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*Original Article*

# Prediction of positron emission tomography/computed tomography (PET/CT) positivity in patients with high-risk primary melanoma

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**Abstract:** Positron emission tomography/computed tomography (PET/CT) is an important tool to identify occult melanoma metastasis. To date, it is controversial which patients with primary cutaneous melanoma should have staging PET/CT. In this retrospective analysis of more than 800 consecutive patients with cutaneous melanoma, we sought to identify factors predictive of PET/CT positivity in the setting of newly-diagnosed high-risk primary melanoma to determine those patients most appropriate to undergo a PET/CT scan as part of their diagnostic work up. 167 patients with newly-diagnosed high-risk primary cutaneous melanoma underwent a PET/CT scan performed as part of their initial staging. Clinical and histologic factors were evaluated as possible predictors of melanoma metastasis identified on PET/CT scanning using both univariate and multivariate logistic regression. In all, 32 patients (19.2%) had a positive PET/CT finding of metastatic melanoma. In more than half of these patients (56.3%), PET/CT scanning identified disease that was not detectable on clinical examination. Mitotic rate, tumor thickness, lymphadenopathy, and bleeding were significantly predictive of PET/CT positivity. A combinatorial index constructed from these factors revealed a significant association between number of high-risk factors observed and prevalence of PET/CT positivity, which increased from 5.8% (with the presence of 0-2 factors) to 100.0%, when all four factors were present. These results indicate that combining clinical and histologic prognostic factors enables the identification of patients with a higher likelihood of a positive PET/CT scan.

**Keywords:** Melanoma, PET, PET/CT, FDG, molecular imaging, nuclear medicine, skin cancer, staging

## Introduction

While melanoma accounts for only 2% of all cutaneous malignancies, it is responsible for the vast majority of cutaneous malignancy deaths [1]. Cutaneous malignant melanoma (CMM) has an unpredictable pattern of dissemination, and it is important to stage these patients accurately in order to plan treatment and estimate prognosis. This is especially true of high-risk primary melanoma, which can metastasize to regional lymph nodes and to visceral organs.

Factors that affect staging include primary tumor thickness, ulceration status, mitotic rate, and presence of lymph node and/or distant metastasis. As described by the American Joint Committee on Cancer's (AJCC) TNM Staging System for melanoma [2], patient prognosis is strongly dependent on the presence of these factors, as survival rates decrease correspondingly with advancing stage [3].

Lymph node, satellite and distant metastasis can be found by physical examination, sentinel node biopsy (SNB), or by radiologic imaging. Physical examination alone can be insufficient to optimally stage many patients with invasive melanoma, as a subset of patients with high-risk melanoma will present with locoregional or distant metastasis at the time of initial diagno-

sis. Identification of these patients would have important implications for choice of surgical therapy. If a patient is found to have a positive PET scan with regional nodal involvement, a therapeutic lymph node dissection should be performed rather than a SNB. Also, prompt initiation of systemic therapy may be rendered if systemic metastases are found, given the recent advances in systemic therapy for metastatic melanoma [4-8].

Fluorine-18 labelled 2-deoxy-2-fluoro-D-glucose (FDG) PET/CT scanning has emerged as a reliable and accurate tool for the identification of melanoma metastasis, given the hypermetabolic nature of clinically detectable melanoma metastases [9-12]. However, to date, the clinical utility of PET/CT scanning in the setting of newly-diagnosed high-risk melanoma is controversial, and the National Comprehensive Cancer Network (NCCN) guidelines recommend the use of PET scanning based on the presence of clinical signs and symptoms [13]. As a result, there is a need for further studies to evaluate the utility of PET/CT in distinct subsets of newly-diagnosed melanoma patients.

## Materials and methods

### *Study design and setting*

This analysis, which was based on a chart review of patients entered into the datasets, was approved by the institutional review board at the California Pacific Medical Center. Eight hundred consecutive patients with a newly diagnosed CMM who possessed accessible electronic records were reviewed in the Center for Melanoma Research and Treatment at California Pacific Medical Center (CPMC). These patients were seen by a dermatological oncologist and an oncological surgeon in the clinic at least once between 2007 and 2014. PET/CT was performed as part of initial staging in patients with either a primary melanoma greater than 2 mm in thickness; or invasive melanoma no greater than 2 mm in thickness with at least one high-risk histological feature present (such as ulceration, vascular invasion, microsatellites, or mitotic rate >3/square mm), and/or having already undergone wide local excision, in whom information from lymphoscintigraphy may have been compromised.

