8 ± 2.14	1.2 ± 0.2	5.8 ± 2.09	2.23 ± 04	82.88	

TP true +ve, TN true -ve, FP false +ve, FN false -ve, Sen sensitivity

\*Significant



**Fig. 2** **1** Axial CT, PET, and PET/CT with MIP images showing FDG avid left anterior chest wall skin and subcutaneous lesions. **2** Axial PET/CT showing FDG avid left rib osteolytic lesion (ribs). **3** Axial PET/CT showing encysted hydro-thorax with peripheral activity of visceral and parietal pleura (lungs). **4** Axial, sagittal, and coronal PET/CT showing free other organs except for the skin, chest wall, and pleural FDG avid lesions



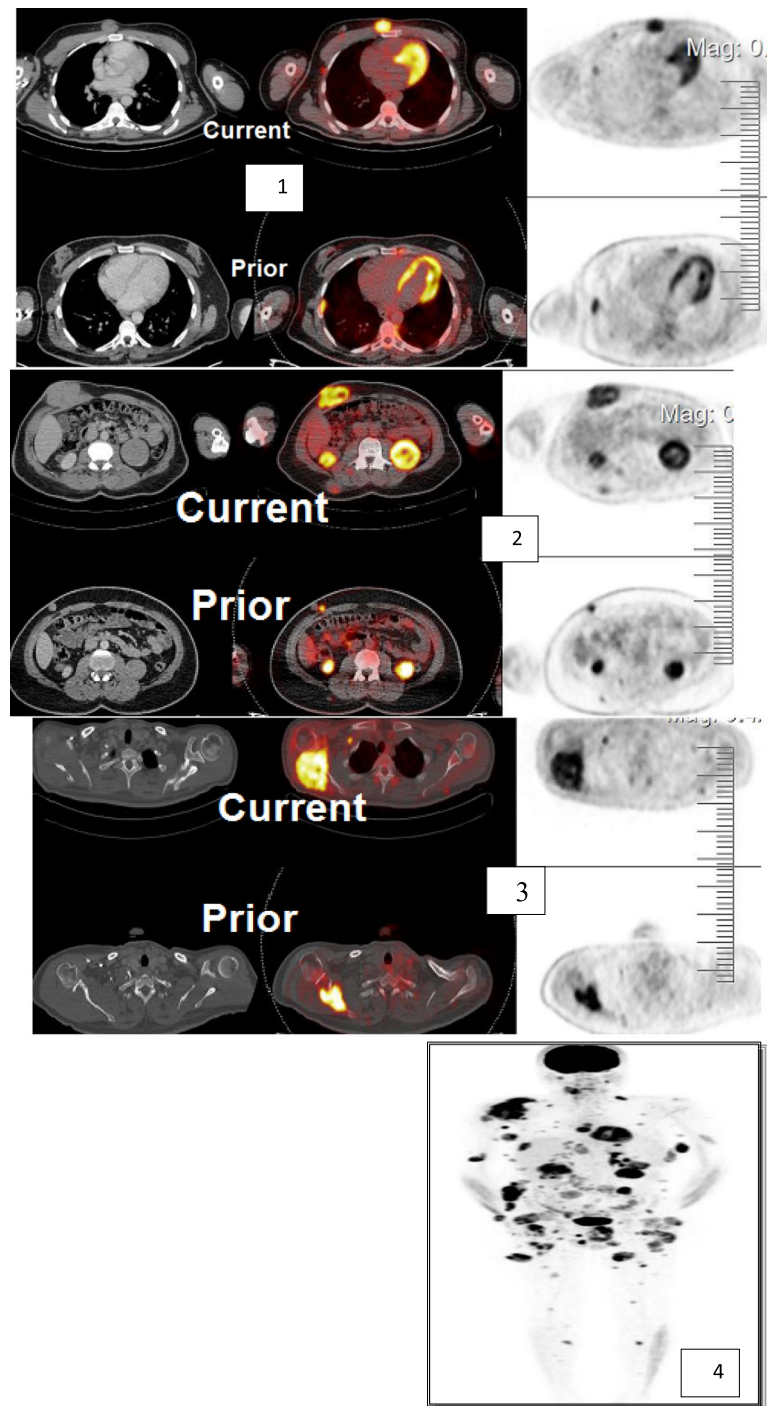
**Fig. 3** **1** Axial CT, PET, and PET/CT images showing regression of FDG avid chest wall lesions except for left anterior chest wall lesion (skin and subcutaneous tissue). **2** Axial CT, PET, and PET/CT images showing metabolic regression of FDG avid osseous lesions, involving sternum, vertebrae, pelvic bones, and femora. **3** Axial CT, PET, and PET/CT images showing metabolic regression of reticulonodular lung infiltration. Left chest wall skin nodular thickening at the operative bed with increased metabolic activity (locoregional recurrence)

