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Association of Tumor Metabolic Activity on PET/CT Scan with Pathological Characteristics in Patients with Malignant Melanoma

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Abstract

Background: Melanoma is one of the most serious types of skin cancer and one of the leading causes of cancer-related mortality worldwide.
Objectives: This study aimed to investigate the association between ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) scan findings and the pathological characteristics of primary tumors in patients with malignant melanoma.
Patients and Methods: In this cross-sectional study, the baseline data of 103 patients with cutaneous or mucosal melanoma (stage III or IV) were recorded, and tumor characteristics and PET/CT scan findings were analyzed. The association between each pathological finding and PET/CT results was also investigated.
Results: Patients without a free margin had a significantly higher mean standardized uptake value (SUV_{max}) of lung metastasis compared to patients with a free margin (3.12 vs. 1.69; P = 0.047). Also, patients with ulceration had a significantly higher mean SUV_{max} of lung metastasis compared to patients without ulceration (3.28 vs. 1.81; P = 0.041). Based on the results, increased primary tumor thickness was associated with a higher SUV_{max} of lung metastasis. However, there was no significant association between the metastasis type (single vs. multiple) and free margin, ulceration, or Ki-67 protein. The mean SUV_{max} of lung metastasis was significantly higher in mucosal melanoma compared to cutaneous melanoma. However, the mean SUV_{max} values of other metastases (bone, liver, and lymph nodes), even the primary lesion itself, were not significantly different between cutaneous melanoma and mucosal melanoma.
Conclusion: The primary tumor margin status, ulceration, tumor thickness, primary tumor location (cutaneous vs. mucosal), and the presence of lung metastasis were significantly associated with PET/CT scan findings.

Keywords: Malignant Melanoma, PET/CT, SUV_{max}, Tumor Characteristics

1. Background

Malignant melanoma is a well-recognized mucosal or cutaneous malignancy, with a high potential for an extensive and unexpected metastasis to different organs (1). The current staging/restaging methods are based on the lesion thickness, lymph node involvement, and metastatic status. Different imaging modalities, such as computed tomography (CT) scan, magnetic resonance imaging (MRI), and recently positron emission tomography/CT (PET/CT) scan, have been used as significant diagnostic tools, especially for more advanced diseases (stage III/IV) (2).

The survival rate of patients with malignant melanoma depends on the size and depth of the lesion, as well as the presence of regional and/or distant metastasis (3-5). Advanced malignant melanoma refers to stage III/IV of the disease according to the American Joint Committee on Cancer (AJCC) criteria and includes melanoma with nodal and/or distant metastasis (6, 7). Lymph node and distant metastases may be identified by clinical examination, sentinel lymph node biopsy (SLNB), and imaging techniques. Overall, early diagnosis and treatment can significantly improve prognosis and survival (8, 9).

^{18}F-fluorodeoxyglucose (FDG) PET/CT scan is based on the evaluation of cellular metabolism; the higher glucose metabolism of cancer cells compared to normal cells can

be very helpful in the detection of tumor lesions (10). FDG PET/CT scan is now considered a standard method for the initial diagnosis, staging, treatment planning, evaluation of treatment response, and tumor restaging after treatment for many cancers (11). Recent evidence suggests that FDG PET/CT parameters, including the maximum standardized uptake value (SUV_{max}), are associated with the prognosis of different malignancies. Although FDG PET/CT may be considered an ideal method for the detection of melanoma metastasis, there is still controversy regarding its clinical application. Some studies have demonstrated that FDG PET/CT is a sensitive and accurate method for staging of advanced melanoma (10, 12, 13). There are also few studies evaluating the association between pathological features and FDG PET/CT findings in patients with advanced melanoma (14). pathological features and immunohistochemical (IHC) markers have been integrated in melanoma staging, disease prognosis, and selection of new treatments (15, 16). Therefore, it can be interesting to determine the association between pathological features and FDG PET/CT findings.

2. Objectives

This study aimed to investigate the association between FDG PET/CT scan findings and tumor pathological features in patients with malignant melanoma.

