

The value of FDG PET/CT in the management of malignant melanoma: a retrospective study

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ABSTRACT

Objectives: Positron Emission Tomography with Computed Tomography (PET/CT) is a valuable imaging method for the restaging of malignant diseases as well as the evaluation of treatment outcomes. As melanoma lesions are mostly FDG-avid, whole-body 18F-fluorodeoxyglucose (18F-FDG) PET/CT imaging modality can be used to determine the spread of the tumor. In the present study, we intended to share our clinical experience with FDG PET/CT in malignant melanoma patients under different kinds of treatment.

Methods: In this retrospective study, the data sets of 122 patients who had surgical resection of known primary tumors, all of which were histopathology-proven malignant melanoma, were analyzed. All patients underwent baseline 18F-FDG PET/CT scan no sooner than 45 days and at least once after surgery. Clinical information, radiological imaging, histopathology, and treatment modalities were noted for all patients, and 18F-FDG PET/CT findings were examined.

Results: All patients were histopathology-proven and 47 of them had acral lentiginous, 37 nodular, 23 amelanotic, and 15 atypical malignant melanoma. Local recurrence was detected by 18F-FDG PET/CT in 13 (10.6%; 3 male, 10 female) of the 122 patients, and the mean recurrence time after diagnosis was 3 ± 1.4 years. 10 patients with brain and bone metastases underwent radiotherapy. 19 patients with lung, bone, and hepatic metastases received chemotherapy and 22 patients immunotherapy.

Conclusions: Malignant melanoma is a type of skin cancer that may involve any organ. In localized cases, complete surgical resection may be adequate for a cure. If diagnosed with the latter type, the whole body of the patient must be examined.

Keywords: FDG PET/CT, malignant melanoma, postoperative recurrence, restaging

The worldwide incidence of malignant melanoma has increased over the past decades [1]. Like other malignancies, melanoma is well-known for local recurrence as well as distant metastasis, which occur through lymphatics and the bloodstream. The treatment of melanoma patients has to be based on the metastatic status of the disease.

The incidence of melanoma, the most common type of skin cancer, is increasing faster than any other

potentially preventable cancer [1]. Most melanoma cases are diagnosed at an early stage; some patients have metastatic disease at presentation, and others develop metastases after their first definitive treatment. Patients with metastatic melanoma should undergo a detailed evaluation before treatment in order to assess the extent of the disease.

The metastases of malignant melanoma are widespread compared to other tumors, and clinicians

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should be aware of different patterns of metastatic involvement. Skeletal muscle or solitary bone metastases are more frequently observed in patients with advanced melanoma, as evidence of systemic spread.

The combination of metabolic and structural information provided by PET/CT has a significant impact on patient management and survival prediction. The diagnostic value of 18F-FDG PET for the follow-up of patients with malignant melanoma has been reported with a sensitivity and specificity of 96% and 92%, respectively [1, 2]. PET/CT can be used for staging and reassessment of metastatic malignant melanoma.

METHODS

Patient Population

The present study analyzed the data sets of 122 patients who admitted to Gülhane Training and Research Hospital Department of Nuclear Medicine between January 2016 and January 2020. Among those patients, 57.4% (n = 70) were female, 42.6% (n = 52) were male, and the mean age was 46.9 ± 14.2 years. They had surgical resection of known primary tumors, all of which were histopathology-proven malignant melanoma. All patients underwent baseline 18F-FDG PET/CT scan no sooner than 45 days and at least once after surgery. The study was approved by the Ethics Committee of Gülhane Training and Research Hospital, Ankara, Turkey.

Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Acquisition

Similar to the protocol specified in the study by Malik *et al.* 18F-FDG PET/CT scan was performed on all patients with blood glucose < 200 mg/dl after at least 6 hours of fasting [3]. The scanning was achieved 45–60 min after the IV injection of 370 MBq (~10 mCi) of 18F-FDG using dedicated hybrid scanners (Discovery 710 or Discovery STE-16; GE Healthcare, Milwaukee, Wisconsin, USA). A vertex-to-toe low-dose scout CT (120 kV, 10 mA) was acquired. Contrast enhancement CT followed by 3D-PET scan was performed in caudocranial direction with an acquisition period of 2 min per bed position using the time-of-flight technique. The reconstructed attenuation-corrected PET, CT, and fused images were

reviewed.