predictive value of 88.88%, and negative predictive value of 100%, for detection of recurrent disease in melanoma patients (Table 4).

The metabolic activity was assessed by standardized uptake value (SUV) in G2,  $n = 11$ , patients with suspicious of recurrent locoregional disease. Table 5 showed

that both SUVmean and SUVmax were significantly higher in true positive than true negative or false-positive patients diagnosed by PET/CT (Fig. 3 1–3).

An example for suspicious of recurrent locoregional disease was a 70-year-old male patient with history of surgically removed left chest wall melanoma received



**Fig. 4** 1 Axial CT, PET, and PET/CT images showing newly developed FDG avid anterior chest wall lesion. Metabolic and morphologic progression of the lesion seen in the left postero-lateral lower chest wall. 2 Axial CT, PET, and PET/CT images showing progression in size of anterior abdominal wall lesion. 3 Axial CT, PET, and PET/CT images showing progression in size of right scapular lesion. 4 PET image showing peritoneal, hepatic, nodal, bone, and skin metastatic lesions

chemo- and radiotherapy. Patient came for restaging after suspicious locoregional recurrence (Fig. 3 1–3).

G3,  $n = 18$  patients, with clinically evident stage IV melanoma underwent whole body FDG-PET/CT scans

for follow-up and detection of metastatic disease after surgical excision of primary tumor and/or chemotherapy and radiotherapy. Their results were compared with reference standards. Fifteen patients out of 18 cases

**Table 4** Sensitivity (Sen), specificity (Spec), accuracy, PPV, and NPV of PET/CT in detection of recurrent disease in G2, n = 11 melanoma patients

		Malignant melanoma					Chi-square	
		TP	TN	FP	FN	Total	$\chi^2$	FE P value
PET/CT	n	8	2	1	0	11	6.273*	0.043*
	%	72.72	18.18	9.09	0	100		
ROC	PET/CT	Sens	Spec	PPV	NPV	Accuracy		
		100	66.66	88.88	100	90.90		

TP true +ve, FN false -ve, TN true -ve, FP false +ve, PPV positive predictive value, NPV negative predictive value,  $\chi^2$  chi-square test, FE Fisher Exact, P P value for comparing between the two studied groups

\*Significant

examined by PET/CT had variable extent of metastatic lesions showing either single or multiple metastatic lesions in different organs (lung, liver, bone, nodal, brain, or combination of more than one lesion) (Table 6).

The whole body FDG-PET/CT scans showed among 18 examined cases 15 true positive, 1 true negative, 2 false positive, and none false-negative scans for the detection of melanoma metastases, with sensitivity 100%, specificity 66.66%, overall accuracy 94.44%, positive predictive value 93.75%, and negative predictive value 100% (Table 7).

The mean and max metabolic activity was assessed by standardized uptake value (SUV) in all 18 patients of follow-up suspicion of distant metastases. Table 8 showed that both SUVmean and SUVmax were significantly higher in true positive than true negative or false-positive patients diagnosed by PET/CT and in cases of multiple metastases.

An example for metastatic melanoma was a 64-year-old male patient with history of metastatic melanoma, under follow-up after 6 months of chemotherapy (Fig. 4 1–4).