Patients eligible for inclusion in the study met the following criteria: new diagnosis of cutaneous malignant melanoma; an FDG-PET/CT scan performed as part of the initial staging; a detailed medical record; and an accessible PET/CT report. Unavailable PET/CT report and non-staging or re-staging PET/CT were excluded. In total, 167 eligible patients were identified who underwent a staging PET/CT scan. No specific cutoff for standardized uptake value was used to define an abnormal or positive PET/CT scan. All positive PET/CT scans were reviewed at the multi-disciplinary melanoma tumor board in order to develop consensus regarding the nature of the radiographic findings observed, and to determine the need for additional intervention (e.g., biopsy or surgical resection). In the PET-positive group, all staging PET/CT scans were performed within a mean of 29 days from day of diagnosis, with a range of 2-79 days.

### *Variables*

Twenty-one clinical or histological factors were recorded at the time of diagnosis of cutaneous melanoma. These comprised clinical features, such as age, gender, skin type, eye and hair color, location of the primary tumor, presence of itching, bleeding and lymphadenopathy, family history of melanoma/other cancer, extent of sun exposure, and history of blistering sunburns. In addition, the following pathological features were included: tumor thickness, mitotic rate, presence of ulceration, vascular invasion, microsatellites, Clark level, and tumor infiltrating lymphocytes. Increased glucose tracer activity was verified by needle biopsy or surgical resection. All histological specimens underwent internal pathology review at CPMC.

### *Statistical methods*

We selected PET/CT scan positivity for melanoma as the focal end point for prediction. We performed both univariate and multivariate logistic regression analyses to identify factors that significantly predicted PET/CT scan positivity. Four prognostic factors were identified as the most highly and independently predictive on this sequence of univariate and multivariate analyses: mitotic rate, tumor thickness, lymphadenopathy, and bleeding.

We developed an index to identify appropriate candidates to undergo a PET/CT scan as part of initial staging for melanoma. Lymphadenopathy and bleeding were dichotomous to begin with.

**Table 1.** Characteristics of PET study sample (N=167)

| | |
|---|---|
| Male gender | 131 (78.4%) |
| Mean age at diagnosis (years) | 62.3 |
| Mean tumor thickness (mm) | 3.63 |
| Mean mitotic rate (mitoses per $mm^2$) | 5.50 |
| Ulceration | 61 (42.1%) |
| Primary skin sites | |
| Head and neck | 59 (35.3%) |
| Groin (incl. genitalia) | 3 (1.8%) |
| Chest/breast | 11 (6.6%) |
| Upper back (incl. shoulder) | 25 (15.0%) |
| Lower back (incl. flank) | 8 (4.8%) |
| Abdomen | 5 (3.0%) |
| Anal | 1 (0.6%) |
| Upper extremities | 25 (15.0%) |
| Lower extremities | 30 (18.0%) |
| T stage* | |
| T1 | 13 (8.3%) |
| T2 | 32 (20.4%) |
| T3 | 59 (37.6%) |
| T4 | 53 (33.8%) |

*T stage was based on a sample size of 157, as 10 cases had missing data on tumor thickness.

Tumor thickness was dichotomized using the T stage, with T4 patients designated as the high-risk group. Mitotic rate was dichotomized with patients with primary tumors with >3 mitoses per $mm^2$ as the high-risk group, the optimal cut-point for predicting survival in our dataset. A combinatorial index was developed that counted the number of high-risk factors present in each patient with complete data on all four factors. The index's association with actual PET/CT results was assessed via the chi-square test.

Unless otherwise specified, all reported statistical tests were non-directional (two-tail *p* values), and $p<0.05$ was considered statistically significant.

## Results

### *Descriptive data*

**Table 1** shows the characteristics of the 167 patients included in our analysis. One hundred thirty-one patients (78.4%) were male, and the mean age at diagnosis of the study sample was 62.3 years. The mean tumor thickness of the cohort was 3.63 mm, with a mean mitotic rate of 5.50 per $mm^2$. The most common site for the primary melanoma was on the head/neck (35.3%), followed by the lower extremities (18.0%), upper extremities (15.0%), and upper back (15.0%). The T stage of the cohort was as follows; 13 patients (8.3%) had T1 disease, 32 patients (20.4%) had T2 disease, 59 patients (37.6%) had T3 disease, and 53 patients (33.8%) had T4 disease. Following completion of the staging work up, including PET/CT scanning and SNB, the AJCC stage at initial diagnosis was as follows: 30 patients (19.7%) had stage I disease, 83 patients (54.6%) had stage II disease, 36 patients (23.7%) had stage III disease, and 3 patients (2%) had stage IV disease.

### *Outcome data*

Of the 167 patients included in the analysis, 135 were PET/CT negative and 32 (19.2%) had a PET/CT scan positive for metastatic melanoma confirmed by pathologic diagnosis. PET/CT scanning separately identified 13 false-positive lesions for melanoma and 5 true positives for other tumors (thyroid cancer, meningioma, metastases from gastrointestinal primaries, and parotid gland adenocarcinoma), all verified and diagnosed through a biopsy. **Figure 1** depicts the staging evaluation of a 72 year-old male with a bleeding lesion on the upper back, which on biopsy revealed melanoma, 7.5 mm thick, ulcerated, with 4 mitoses/$mm^2$. Staging PET/CT revealed an FDG avid focus in his left upper extremity. The presence of the nodule was confirmed with ultrasound (**Figure 2**), and excision of the nodule was performed. Pathologic evaluation of the nodule revealed metastatic melanoma, representing stage IV disease.