The scans were retrospectively assessed by two nuclear medicine physicians who were aware of the clinical findings of the patients. Any positive findings in the form of focal tracer uptake on 18F-FDG PET were anatomically localized on contrast-enhanced CT images. The maximum standardized uptake values (SUVmax) for semi-quantitative assessment were obtained by assigning a region of interest over the lesion with the highest tracer uptake.

Statistical Analysis

SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. The predictive values of 18F-FDG PET/CT in detecting recurrence and metastasis in patients with malignant melanoma were compared at different periods of treatment with regard to localization of the primary tumor, age, and gender.

RESULTS

Patient Characteristics

In the present study, the scans and clinical data of 122 patients (70 female, 52 male, mean age 46.9 ± 14.2 years) were analyzed retrospectively. All patients were histopathology-proven and 47 of them had acral lentiginous, 37 nodular, 23 amelanotic, and 15 atypical malignant melanoma. The primary tumor was localized in 42 patients (34.4%) in the lower extremity, in 17 (13.9%) in the upper extremity, in 20 (16.4%) in the trunk, in 38 (31.1%) in the head or neck, and in 5 (4.1%) in the pelvis. Table 1 and Table 2 represent the lesion types by localization and lesion localization by gender.

Outcome of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Clinical information, radiological imaging, histopathology, and treatment modalities were noted for all patients, and 18F-FDG PET/CT findings were examined. The lesions not proven by pathology were excluded. Local recurrence was detected with 18F-FDG PET/CT in 13 (10.6%; 3 male, 10 female) of the 122 patients, and the mean recurrence time after diagnosis was 3 ± 1.4 years. The mean SUVmax of recurrent lesions was 5.08 ± 3.08 g/dl. Local recurrence according to localization is presented in Table 3.

Table 1. Lesion type by lesion localization

	Lesion Localization						Total n (%)
	Lower extremity n (%)	Upper extremity n (%)	Back n (%)	Chest n (%)	Head-neck n (%)	Pelvic n (%)	
Acral lentiginos type	33 (27.00)	11 (9.00)	1 (0.80)	1 (0.80)	1 (0.80)	0 (0.00)	47 (38.50)
Noduler type	7 (5.70)	5 (4.10)	3 (2.50)	5 (4.10)	14 (11.50)	3 (2.50)	37 (30.30)
Amelanocitic type	0 (0.00)	1 (0.80)	3 (2.50)	1 (0.80)	18 (14.80)	0 (0.00)	23 (18.90)
Atypic Melanositic Melanoma	2 (1.60)	0 (0.00)	3 (2.50)	3 (2.50)	5 (4.10)	2 (1.60)	15 (12.30)
Total	42 (34.40)	17 (13.90)	10 (8.20)	10 (8.20)	38 (31.10)	5 (4.10)	122 (100)

The mean follow-up time of patients without recurrence was 4 ±2.4 years. Locoregional lymph nodes were detected in 99 patients, brain metastasis was seen in 10 (8.2%), lung metastasis in 9 (7.4%), bone metastasis in 10 (8.2%), and intramuscular metastatic lesions in 8, all of which were histopathology-proven. 6 patients had distant metastasis to the liver, and 1 to the parotid gland. Multiple peritoneal metastases were detected in 1 patient.

PET/CT imaging identified a) focal, and b) diffuse

FDG uptake by the thyroid gland, which were correlated with thyroiditis through ultrasound and thyroid function tests (Fig. 1).