3. Patients and Methods

In this cross-sectional study, the baseline information of adult patients (age > 18 years) with a definitive diagnosis of cutaneous or mucosal melanoma (stage III or IV according to the pathological findings and the AJCC criteria), who were admitted to Masih Daneshvari Hospital (Tehran, Iran) for FDG PET/CT scan during 2016 - 2021, was collected by reviewing their medical records. The demographic information of all patients, including age and sex, as well as their medical history, was also retrieved. The inclusion criteria were as follows: (1) age over 18 years; (2) a definitive diagnosis of advanced melanoma stage III or IV according to the AJCC criteria, confirmed by a histological evaluation; (3) availability of pathological and FDG PET/CT scan findings; and (4) a signed informed consent form. On the other hand, patients who met the following criteria were excluded from the study: (1) a concomitant malignancy or a history of malignancy in the last 10 years; (2) a history of systemic treatment for melanoma or metastasectomy; and (3) unwillingness to continue the study at any stage. The variables under study included age, sex, cutaneous versus mucosal lesions, primary tumor thickness, ulceration, tumor margin, metastasis, Ki-67, and SUV_{max}.

All PET/CT images were acquired using a Discovery 690 VCT system (GE Healthcare, Milwaukee, USA), equipped with a 64-slice CT scanner (LightSpeed VCT, GE Healthcare, Milwaukee, USA). The calculation of SUV_{max} was automatically performed on a 4.5 advantage PET/CT workstation in the defined region of interest (ROI) for all lesions. Finally, the association between each pathological feature and FDG PET/CT findings was investigated. This study was approved by our institutional review board (IRB) with the ethical code, IR.SBMU.MSP.REC.1399.564.

3.1. Statistical Analysis

Data were analyzed using SPSS version 22 (released in 2013, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). Frequency was calculated for qualitative variables, such as cutaneous versus mucosal lesions, ulceration, tumor margin, and metastasis, and for quantitative variables with a normal distribution, such as the primary tumor thickness, Ki-67, and SUV_{max}, the mean and standard deviation (SD) were calculated; the median value was compared if the distribution was not normal. Besides, the association of SUV_{max} and the frequency of metastases with the lesion size and diameter was examined using Pearson's correlation test. The mean values of the two groups were compared using Student's *t*-test and Mann-Whitney test. For multiple-group comparisons, one-way analysis of variance (ANOVA) or Kruskal-Wallis test (or median test) was used for parametric or non-parametric data, respectively. A P-value less than 0.05 was considered statistically significant.

4. Results

A total of 103 patients with malignant melanoma were included in this study, with a mean age of 54.7 $\pm$ 16.99 years. Sixty-four patients (62.1%) were male, and 39 (37.9%) patients were female. The baseline demographic and clinical characteristics of the patients are presented in Table 1.

The most common pathological types were acral lentiginous melanoma and nodular melanoma with frequencies of 53.2% and 34%, respectively. The mean thickness of the primary tumor was 5.03 mm, and the mean mitotic rate was 3.32 per mm^3. In most cases (44.7%), the

Table 1. The Basic Demographic and Clinical Characteristics of the Patients

Factors	No. (%)
Sex	
Male	64 (62.1)
Female	39 (37.9)
Reasons for PET scan	
Initial staging	24 (23.3)
Metastatic evaluation	46 (44.7)
Recurrence	2 (1.9)
Treatment response	11 (10.7)
Restaging	20 (19.4)
Primary tumor location	
Sinus	5 (5.0)
Limb	67 (67.0)
Anal	4 (4.0)
Eye	4 (4.0)
Scalp	11 (11.0)
Mouth	2 (2.0)
Chest	2 (2.0)
Esophagus	1 (1.0)
Abdomen	3 (3.0)
Vagina	1 (1.0)
Primary location	
Cutaneous	83 (83.0)
Mucosal	17 (17.0)
Brain metastasis	
Yes	2 (2.0)
No	100 (98.0)
Bone metastasis	
Yes	13 (12.7)
No	89 (87.3)
Lung metastasis	
Yes	49 (48.0)
No	53 52.0 ()
Liver metastasis	
Yes	11 (10.8)
No	91 (89.2)
Regional lymph node metastasis	
Yes	66 (65.3)
No	35 (34.7)
Other metastases	
Yes	48 (48.0)
No	52 (52.0)
Metastasis type	
No metastasis	18 (17.6)
Single metastasis	24 (23.5)
Multiple metastases	60 (58.8)
Type of pathology	
Nodular	16 (34.0)
Acral lentiginous melanoma	25 (53.2)
Superficial	1 (2.1)
Spindle	2 (4.3)
Epithelioid	2 (4.3)

