Acta Dermatovenerol Croat 2025;33(3):114-119 ORIGINAL SCIENTIFIC ARTICLE

Predictive Value of Preoperative Positron Emission Tomography/Computed Tomography (PET/CT) in Staging of Patients with High-Risk Melanoma

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ABSTRACT Accurate staging of high-risk melanoma patients is imperative to ensure effective and appropriate therapy but also to estimate the potential risk of recurrence. Despite numerous studies previously conducted, no consensus has been reached on the optimal posttreatment follow-up method for high-risk melanoma patients. There are no clear indications for PET/CT in follow-up or initial staging of clinically asymptomatic high-risk melanoma patients. The aim of our study was to determine the predictive value of preoperative PET/CT in staging of such patients and its implication on further therapeutic decisions.
A retrospective cohort study of 85 patients with T3 and T4 melanoma without clinical signs of nodal involvement or distant metastases was conducted. Patients underwent PET/CT as a part of preoperative staging and results were compared with SLNB.
In this study combined sensitivity and specificity of PET/CT for identifying regional and metastatic disease were 54% and 98%, respectively. The positive predictive value (PPV) of PET/CT was 95% while negative predictive value (NPV) was 71%. Preoperative PET/CT changed the treatment plan for 26 patients (31%)
Our study showed that PET/CT certainly has a role in the preoperative staging of high-risk melanoma patients, but it also requires a mandatory sentinel lymph node biopsy afterwards.

KEYWORDS: melanoma; PET/CT, high risk; preoperative; staging

INTRODUCTION

The incidence of melanoma has increased significantly on a global scale over the past few decades. Despite greater knowledge of this disease and numerous preventive campaigns that have been held over the past years, the incidence of this malignant tumour has risen faster than any other cancer since the 1950s in most developed countries (1). Only in 2020 there were more than 320,000 new melanoma cases worldwide (2).

Melanoma prognosis is highly dependable on the stage of the disease at initial diagnosis with 5-year survival rate of 99.4% for localized melanoma, 68% for regional melanoma, and 29,8% survival rate for disseminated disease (3). Even though melanoma shows an unpredictable pattern of spread to regional lymph nodes and visceral organs, if detected early, it can be curable after surgical excision. However, despite complete removal, high-risk resected melanomas have a significant rate of both local and distant

Acta Dermatovenerol Croat
2025;33(3):114-119

recurrence, sometimes with signs of extended disease already at the time of diagnosis. Such high-risk patients, even though usually asymptomatic, require adequate initial staging as well as follow-up for early disease relapse detection.

Despite numerous studies previously conducted, no consensus has been reached on the optimal post-treatment follow-up method for high-risk melanoma patients. Whole-body positron emission tomography (PET) is a non-invasive, high resolution imaging method that is often used for confirmation of clinical suspicion of metastases or evaluation of recurrent melanoma. Due to its lack of anatomical resolution, it is most often combined with diagnostic computed tomography (CT) in evaluation of melanoma as well as other oncological diseases. Despite its high sensitivity and specificity, which are superior to those of conventional imaging methods, PET/CT has not been included in recommendations or guidelines for routine follow-up of melanoma patients and it is most often used according to clinical indication (4,5). Its role in initial staging of clinically asymptomatic high-risk melanoma patients has not yet been established as well. The aim of our study was to determine the predictive value of preoperative PET/CT in staging of patients with high-risk melanoma and its implication on further therapeutic decisions for such patients. Additionally, we wanted to investigate the sensitivity of PET/CT for positive lymph node confirmed by sentinel lymph node biopsy (SLNB) which is the golden standard for detecting regional nodal melanoma metastases.

MATERIALS AND METHODS

PATIENTS

This study is a retrospective analysis of all high-risk melanoma patients at the Department of Dermatology and Venereology at Sestre milosrdnice University Hospital Centre in Zagreb, Croatia who underwent PET/CT as a part of preoperative staging in a three-year period, between January 2019 and December 2021. In all patients, PET/CT was done prior to SLNB so that the results of these two methods could be compared. The patients did not present with any clinical signs of nodal involvement or distant metastases at the time they were referred for PET/CT.