Follow-up study (stage IV) demonstrates as follows:

Newly developed hypermetabolic soft tissue, peritoneal, lymph nodal, and right diaphragmatic crus deposits.

Morphologic progression despite of metabolic regression of the osseous and left renal metastatic deposits as described.

Metabolic regression with no size change of the hepatic deposit.

Six out of 18 recurrent and metastatic MM patients died within 24 months. The dead patients were aged above 50 years, primary site of tumor located in the head and neck (3 patients), trunk (2 patients), and one in lower extremities. The tumor was of nodular type (5

patients) and acral lentiginous (1 patient). Five patients had multiple metastases in more than one site.

The overall survival (OS) of MM patients depend on age, the site, histological type, stage of tumor, recurrence, the number of metastases as well as SUVmax which represent prognostic factors.

Thus, melanoma specific survival (MSS) of MM patient with multiple metastasis was associated with a significantly shorter MSS than the single metastatic nodule ( $24.2 \pm 2.6$  vs  $38.8 \pm 7.8$  months,  $P = 0.01$ ). SUVmax > 2.9 was a significant prognostic factor for shorter MSS ( $23.4 \pm 3.5$  vs  $44.2 \pm 4.6$  months,  $P \leq 0.01$ ). Survival analysis after combining both multiple metastases and SUVmax > 2.9 demonstrated significantly shorter MSS (Table 9).

During the follow-up of the survived MM cases with metastatic disease (9 cases) to evaluate their treatment response after surgical excision and/or chemotherapy and radiotherapy, we found that four cases of distant metastases after 6 months showed regression of lesions size and its SUVmax, while the rest shows progression in lesions size and its SUVmax.

### Discussion

The purpose of this study was to assess the value of PET/CT for diagnosis, restaging, and follow-up of MM patients with curative intend. It was analyzed through a retrospective design. It aimed to develop a medical algorithm for PET in regular follow-up programs of CMM.

CMM staging is required for appropriate treatment decision-making. Autopsies of patients with known CMM revealed a higher frequency of metastases than regularly clinically reported, indicating that clinical evaluation and conventional imaging techniques (chest radiography, ultrasonography, computed tomography

**Table 5** The diagnostic value of SUVmean and SUVmax in 11 patients of suspicion of recurrent locoregional disease

Prognostic factor	TP (n = 8)	TN (n = 2)	FP (n = 1)	FN (n = 0)	Sen	P value
SUVmean $\pm$ SD	17.6 $\pm$ 3.02	0.9 $\pm$ 0.54	6.26 $\pm$ 1.12	0	100	0.041*
SUVmax	19.44 $\pm$ 4.21	1.2 $\pm$ 0.82	6.26 $\pm$ 1.12	0	100	

TP true +ve, TN true -ve, FP false +ve, FN false -ve, Sen sensitivity, Spec specificity

\*Significant



**Table 6** Distribution of metastases in different organs (n = 15)

Site of distant metastasis	Number of patients	Percentage (%)	Sex of patients	
			Male	Female
Lung	1	7.14	0	1
Liver	2	14.28	1	1
Bone	2	14.28	1	1
Nodal	1	7.14	1	0
Brain	1	7.14	1	0
Lung and liver	3	21.42	2	1
Lung, liver, bone, and nodal	3	21.42	2	1
Liver and bone	2	14.28	1	1

[CT], and magnetic resonance [MR] imaging) lead to underestimation of disease extent. Conventional imaging techniques will only reveal metastases when they are morphologically different from normal tissue in terms of size or structure [3, 11].

The present study revealed that malignant melanoma is much more common in males (n = 28.56%) than females (n = 22.44%) with mean age 55.94 + 13.04 years. The great number of cases was between 66 and 74 years more in males (9 cases) than females (8 cases). This is in harmony with the previous findings of Malik et al. [12], who showed during studying 54 patients that the clinical risk factors for malignancy are related to age and the mean age of their studied patients was 51.3 + 16.4 years. Previously, Frary et al. [13] showed during studying of 46 cases of MM that males were more common than females (26 males “56.53%” and 20 “43.47%” females), similar to our present findings.