Abbreviation: PET, positron emission tomography.

reason for FDG PET/CT request was metastasis evaluation. Lymph node metastasis was the most common type of metastasis, as reported in 65.3% of cases. The prevalence of bone, liver, and brain metastases was also estimated at 12.7%, 10.8%, and 2%, respectively. More than half of the patients (58.8%) had multiple metastases. The metastasis data were presented based on the current PET/CT findings, and no previous data were included. The mean SUV_{max} values for metastases and pathological features are shown in Table 2. There was a significant association between the SUV_{max} of lung metastasis and the primary tumor thickness (P = 0.029). Associations between the pathological features and the SUV_{max} of primary tumor and metastasis, based on Spearman's test, are described in Table 3.

The analysis of the association between the SUV_{max} and free margin revealed a significant association between the SUV_{max} of lung metastasis and free margin (P = 0.047). In other words, patients without a free margin had a significantly higher mean SUV_{max} of lung metastasis compared to patients with a free margin (3.12 vs. 1.69; P = 0.047). Regarding the association between the SUV_{max} and ulceration, a significant relationship was found between the SUV_{max} of lung metastasis and ulceration (P = 0.041). In other words, patients with ulceration had a significantly higher mean SUV_{max} of lung metastasis compared to patients without ulceration (3.28 vs. 1.81; P = 0.041). However, no significant association was observed between the SUV_{max} of each metastasis and regional lymph node involvement.

Moreover, the associations between the primary tumor location and pathological features are shown in Table 4. There was a significant association between the primary tumor location and the primary tumor thickness (P = 0.021). In other words, the mean primary tumor thickness in patients with mucosal involvement was significantly higher than that of patients with skin involvement (15.60 vs. 3.97; P = 0.021). In contrast, the mean Ki-67 index was significantly higher in patients with skin involvement compared to patients with mucosal involvement (22.0 vs. 1.0; P = 0.008). Nevertheless, no significant association was observed between the primary tumor location (cutaneous vs. mucosal) and the tumor mitotic rate.

Considering the association between the metastasis type (no metastasis vs. single or multiple metastases) and pathological features, no significant association was found between the metastasis type and free margin, ulceration, or Ki-67 index. Associations between the metastasis type and pathological features are demonstrated in Table 5.

Table 2. The Mean SUV_{max} for Each Metastasis and Pathological Feature

Parameters	Valid N	Mean ± SD	Median	25th percentile	75th percentile
Age	102	54.70 ± 16.99	56.50	42.00	68.00
SUV_{max} of involvement in the primary lesion	63	7.89 ± 5.83	6.10	3.20	10.50
SUV_{max} of brain metastasis	0	-	-	-	-
SUV_{max} of bone metastasis	12	5.50 ± 5.71	4.35	0.00	9.00
SUV_{max} of lung metastasis	87	2.80 ± 4.27	0.00	0.00	4.20
SUV_{max} of liver metastasis	83	0.76 ± 2.85	0.00	0.00	0.00
SUV_{max} of regional lymph node metastasis	100	3.80 ± 4.94	2.75	0.00	5.85
Primary tumor thickness (mm)	55	5.03 ± 7.61	4.00	1.60	5.00
Mitotic rate	25	3.32 ± 4.33	1.00	1.00	4.00
IHC marker: Ki-67	22	20 ± 20	20	1	30

Abbreviations: SUV, standardized uptake value; IHC, immunohistochemical assay; Ki-67, mitotic index indicating the number of cells dividing.