We considered only patients with high-risk primary lesions of at least 2 mm thickness, i.e., stage T3 and T4 patients according to the latest 8th American Joint Committee on Cancer classification (AJCC) (5). The study also included 2 patients with melanomas thinner than 2 mm (and above 1 mm) with other unfavourable histological features, such as large share of regression, lymphovascular or perineural invasion.

PET/CT imaging

The PET/CT scan was performed in fasting patients 60 minutes after the intravenous administration of fluorine-18 fluorodeoxyglucose (FDG) injection (180-370 MBq). Blood sugar and creatinine levels were checked before the scan and before the administration of radiopharmaceutical. CT imaging was performed immediately after PET-imaging with the patient exactly in the same position. Both modalities involved imaging in craniocaudal direction from the base of the skull to the level of toes. In 2019, the images were made using hybrid PET/CT scanner Philips Gemini TF 64, and in 2020 and 2021 using Philips Vereos PET/CT scanner. The images were analysed visually and semiquantitatively by calculating maximum standardized uptake value (SUVmax), defined as the ratio of activity per millilitre of tissue to activity in the injected dose corrected for decay and for the patient's body weight.

Clinical outcome

Patients' information was obtained from the hospital information system. All PET/CT findings were classified as true positive, false positive, true negative, and false negative. A true positive PET/CT result was defined as a finding highly suspicious for metastatic melanoma that proved to be a metastatic melanoma on further radiologic, cytologic or histologic evaluation. A false positive PET/CT result was defined as a finding highly suspicious for metastatic melanoma in a patient that had no evidence of disease progression on further evaluation and required no further treatment. A false negative result represented a PET/CT finding with no detected pathological accumulation of FDG indicative of metastatic melanoma after which further evaluation, most often sentinel lymph node biopsy, revealed a nodal or visceral metastasis. A true negative result was a finding in which no pathological accumulation of FDG was observed and SLNB was negative as well.

Diagnostic performance of PET/CT was expressed in terms of sensitivity, specificity, positive predictive value (PDV) and negative predictive value (NPV).

Sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB) is a diagnostic method in which the sentinel or "guardian" lymph node is detected, surgically removed, and sent for a histopathological and immunohistochemical analysis. In our patients that underwent SLNB, a lymphoscintigram was obtained on the same day of the pro-

Table 1: Patient and melanoma characteristics (n=85).

Gender		Histology	
male	48	ulceration	68
female	37	mitotic rate (mm^2) - range	2-50
		regression	4
Melanoma localization		microsatellites	4
head and neck	17	lympho-vascular invasion	5
trunk	32	perineural invasion	1
extremities	36		
Tumour thickness			
<2 mm	2	>10 mm	10
2-4 mm	21	unknown (T_x)	1
4-10 mm	51		

cedure to determine the first lymph node located on the direct drainage pathway from the primary lesion to the regional lymph pool. A 99m-technetium with activity of 18.5-30 MBq was used as a radiopharmaceutical and injected intradermally around the primary tumour. Upon completion of lymphoscintigraphic imaging, the localization of the sentinel lymph node was marked with a radioactive marker under a gamma camera in two projections and the location of the node was then checked with a gamma probe with appropriate sound and numerical signal. The node localization on the skin was marked with an indelible colour as a guide mark for a surgeon. After the surgical extirpation of the sentinel lymph node under general or spinal anaesthesia, successful lymph node extirpation was checked above the resected area with a gamma probe. The lymph node/s were sent for a histopathological and immunohistochemical analysis.