The mean SUVmax of metastatic lung lesions (n = 9) was 5.17 ± 3.89 g/dl, bone lesions (n = 10) 5.9 ± 3.49 g/dl, and muscle lesions (n = 8) 9.18 ± 3.51 g/dl. Ten patients with brain and bone metastases underwent radiotherapy. Nineteen patients who had lung, bone, and hepatic metastases with multiple unresectable lesions given chemotherapy and 22 patients

Table 2. Lesions' localizations by gender

	Lesion Localization						Total n (%)
	Lower Extremity n (%)	Upper Extremity n (%)	Back n (%)	Chest n (%)	Head-neck n (%)	Pelvic n (%)	
Male	21 (17.20)	2 (1.60)	6 (4.90)	3 (2.50)	16 (13.10)	4 (3.30)	52 (42.60)
Female	21 (17.20)	15 (12.30)	4 (3.30)	7 (5.70)	22 (18.00)	1 (0.80)	70 (57.40)
Total	42 (34.40)	17 (13.90)	10 (8.20)	10 (8.20)	38 (31.10)	5 (4.10)	122 (100)

Table 3. Local recurrence according to localization

Localization	Locally recurrence		
	Yes n (%)	No n (%)	Total n (%)
Lower extremity	8 (6.6)	34 (27.9)	42 (34.4)
Upper extremity	0 (0.0)	17 (13.9)	17 (13.9%)
Back	0 (0.0)	10 (8.2)	10 (8.2%)
Chest	2 (1.6)	8 (6.6)	10 (8.2%)
Head-neck	3 (2.5)	35 (28.7)	38 (31.1%)
Pelvic	0 (0.0)	5 (4.1)	5 (4.1%)
Total	13 (10.7)	109 (89.3)	122 (100%)