Table 3. Association Between Pathological Features and SUV_{max} of Primary Tumor and Metastasis

Variables	SUV_{max} of involvement in the primary PET	SUV_{max} of bone metastasis	SUV_{max} of lung metastasis	SUV_{max} of liver metastasis	SUV_{max} of regional lymph node metastasis
Spearman's correlation					
N	62	12	85	81	100
Primary tumor thickness (mm)					
Correlation coefficient	0.232	0.289	0.316	0.153	0.117
P-value	0.216	0.637	0.029 [a]	0.317	0.397
N	30	5	48	45	55
Mitotic rate					
Correlation coefficient	-0.250		-0.014	-0.271	0.015
P-value	0.410		0.956	0.276	0.943
N	13	1	19	18	25
IHC marker: Ki-67					
Correlation coefficient	0.039	-1.000 [b]	0.070		0.273
P-value	0.900	NA	0.789		0.230
N	13	3	17	15	21

Abbreviations: SUV, standardized uptake value; PET, positron emission tomography; IHC, immunohistochemical assay.
[a] Statistically significant.
[b] An inverse association.

Table 4. The Association Between the Primary Tumor Location and Pathological Features

Variables	Primary location						P-Value [a]
	Cutaneous			Mucosal			
	Valid N	Mean ± SD	Median	Valid N	Mean ± SD	Median	
Primary tumor thickness (mm)	50	3.97 ± 4.47	3.00	5	15.60 ± 19.60	9.00	0.021 [a]
Mitotic rate	24	3.42 ± 4.39	1.00	1	1.00	1.00	0.401
IHC marker: Ki-67	20	22 ± 20	20	2	1 ± 0	1	0.008 [a]

Abbreviation: IHC, immunohistochemical assay.
[a] Statistically significant.

Table 5. Association Between Metastasis Type and Pathological Features

Variables	Metastasis type									P-Value
	No metastasis			Single metastasis			Multiple metastases			
	Valid N	Mean ± SD	Median	Valid N	Mean ± SD	Median	Valid N	Mean ± SD	Median	
Primary tumor thickness (mm)	9	3.26 ± 1.97	4.00	11	2.74 ± 1.51	3.00	35	6.21 ± 9.30	4.00	0.322
Mitotic rate	5	2.80 ± 2.17	2.00	5	3.20 ± 3.90	1.00	15	3.53 ± 5.13	1.00	0.887
IHC marker: Ki-67	6	14 ± 14	10	5	22 ± 21	30	10	25 ± 24	20	0.659

Abbreviation: IHC, immunohistochemical assay.

Table 6. Association Between the Primary Tumor Location and SUV of Primary Tumor and Metastasis

Variables	Primary location						P-value
	Cutaneous			Mucosal			
	Valid N	Mean ± SD	Median	Valid N	Mean ± SD	Median	
SUV_{max} of involvement in the primary PET	52	7.40 ± 5.49	5.85	8	11.10 ± 7.68	8.10	0.123
SUV_{max} of lung metastasis	10	4.03 ± 4.89	2.50	2	12.85 ± 3.75	12.85	0.049 [a]
SUV_{max} of bone metastasis	70	2.61 ± 4.16	0.00	15	3.38 ± 4.64	0.00	0.476
SUV_{max} of liver metastasis	68	0.63 ± 2.35	0.00	14	1.48 ± 4.69	0.00	0.401
SUV_{max} of regional lymph node metastasis	82	3.33 ± 4.26	2.50	15	6.80 ± 7.46	6.00	0.135

Abbreviations: SUV, standardized uptake value; PET, positron emission tomography.
[a] Statistically significant.

Moreover, the relationship between the primary tumor location and the SUV values of primary tumor and metastases is shown in Table 6. The mean SUV_{max} of lung metastasis was significantly higher in mucosal melanoma compared to cutaneous melanoma. However, the mean SUV_{max} values of other metastases (bone, liver, and lymph node), and even that of the primary lesion itself, were not significantly different between the two groups (Figures 1 & 2).