RESULTS

TUMOUR RESULTS

In this study, we evaluated 85 patients with high-risk melanomas, confirmed by histopathological and immunohistochemical analysis, who underwent PET/CT as a part of preoperative staging. The study included 48 (56.5 %) male and 37 (43.5%) female patients. The average age of patients was 66.4 ± 13.7 (range 32-92). Seventeen melanomas (20.0%) were located on the head and neck, 32 (37.6%) on the trunk, and 36 (42.4%) on the extremities. A more detailed review by localization can be seen in figure 1. The average

Table 2: Sentinel lymph node biopsy (SLNB) results.

	Yes	No
SLNB	63 (74%)	22 (26%)
Positive SLNB	29 (46%)	34 (54%)
Positive SLN and a positive node on PET/CT	11 (38%)	18 (62%)

tumour thickness was 6.25 ± 3.8 mm (range: 1.49-21 mm). One patient had a large, inoperable melanoma located on the heel of the foot in which the maximum tumour thickness could not be established histologically. Sixty-eight (80.0%) melanomas were histologically ulcerated, and the average mitotic rate was 11.25 per millimetre square (range 2-50). As for additional histological features, 4 (4.7%) melanomas showed microsatellites, 4 (4.7%) showed regression, 5 (5.9%) melanomas showed lympho-vascular invasion, and one (1.2%) perineural invasion (Table 1.).

PET/CT RESULTS

In all our patients PET/CT was done approximately 5-6 weeks after the primary excision. Positive PET/CT scans were identified in 22 (25.9%) patients with high-risk melanoma. Specifically, pathological FDG accumulation was detected in 2 local sites (near primary melanoma), 19 regional sites (lymph nodes), and 5 distant sites. Out of the total number of positive PET/CT findings, only one (4.5%) was false positive, i.e., a metastatically altered retroclavicular lymph node was suspected which was later shown to be lymphoid hyperplasia on cytology.

Other 21/22 positive PET/CT scans proved as true positive after further diagnostic evaluation. In 15 patients with positive regional lymph nodes, an ultrasound and cytological puncture of the lymph node were performed to confirm the presence of a

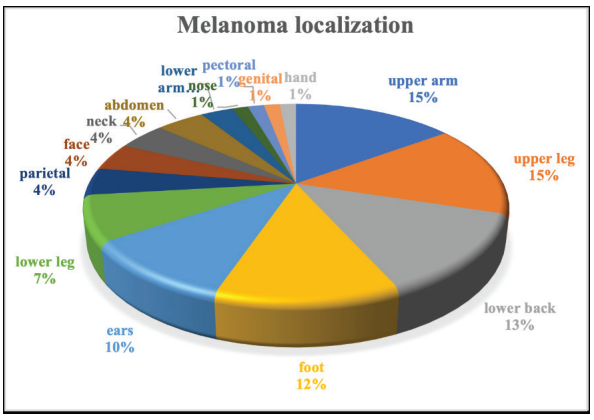

Figure 1. Detailed data of melanoma localization.

Acta Dermatovenerol Croat
2025;33(3):114-119

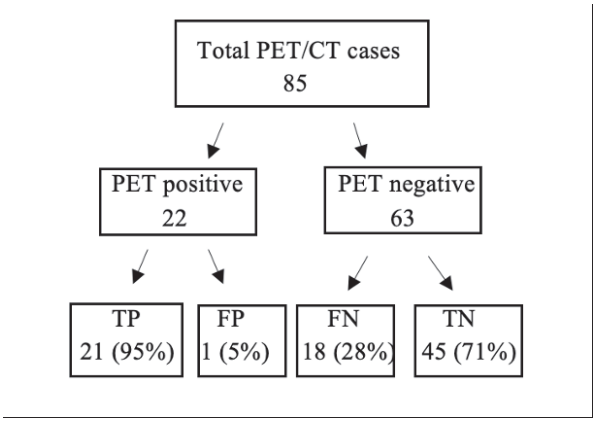

Figure 2. Metastases according PET/CT and SLNB.

nodal metastasis. Thirteen patients then underwent regional lymph node dissection of which 8 patients later received adjuvant targeted BRAF/MEK inhibitor therapy, and one patient underwent adjuvant radiotherapy. One patient with a solitary lung metastasis was treated surgically while in 4 patients with disseminated metastatic diseases immunotherapy was initiated. One patient with an inoperable primary melanoma and positive regional lymph nodes was also treated with immunotherapy while two patients; one with regional and one with disseminated diseases, refused any further treatment.