The male sex predilection of skin cancer in Egypt could be explained by the fact that men represent the main workforce (outdoor work) with more risk for ultra violet exposure (predisposing factor of melanoma) than women as had previously mentioned by Hussein [14].

The primary sites for MM in our study were the head and neck (face) (36%), trunk (30%), extremities (30%), and groin (4%). This is in harmony with the previous findings of Daniesen et al. [15], who showed during studying 167 cases that the primary sites for MM

were the head and neck (35.3%), trunk (32%), and extremities (33%).

The present study showed that the vast majority of the patients had nodular melanoma (84%) followed by acral lentiginous melanoma (10%) then finally superficial spreading (6%). This was in harmony with the previous findings of Hussein [14] who found that compared to Western societies, melanomas among Egyptians differ in being: (1) rare neoplasms, (2) have a definite male sex predilection with older age incidence, and (3) of nodular growth pattern.

As in all cancers, accurate initial staging is essential for developing the appropriate treatment strategy. 18F-FDG PET/CT findings of G1, 21 patients, in our study for initial staging were compared with the reference standards and showed the sensitivity of 93.33%, specificity of 60%, and accuracy of 85.71% for primary staging.

SUVmean and SUVmax in all the 21 patients of initial staging were significantly higher in true positive more than true negative or false-positive patients diagnosed by PET/CT with high sensitivity 82.88%.

The two false-positive cases in our study were one inflamed epidermal cyst and the other had popliteal neurinoma. Our findings were similar to Essler et al. [16], who detected two false-positive patients, one had a popliteal neurinoma, and the other false-positive patient had a chronic lymphatic leukemia. The false-negative patient in our study had brain focal lesion which could not be

**Table 7** Sensitivity, specificity, accuracy, PPV, and NPV of PET/CT in detection of distant metastasis of G3, n = 18 melanoma patients

		Malignant melanoma				Total	Chi-square	
		TP	TN	FP	FN		χ <sup>2</sup>	FE P value
PET/CT	n	15	2	1	0	18	11.224*	0.002*
	%	83.33	5.55	11.11	0	100		
ROC	PET/CT	Sens	Spec	PPV	NPV	Accuracy		
		100	66.66	93.75	100	94.44		

TP true +ve, FN false -ve, TN true -ve, FP false +ve, PPV positive predictive value, NPV negative predictive value, χ<sup>2</sup> chi-square test, FE Fisher Exact, P P value for comparing between the two studied groups

\*Statistically significant at P ≤ 0.05

**Table 8** The diagnostic value of SUVmean and SUVmax for G3, *n* = 18 patients of suspicion of distant metastases

Prognostic factor	TP ( <i>n</i> = 15)	TN ( <i>n</i> = 2)	FP ( <i>n</i> = 1)	FN ( <i>n</i> = 0)	Sen	<i>P</i> value
SUVmean ± SD	28.6 ± 3.02	1.6 ± 0.4	7.28 ± 2.12	0	100	0.003*
SUVmax	32.4 ± 4.30	1.7 ± 0.9	9.46 ± 4.12	0	100	

TP true +ve, TN true -ve, FP false +ve, FN false -ve, Sen sensitivity, Spec specificity

\*Statistically significant at *P* ≤ 0.05

detected due to the high physiological glucose metabolism in the brain. Such findings supported the previous finding of Essler et al. [16], who detected false-negative results in two patients of brain metastases. This may be explained by brain hyperthermia. Hyperthermia might alter the follow-up of patient by ET-CT. We can overcome this problem by newly cooling system used practically in the brain cooling named by a zero-heat-flux Spot On sensor [17].

All G1 patients, *n* = 21, had surgical excision of lesions at primary sites, and 12 patients who had high SUVmax also received either chemotherapy or combination of chemotherapy and radiotherapy in addition to the surgical treatment according to level of metabolic activity. Our findings were nearly similar to those of Malik et al. [12], who found that in 54 patients that all of them had surgical excision of lesions at primary sites and 10 patients also received either chemotherapy or combination of chemotherapy and radiotherapy in addition to the surgical treatment.