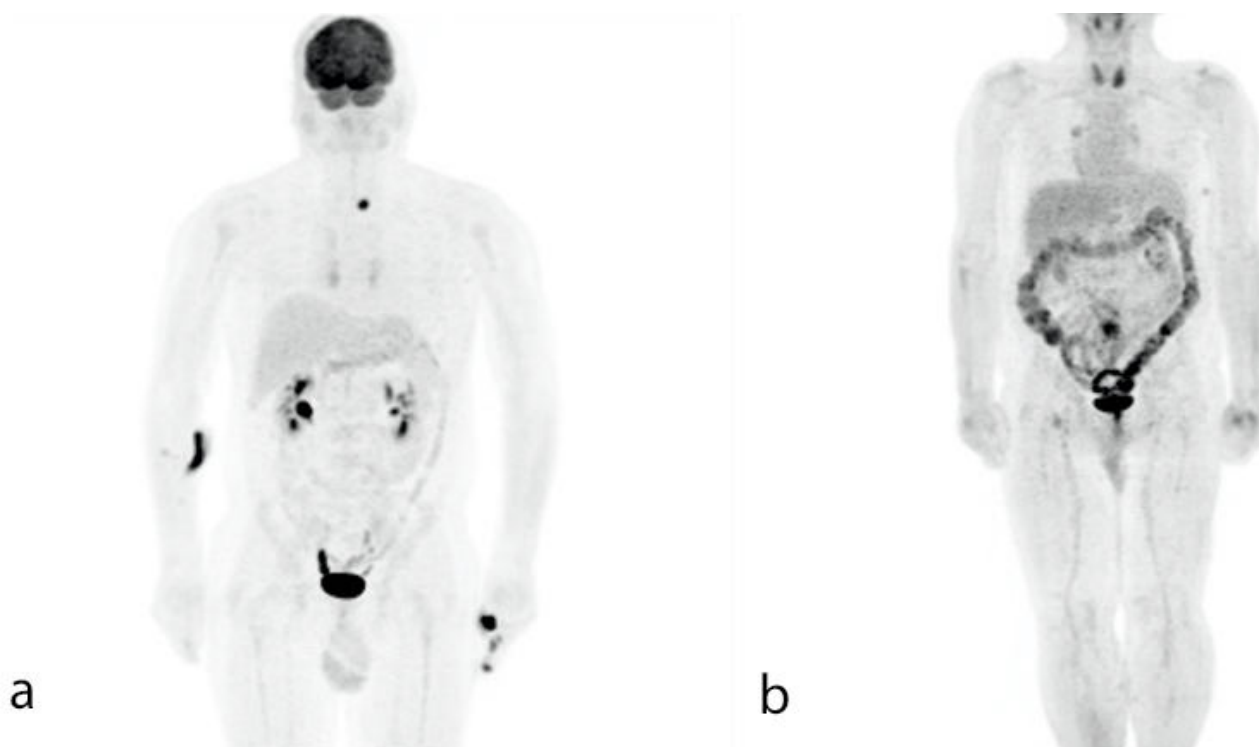


Fig. 1. Malignant melanoma patients who received immunotherapy. PET/CT imaging identified (a) focal, and (b) diffuse FDG uptake by the thyroid gland, which were correlated with thyroiditis through ultrasound and thyroid function tests.

were given immunotherapy. Parotid gland metastases with recurrent tumor foci were surgically resected. After resection, the patients were treated with chemotherapy and immunotherapy protocols.

DISCUSSION

Malignant melanoma patients have follow-up examinations every 3 to 6 months for at least 3 years after surgery. Whole-body ^{18}F -FDG PET/CT is a valuable diagnostic imaging modality for detecting distant metastasis from malignant melanoma [1, 2].

Differentiation between scar tissue and new or recurrent tumor after surgery is challenging. PET/CT provides benefits in estimating tumor extent when considering surgical resection, especially in entities with high glucose consumption, which is often the case in malignant melanoma [4]. FDG is not cancer-specific as it is also trapped in tissues with high glycolytic activity. Due to the high rate of false-positive findings associated with this phenomenon, additional imaging or, if possible, pathological assessment should be considered. In the present investigation, the lesions were histopathology-proven. The SUVmax

cutoff value of 2.2 was used to estimate recurrence in patients. All patients underwent surgical excision of the primary melanoma lesions before ^{18}F -FDG PET/CT, and SUVmax was determined for the recurrent lesions. The mean SUVmax of locally recurrent melanoma lesions was 5.08 ± 3.08 g/dl. These results pertained to histopathologically proven lesions, while false-positive FDG PET/CT findings were excluded. Residual metabolic tumor activity in the surgical site could not be ruled out, since the granulation tissue formed in wound healing leads to moderate FDG accumulation but at a lower level than in malignant processes. We recommended reassessment for 17 patients, and 13 turned out true-positive. Correlation with the patient's history and other imaging modalities may be necessary for correct diagnosis.

Cancer patients have an approximately two-fold risk of developing additional primary cancer compared to cancer-free patients of the same sex and age [5]. In our present study, second primary malignancy was present in 5 patients. 4 were free of metastasis from malignant melanoma, such as rectosigmoid, breast, hard palate, and endometrial cancer. Non-small cell lung cancer was detected in 1 patient.

Muscle metastases from malignant tumors are rare

[6]. Solitary skeletal muscle metastases are less common than multiple skeletal muscle metastases on 18F-FDG PET/CT imaging. Herring *et al.* [6]. reported on a series of 15 patients with skeletal muscle metastasis, of which only 2 of the primary tumors were melanoma. Gómez Portilla *et al.* [7] reported a case of isolated rectus abdominis metastasis from melanoma. In the present investigation, 8 patients had intramuscular metastatic lesions; 1 was solitary, and 4 had multiple subcutaneous nodules. The mean SUVmax of muscular metastatic lesions was 9.18 g/dl.

There is limited literature on the relationship between location of lesion and age and gender. Gillgren *et al.* [8] mentioned that melanoma lesions occur more often on the trunks of men and in the lower extremities of women [8]. In the present study, the lower extremity was the most common site, followed by head and neck, and the upper extremity. Gender did not differ significantly in the lower extremity group, but the ratio of female to male was higher for the other regions. In addition, lung (n = 7) and bone (n = 7) metastases were more frequent in women. Our investigation also showed that the majority of the patients had acral lentiginous (38.5%, n = 47) and nodular melanoma (30.3%, n = 37), followed by amelanotic (18.9%, n = 23) and atypical (12.3%, n=15) melanoma.