Out of 63 (74.1%) negative PET/CT scans, 45 (71.4%) were confirmed as true negative with SLNB, while 18 scans (28.6%) were false negative, i.e., preoperative PET/CT scan showed no pathological accumulation of FDG, but SLNB showed a metastasis in one or more regional lymph nodes (Figure 2).

Among those 18 patients, 2 were subsequently treated with immunotherapy, 2 with radiotherapy, 4 with combined targeted therapy (2 of them previously underwent regional lymph node dissection), one patient refused further treatment, and in 8 patients (with micrometastases and without capsule invasion) no active treatment was performed, only regular follow-up. Interestingly, in one patient SLNB showed an axillar lymph node micrometastasis of a previously resected breast cancer who then underwent complete left axillar dissection.

In 12 (14.1%) patients, PET/CT showed incidental tumours that required further evaluation. Nine patients had benign tumours - 3 had a colon adenoma, one patient had Whartin tumour of the parotid gland, one had uterine leiomyoma, and 4 patients had suprarenal adenomas. In three patients, PET/CT showed incidental malignant tumours – one patient had a bladder cancer, one had a primary lung cancer, and one had a primary breast cancer.

SLNB RESULTS

Following PET/CT, 63 patients (74.1%) underwent sentinel lymph node biopsy (SLNB) - a routine diagnostic procedure for patients with melanomas of thickness equal or higher than 0.8 mm, according to latest American Joint Committee on Cancer (AJCC) classification. Twenty-two patients (25,9%) did not undergo SLNB; 8 (9.4%) patients because PET/CT scan showed dissemination of the disease, 10 (11.8%) patients older than 85 years because of risks of general anaesthesia, and 3 (3.5%) refused further diagnostic and therapeutic procedures. In one patient (1.2%) the sentinel lymph node could not be detected with lymphoscintigraphy.

Among 63 patients that underwent SLNB, 29 (46.0%) patients had a positive result, i.e., a metastasis in one or more regional lymph nodes, and 34 (53.0%) patients had a negative SLNB. Out of the 29 patients that had a positive SLNB result, 18 patients had a negative PET/CT in which no pathological accumulation of FDG was detected, but all of them had micrometastases of diameter less than 1.2 mm (Table 2).

In our study, the sensitivity and specificity of PET/CT for detecting melanoma metastases were 54% and 98%, respectively. The positive predictive value (PPV) of PET/CT was 95% while the negative predictive value (NPV) was 71%.

Due to preoperative PET/CT findings, 13 patients with regional disease proceeded directly to therapeutic lymph node dissection while in one patient with inoperable melanoma and positive regional lymph nodes immunotherapy was initiated. In 5 asymptomatic patients, PET/CT scan showed a disseminated disease and thus enabled the early initiation of systemic and surgical therapy.

DISCUSSION

Accurate staging of high-risk melanoma patients is imperative to ensure effective and appropriate therapy but also to estimate the potential risk of recurrence. Today's recommendations for monitoring such high-risk patients include regular dermatological examinations with obligatory dermoscopy of all cutaneous and mucosal lesions, ultrasound of primary melanoma postoperative area, regional lymph nodes, and abdomen, and also standard lab tests including LDH and S-100B. Recommendations do not include routine implementation of other radiological methods such as CT, PET/CT, or MRI but physicians often use them, usually according to clinical indication. However, despite the development of technologically advanced imaging modalities, the probability of detecting occult metastases through radiologic

means is often low in these patients.

PET/CT is the most sensitive nuclear medicine imaging method for the assessment of tumour localization and disease progression, treatment evaluation, detection of local recurrence and distant metastases, more precise treatment planning in patients with different tumours, and assistance in determining the radiation field. Nevertheless, PET/CT still does not have a clearly defined role in initial staging or follow-up of melanoma patients.