18F-FDG PET/CT scan was done in the present study for 11 clinical suspicion patients of relapse after treatment (G2) and showed the sensitivity of 100%, specificity of 66.66%, positive predictive value 88.88%; negative predictive value 100%; and accuracy of 90.90%.

The reported maximum value (SUVmax) was 22, while the recorded minimum value was 6.26. SUVmax in all the suspicion patients of relapse was above 2.9 in recurrent cases with high sensitivity of 100%. Our findings coincided with those of Malik et al. [12], who 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. They recorded SUVmax above 2.7 in all their examined recurrent and metastatic cases.

Whole body PET-CT was done in the present study for G3, *n* = 18, case come with stage IV melanoma for detection of metastasis and show sensitivity of 100%, specificity of 66.66%, and overall accuracy of 94.44%. SUVmax was above 2.9 ranging from 22.4 to 34.6 in patients with distant metastasis. Our finding coincided with those of Holder et al. [18] who showed that PET is sensitive, 94.2%, and very specific, 83.3%, for identifying malignant melanoma; also, Akcali et al. [19] showed that PET is efficient in detecting melanoma with a high overall specificity of 92%, sensitivity of 91%, and accuracy of 92%. The false-positive results in our metastatic group (G3) were due to increased accumulation of FDG in some benign processes as inflammation or infection as had been previously detected by Long and Smith [20].

A number of study had suggested that for early stage of MM (I–II), PET-CT was of limited diagnostic value, due to its low sensitivity in detecting microscopic lymphatic disease. It had been posted that in danced stage of MM (III–IV) can be of great value by locating distant metastasis, thereby influencing treatment decision and informing prognosis [21].

Six of our 18 MM (G3) died within 24 months; the dead patients were aged above 50 years, primary site of tumor located in the head and neck. All six patients were stage IV and had distant metastases. Five of the patients had multiple metastases; this finding matched with Robinson and Roenigk [22] who showed that the old age was more affected which could be as a result of weakening of the immune system.

In our wok, we found that the overall survival (OS) of MM depended on the age, site, histological type, stage of tumor, number of metastasis as well as the SUVmax which present prognostic factor. This is similar to the finding of de Vries et al. [23].

**Table 9** Melanoma-specific survival of patients with metastases and maximum standardized uptake value

Prognostic factor	Variables	MSS months, mean + SD	<i>P</i> value
Number of metastases	Single metastatic nodules	18.8 ± 5.6	0.001*
	Multiple metastatic nodules	12.2 ± 2.6	
SUVmax	> 2.9	11.4 ± 3.5	0.001*
	< 2.9	22.3 ± 4.6	
SUVmax > 2.9 and multiple metastatic nodules	Absent	23.6 ± 2.8	0.001*
	Present	10.3 ± 3.7	

MSS melanoma-specific survival, SUVmax maximum standardized uptake value

\*Significant

Thus, melanoma specific survival (MSS) of MM patients with multiple metastasis was associated with a significantly shorter MSS than in the single metastatic nodule as shown in our results  $24.2 \pm 2.6$  vs  $38.8 \pm 7.8$  months,  $P = 0.01$ . In the present study,  $SUV_{max} \geq 2.9$  was a significant prognostic factor for shorter MSS ( $23.4 \pm 3.5$  vs  $44.2 \pm 4.6$  months,  $P = 0.01$ ). We found that survival analysis after combining both multiple metastasis and  $SUV_{max} \geq 2.9$  demonstrated significantly shorter MSS; this is matched with Malik et al. [12].

We found that five of our dead patients had multiple metastases. This was similar to the findings of Essler et al. [16] who compared the melanoma associated mortality risk of patients with different numbers of metastases.

From the forgoing, PET/CT scanning has high sensitivity and specificity for detecting late stages as III and IV metastatic melanomas. The CT component of PET/CT helps to establish the correct anatomical location of the lesions and to differentiate between physiological and non-physiological  $^{18}F$ -FDG uptake, thus facilitating appropriate interpretation of the PET scan and decreasing the numbers of false-positive and false-negative results.