Bone is a site of metastatic spread from melanoma, but this usually occurs in patients with already-widespread metastasis. Therefore the bone must be considered as a site for late-onset metastasis. Brountzos *et al.* [9] reported on a series of 28 patients with bone metastases from melanoma, and some other clinical studies have shown that bone metastases from malignant melanoma are less frequent than liver or brain metastases. In our investigation, bone metastasis was detected in 9 patients who already had lung metastasis, and 3 of these had liver metastasis as well. All cases of bone metastasis were multifocal, and 1 was solitary spinal metastasis from pelvic malignant melanoma.

Since melanoma pathology features a wide variety of clinical presentations, FDG PET/CT promises improved detection of metastases and better assessment of treatment decisions. Bastiaannet *et al.* [10] reported that FDG PET/CT offered the most accurate combination in diagnosis, restaging a large proportion of patients so as to reduce the number of inappropriate surgical procedures. In the present study, FDG PET/CT findings showed that liver and parotid gland

lesions were resected. However, the lung lesions in our case series were multiple and accompanied by mediastinal lymph nodes, compelling the clinicians to non-surgical treatment strategies.

A combination of chemotherapy, radiotherapy, and targeted molecular therapy may result in the most effective treatment modality for metastatic melanomas [11, 12]. Immunotherapy is an efficient therapeutic strategy in melanoma due to the high immunogenicity of that type of tumor. A major feature of immunotherapy is its success in cases with resistance to radiation therapy and cytotoxic chemotherapy [11-13]. Twenty-two of our patient population received immunotherapy with immune checkpoint inhibitors (ICI). All were metastatic melanomas; 8 had lung and bone metastases, 8 had intramuscular and 6 had hepatic metastatic lesions. Immune-related adverse events (such as colitis, thyroiditis, etc.) should be taken into account in the interpretation of FDG PET/CT images, as these are associated with false-positive findings especially in the colon and the thyroid. In the present study, high thyroid metabolic activity was detected in 3 patients among the ones who received immunotherapy. Thyroid ultrasound was performed on these patients, and no thyroid nodules or biochemical thyroid disorders were observed. With regard to colonic activity, it is reported that focal FDG uptake has up to a 70-80% probability of unveiling corresponding abnormal histopathological observations [14]. In our study population, 1 patient had focal uptake of FDG localized to the rectosigmoid junction, for whom colonoscopy was recommended. Rectosigmoid cancer was proven by histopathology in that case.

For patients who are suspected to have metastatic disease the approach to imaging should focus on symptomatic sites. Radiologic evaluation is therefore more likely to be more clinically useful if it is focused on disease site and symptoms. Nodal status and lung metastasis are critical for decision-making regarding adjuvant therapy. Contrast-enhanced CT scanning is a widely used radiographic method for evaluating intrathoracic lesions as well as the metastatic disease of liver. MRI is the preferred imaging modality when brain metastases, soft tissue and bony lesions are suspected. Metastatic lesions involving the gastrointestinal tract are relatively common and abdominopelvic CT scan can evaluate the GI tract but the patients are often asymptomatic.

Our study focused on the implications of metastatic malignant melanoma localization. Anatomic imaging modalities, physical examination and laboratory signs are used in long-term follow-up of these patients. Among those patients, PET/CT imaging is not preferred due to its radiation exposure and high cost until the patients become symptomatic. Anatomical and metabolic status of the whole body lesions can be obtained with PET/CT in one session to define the total body burden of metastases, as well as to provide more specific information regarding specific sites, such as the lung, mediastinum, and abdomen. FDG PET/CT, is a preferred modality for treatment response and in the term of recurrence. Involvement of skin or subcutaneous tissue may be the first sign of metastatic disease; PET/CT can be more accurate for the detection of multifocal abnormalities even in the long-term follow-up these patients.

Limitations

The present study has some limitations: (a) The retrospective design of the study has constrained the patient population. (b) There may have been misjudgments in the evaluation of clinical images by the physicians. (c) The patient cohort was from a single center, which may have influenced the results. (d) The patients' staging FDG PET/CT scans were not included, and this may have affected the recurrence time.