Several studies have shown that PET/CT should not be used in the initial staging of primary cutaneous melanoma when there is no clinical evidence of local or distant metastatic spread. The reason for this is the small size/volume of most nodal metastases (6-11).

In a study by Yancovitz *et al.* (12), the inadequacy of PET/CT for detecting regional metastasis has been emphasized; a 2% true positive and 12% false negative rates were observed when compared to the golden standard of SLNB. Imaging at the time of initial diagnosis of melanoma was of low yield with a high false-positive rate and did not lead to upstaging or change in initial surgical management.

A similar study by Clark *et al.* (13) conducted research in 64 patients with T2 to T4 melanomas. PET/CT did not reveal occult distant metastases in any of the patients. Nineteen of 64 patients had positive SLNs, and only two (11%) were identified on PET/CT. In a more recent study by Barsky *et al.* (14) the recommendation was to exclude PET/CT imaging preoperatively for asymptomatic patients, even in the case of higher risk. SLNB revealed nodal disease in 94% (49/55) of patients testing negative by imaging and an additional six patients had false positive imaging studies, indicating the predictive value of PET/CT is not sufficient to replace SLNB.

However, Arangoiz *et al.* (15) showed that patients with thick melanomas can benefit from a preoperative PET/CT. The combined sensitivity and specificity of PET/CT for identifying regional and metastatic disease were 45% and 88%, respectively. The combined positive predictive value (PPV) and negative predictive value (NPV) for identifying regional and metastatic disease were 82% and 55% but most importantly, preoperative PET/CT modified the treatment plan in 18% of their patients.

In our study, the results were more compliant to those of Arangoiz *et al.* (15). Combined sensitivity and specificity of PET/CT for identifying regional and metastatic disease were 54% and 98%, respectively. The positive predictive value (PPV) of PET/CT was 95% while negative predictive value (NPV) was 71%. Since PET/CT findings in our study did contribute important information that led to the modification of the original treatment plan for 26 patients (31%), this study suggests that high-risk melanoma patients could benefit from a preoperative PET/CT. The earlier the exact extent of the disease is assessed, the faster will be to determine the most appropriate form of treatment for an individual patient that will affect the disease prognosis and improve survival. Additionally, PET/CT findings

discovered incidental tumours in 12 (14.1%) patients that required further evaluation with three of them having malignant tumours that required further treatment.

However, due to a high rate of false negative findings in our study (21.2%), negative preoperative PET/CT does not exclude the presence of sentinel lymph node metastasis, therefore SLNB remains the gold standard in detecting regional nodal melanoma metastases.

In our opinion, PET/CT certainly has a role in the preoperative staging of high-risk melanoma patients, but it also requires a mandatory sentinel lymph node biopsy afterwards. The main disadvantage of PET/CT is precisely the inability to detect micrometastases in regional lymph nodes, which is also confirmed by data from our research in which all 18 patients in whom PET/CT could not detect a positive sentinel lymph node actually had micrometastases smaller than 1.2 mm in size.

CONCLUSION

As the role of PET/CT in preoperative staging of patients with high-risk primary melanoma is not yet clearly defined, although the previously published results, including ours, are promising, further research is needed with more patients to determine the undoubted benefit of PET/CT scans in such patients.

STATEMENT OF ETHICS

This study was conducted using anonymized data obtained exclusively from the hospital's electronic medical records system. No direct patient contact occurred, and no identifiable personal information was accessed. Therefore, informed consent from participants and approval from the institutional ethics committee were not required in accordance with local regulations and hospital policy.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

Dr. Filipovic and Dr. Kosuta participated in data collection, statistical analysis and writing of the manuscript. Dr. Divosevic analysed and wrote all the PET/CT finding. Prof. Buljan and Prof. Situm managed patients referred for sentinel biopsy and supervised and edited the writing of the manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [N.F.] upon request.

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