Therefore, the main indication of PET/CT in cutaneous melanoma is to detect recurrence or to restage disease following the detection of recurrence, particularly in patients with high-risk melanoma who are candidates for resection with curative intent. As patients therapy that showed no response could be changed, saving the patients from ineffective therapy and associated toxicities and costs.

When patients are being considered for surgical resection of isolated distant metastatic lesions, FDG-PET/CT imaging is used to accurately assess disease extent. Additional lesions identified on FDG-PET/CT imaging make surgical resection unwarranted.

Advanced melanoma carries a poor prognosis, mandating development of new therapies. FDG-PET/CT imaging can provide an early indicator of response to therapy for melanoma patient.

Malignant melanoma patients need continuous follow-up by PET/CT which enhanced diagnostic performance in detection of the primary malignancy, in follow-up of high-risk patients and patients with suspected or known local or distant recurrence, and in restaging of patients with known distant metastatic disease to assess tumor response; thus, it is highly recommended to be imaging of choice especially in follow-up or postoperative. If PET/CT will be adding to routine follow-up program of CMM patients, it would be strongly helpful if the radiation could be restricted to an absolute minimum. New dosimetry studies performed with phantoms of identical characteristics, using thermoluminescent dosimeters

(TLDs) placed in regions close to the region where this study conducted, and identified lower dose values [24]

This study had many limitations: the nature of study as a retrospective, small number size of studied patients in each group, and high dose of radiation; we should use low-dose radiation CT if follow-up done as a protocol, high cost of PET-CT especially in developing countries.

One of most important limitation of the study did not identify the patients needed, and the other excluded from follow-up by PET-CT and did not identify the time schedule of follow-up; surveillance part of study is also needed to be extended over large number of patients.

## Conclusion

FDG-PET/CT imaging improved accuracy of in staging over other imaging methods that provides important prognostic information and has a significant impact on management and follow-up of patients with melanoma.  $SUV_{max}$  could be used as a prognostic factor for tumor response or progress as the higher  $SUV_{max}$  demonstrated especially at metastatic lesion was correlated significantly with shorter melanoma-specific survival rate. Further studies are highly recommend aiming to implant FDG-PET/CT in routine follow-up for certain cases of MM patients.

## Abbreviations

CMM: Cutaneous malignant melanoma; PET/CT: Positron Emission Tomography with Computed Tomography; PET: Positron Emission Tomography; MM: Malignant melanoma; AJCC: American Joint Committee on Cancer; TNM: Tumor nodal metastases; FDG: F-18-fluorodeoxyglucose; GLUT: Glucose transporters; SUV: Standardized uptake value; TP: True +ve; FN: False -ve; TN: True -ve; FP: False +ve; PPV: Positive predictive value; NPV: Negative predictive value; (\*): Significant;  $\chi^2$ : Chi-square test; FE: Fisher Exact;  $P$ :  $P$  value for comparing between the two studied groups; Sen: Sensitivity; Spec: Specificity; OS: The overall survival; MSS: Melanoma specific survival; CT: Computed tomography; MR: Magnetic resonance imaging

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Not applicable. Having advised of English editor and consulted with my co-author with your permission, we propose adjusting the title to PET/CT in restaging, prognosis, and recurrence in patients with malignant melanoma.

## Authors' contributions

KH analyzed and interpreted the patient data regarding the skin malignant melanoma disease. SA has a role in design. EM performed the statistical analysis. MH and RA performed the analysis and grouping of patients, follow-up of cases, and were the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

This prospective interventional study was carried out following the approval of the Research Ethical Committee of Faculty of Medicine, Tanta University, from November 2017 to September 2019, on fifty (50) patients age range

28–74 years with blood glucose levels below 150 mg/dL, histopathologically proven to have malignant melanoma. The reference number is “not applicable.”

Informed written consent was obtained from all participants prior to use of PET/CT after full explanation of the benefits and risks of the procedure. This consent is “not applicable.”

#### Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian. I accept and all authors to publish the paper.

#### Competing interests

No conflict of interest.

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