CONCLUSION

Metastatic behavior of malignant melanoma is generally unpredictable because the sites of metastasis are widespread compared to other tumors. The choice of appropriate treatment approach for melanoma requires accurate localization of the site, number, and size of metastases. Our investigation showed that 18F-FDG PET/CT yielded enhanced diagnostic performance in malignant melanoma with suspected recurrence.

Authors' Contribution

Study Conception: AÇ; Study Design: AÇ, Sİ; Supervision: AÇ, Sİ; Funding: AÇ, Sİ; Materials: AÇ, ÜNG; Data Collection and/or Processing: AÇ, Sİ; Statistical Analysis and/or Data Interpretation: AÇ, Sİ; Literature Review: AÇ, ÜNG; Manuscript Prepara-

tion: AÇ, Sİ and Critical Review: AÇ, Sİ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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REFERENCES

- Roses DF, Karp NS, Oratz R, Dubin N, Harris MN, Speyer J, et al. Survival with regional and distant metastases from cutaneous malignant melanoma. *Surg Gynecol Obstet* 1991;172:262-8.
- Reinhardt MJ, Joe, AY, Jaeger U, Huber A, Matthies A, Bucerius J, et al. Diagnostic performance of whole-body 18FDG PET/CT imaging for N- and M-staging of malignant melanoma: experience with 250 consecutive patients. *J Clin Oncol* 2006;24:1178-87.
- Malik D, Sood A, Mittal BR, Basher RK, Bhattacharya A, Singh G. Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in restaging and prognosis of recurrent melanoma after curative surgery. *World J Nucl Med* 2019;18:176.
- Garcia GA, Fernandez F, Satue E, Buelta L, Val-Bernal J. Metastasis of malignant neoplasms of skeletal muscle. *Rev Esp Oncol* 1984;31:57-67.
- Anwar H, Sachpekidis C, Winkler J, Kopp-Schneider A, Haberkorn U, Hassel JC, et al. Absolute number of new lesions on 18F-FDG PET/CT is more predictive of clinical response than SUV changes in metastatic melanoma patients receiving ipilimumab. *Eur J Nucl Med Mol Imaging* 2018;45:376-83.
- Herring CL, Harrerlson JM, Scully SP. Metastatic melanoma with an unknown primary. *Br J Plast Surg* 1990;43:367-8.
- Portilla G, Cruz A, Juan N, Malo P, Lopez de Heredia E, Larrañaga M, et al. Isolated rectus abdominis metastasis from melanoma, an extremely rare case. *Int J Surg Case Rep* 2016;26:121-3.
- Gillgren P, Månsson-Brahme E, Frisell J, Johansson H, Larsson O, Ringborg U. Epidemiological characteristics of cutaneous malignant melanoma of the head and neck--a population-based study. *Acta Oncol* 1999;38:1069-74.
- Brountzos E, Panagiotou I, Bafaloukos D, Kelikis D. Bone metastases from malignant melanoma; a retrospective review and analysis of 28 cases. *Radiol Oncol* 2001;35:209-14.
- Bastiaannet E, Oyen WJ, Meijer S, Hoekstra OS, Wobbes T, Jager PL, et al. Impact of [18F] fluorodeoxyglucose positron emission tomography on surgical management of melanoma patients. *Br J Surg* 2006;93:243-9.
- Schumacher TN, Schreiber RD. Neo antigens in cancer immunotherapy. *Science* 2015;348:69-74.
- Sadozai H, Gruber T, Hunger RE, Schenk M. Recent suc-

cesses and future directions in immunotherapy of cutaneous melanoma. *Front Immunol* 2017;8:1617.

13. Tawbi HAH, Forsyth PA, Algazi AP, Hamid O, Hodi FS, Moschos SJ, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to

the braIn: Results of the phase II study CheckMate 204. *J Clin Oncol* 2017;35(Suppl):9507.

14. Gutman F, Alberini JL, Wartski, M, Vilain D, Le Stanc E, Sarandi F, et al. Incidental colonic focal lesions detected by FDG PET/CT. *AJR Am J Roentgenol* 2005;185:495-500.



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