5. Discussion

This study aimed to investigate the association between FDG PET/CT findings and the pathological features of primary tumors in melanoma patients. The results revealed that patients with a free margin had a significantly lower SUV_{max} of lung metastasis compared to patients without a free margin. Patients with ulceration also had a significantly higher SUV_{max} of lung metastasis compared to those without ulceration. There was also a significant relationship between the SUV_{max} of lung metastasis and the primary tumor thickness. In other words, an increase in the primary tumor thickness was associated with a higher SUV_{max} of lung metastasis.

Moreover, the present findings demonstrated that patients with single metastasis and multiple metastases had higher SUV_{max} values than those without metastasis. A significant association was also observed between the location of melanoma lesion (cutaneous versus mucosal), the level of Ki-67 protein (an IHC marker), and the primary tumor thickness. These results indicate that increased tumor thickness, ulceration, and margin involvement on pathology reports are likely to be associated with higher SUV_{max} values, especially in lung metastases. Therefore, it can be interpreted that higher SUV_{max} values are potentially associated with more significant high-risk pathological features and a poorer prognosis.

A high SUV in lymph node metastasis is an independent negative prognostic factor for disease-free survival; however, it has no impact on the overall survival (17). In a previous study, Rasmussen et al. examined the association between the expression of IHC markers, including Bcl-2, β-tubulin-1 and 2, EGFR, Ki-67, and glutathione-s-transferase,

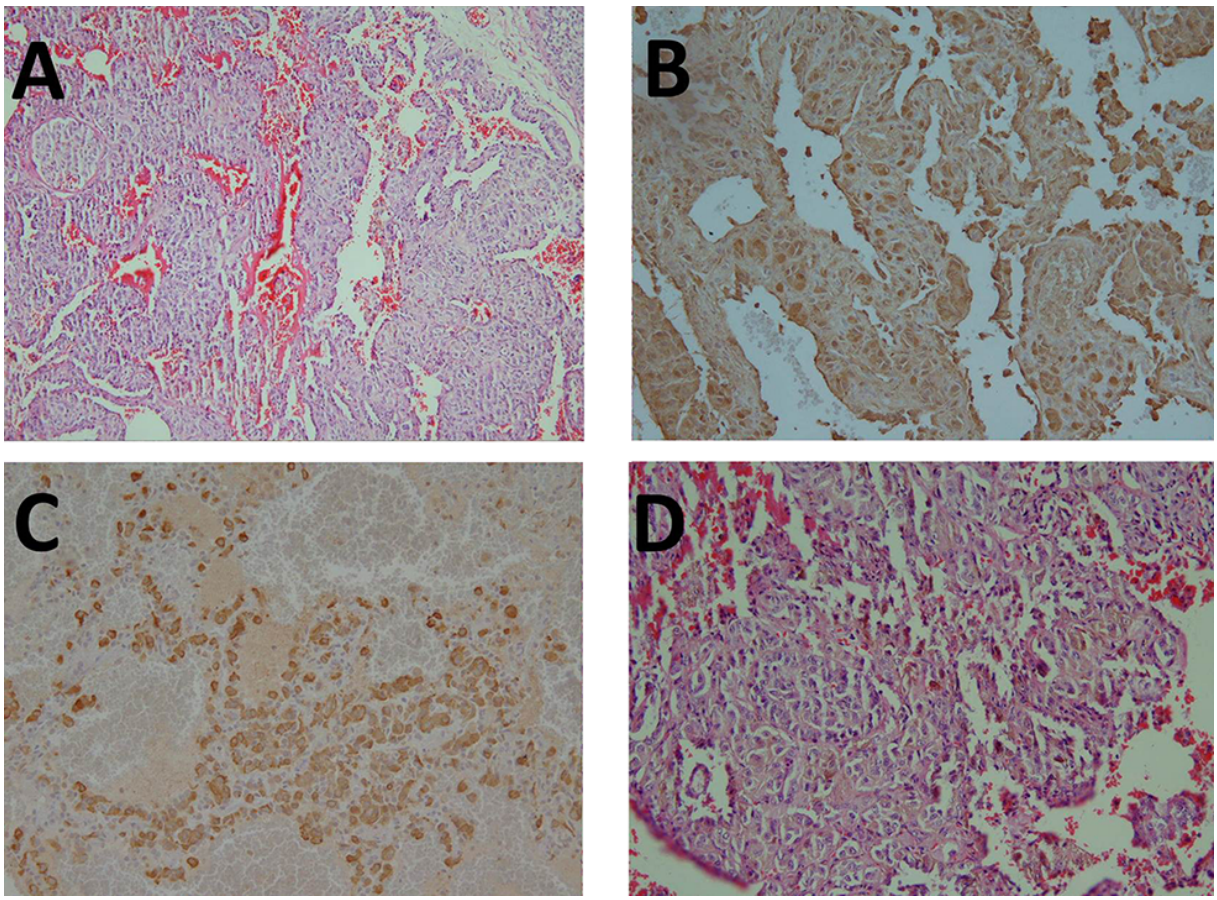

Figure 1. A, A lung tissue with interstitial infiltration of atypical cells with a clear cytoplasm; B, Some tumor cells are positive for S-100 protein; C, All cells are positive for human melanoma black-45 (HMB45) as a monoclonal antibody that reacts against an antigen in melanocytic tumors, such as melanomas; D, Some pigment deposition is present.

and PET parameters in head and neck squamous cell carcinoma. They found a significant negative relationship between the SUV_{max} and the expression of Bcl2 and β-tubulin I and II. They concluded that there was a significant relationship between the expression of IHC parameters in primary tumors and FDG PET/CT results (18).

In another study, Bitencourt et al. evaluated the relationship between the expression of IHC biomarker and PET results in 50 patients with breast cancer. Their findings showed a significant positive relationship between the SUV_{max} and histology type, histology grade, molecular subtype, tumor diameter, mitotic index, and Ki-67 expression (19). It is generally accepted that some pathological features of melanoma patients are associated with positive FDG PET/CT findings. These pathological features include a mitotic rate > 3/mm^2, tumor thickness > 4 mm, regional lymphadenopathy, and bleeding/ulceration (5, 20). PET is more useful in detecting distant metastasis than regional metastasis, given the established role of SLNB (21).

FDG PET/CT may be a highly useful tool for the surveillance of melanoma patients. For the follow-up of patients with advanced stage melanoma (stage III/IV), the National Comprehensive Cancer Network (NCCN) guidelines recommend imaging (including PET/CT) every three to 12 months to screen for recurrence or metastatic disease. However, routine imaging to screen asymptomatic cases is not recommended after three to five years (22). According to our literature review, few researchers have investigated the association between FDG PET/CT scan findings and pathological features of patients with malignant melanoma. This may be considered the novelty of our study, although we could only demonstrate few associations, and further studies are strongly recommended.

In conclusion, based on on the results of the present

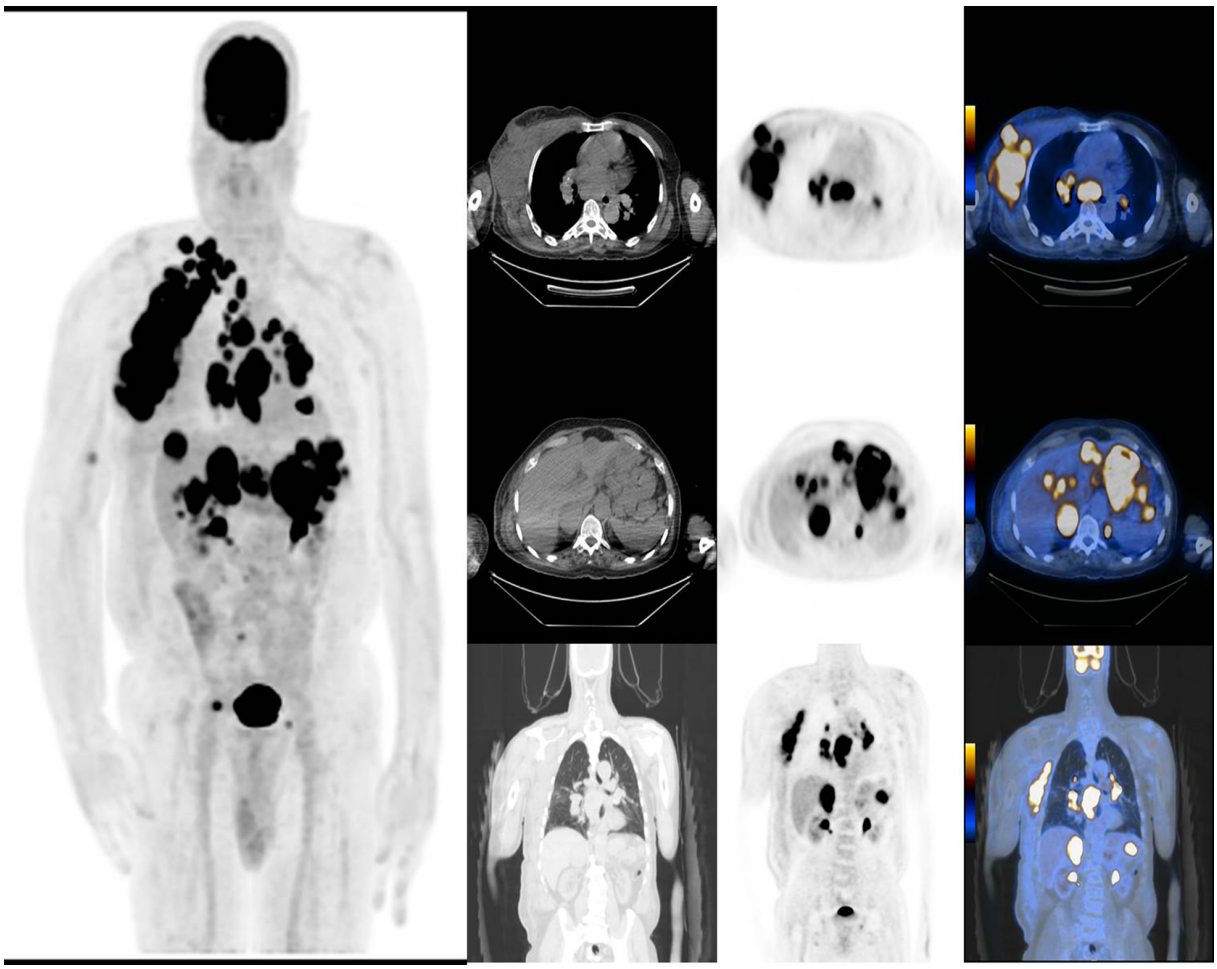

Figure 2. A very aggressive case of melanoma with extensive lung, liver, and lymph node metastases. The maximum intensity projection (MIP) image is on the left, and the selected axial and coronal images on the right are merged together.

study, there may be an association between FDG PET/CT findings and some pathological features of melanoma patients. Factors, such as the primary tumor thickness, cutaneous versus mucosal tumor location, metastasis type, free margin, and ulceration, were significantly associated with PET/CT findings. Further multicenter and community-based studies are recommended with a larger sample size to obtain more reliable results.

Footnotes

Authors' Contributions: Mohammad Reza Erfaghi: Data collection, patient coordination, writing the first draft of the manuscript; Abtin Doroudinia: Revising the manuscript, adding images, and pathology consultation; Mehrdad Bakhshayesh Karam: Supervision of the study; and Habib Emami: Data analysis.

Conflict of Interests: There is no conflict of interest to declare.

Data Reproducibility: Raw and processed data are available upon request if required. All patient data are kept confidential, and the results are reproducible.

Ethical Approval: This study was approved by our institutional review board (IRB) with the ethics code, IR.SBMU.MSP.REC.1399.564 (link: ethics.research.ac.ir/EthicsProposalView.php?id=172379).

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Informed Consent: All participating patients signed an

informed consent form.

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