We analyzed the impact of the clinical and histologic factors collected on the prevalence of PET/CT scan positivity. The ability of each factor to predict PET positivity was assessed via univariate logistic regression (**Table 2**). The statistically significant factors included lymphadenopathy ($p<0.00005$), bleeding of the primary tumor ($p=0.0008$), sentinel lymph node status ($p=0.002$), mitotic rate ($p=0.009$), tumor thickness ($p=0.033$), Clark level ($p=0.029$), male gender ($p=0.045$), eye color ($p=0.025$), and history of blistering sunburns ($p=0.045$). The

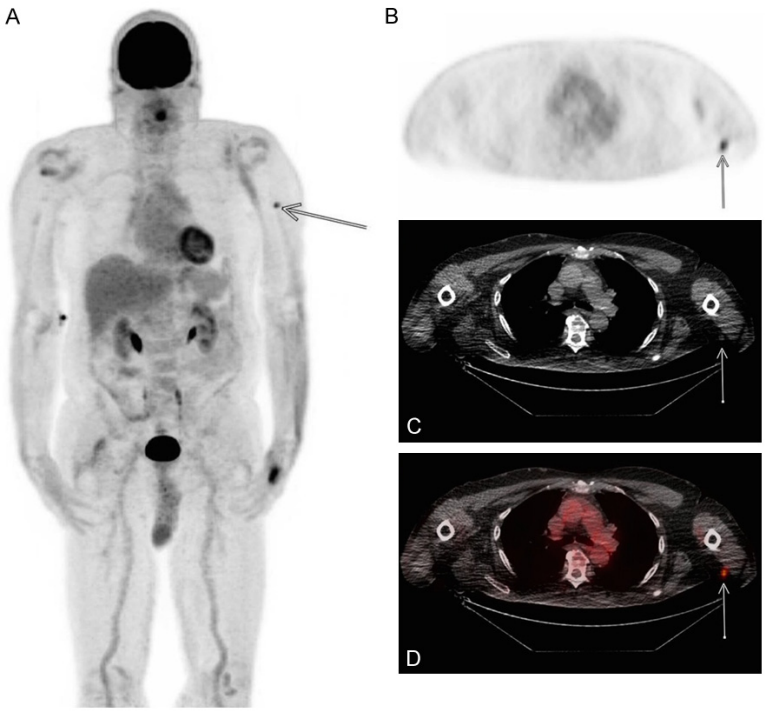


**Figure 1.** (A) Whole body PET together with (B) transaxial PET, (C) low dose CT and (D) fused PET/CT of a male patient with a primary melanoma in the upper back following a shave biopsy from an outside institution. A small hypermetabolic soft tissue nodule was identified on the pre-op PET in the subcutaneous tissues of the left upper extremity as indicated by the arrows.

remaining factors lacked statistical significance, even on a one-tailed basis.

Additional analyses focused on the following four factors: mitotic rate, tumor thickness, bleeding of the primary tumor, and lymphadenopathy. SNB status, which was significant in the univariate analysis, was eliminated as a candidate, as we aimed to predict PET/CT positivity without including its results. 80.4% of the cohort analyzed had at least one of the four high-risk factors, including 77.7% of patients with a negative PET/CT scan, and 92.6% of the patients with a positive PET/CT scan.

A stepwise multivariate logistic regression analysis with backward elimination removed Clark level, due to its high positive correlation with the four aforementioned factors, and indicated that bleeding ($p$=0.02) and lymphadenopathy ($p$=0.01) remained independently statistically significant on a two-tail basis. Tumor thickness ($p$=0.055) and mitotic rate ($p$=0.055) were almost, but not quite independently significantly predictive of PET/CT positivity on a one-tail basis (**Table 3**). The four factors, when combined together, provided a highly significant prediction of PET/CT positivity (likelihood ratio chi-square $p$=0.0001).

We then assessed the impact of combining these four factors in the prediction of PET/CT positivity. A combinatorial index was developed for high-risk primary melanoma patients that counted the number of high-risk features present. Patients possessing 0-2 factors at the high-risk level had positive PET/CT scans in 5.8% of cases. This proportion increased to 47.4% in patients with three high-risk features present, and to 100.0% in patients with all four high-risk features present (**Table 4**). The index's association with actual PET/CT results was assessed via the chi-square test, comparing patients with 0-2 high-risk features with those possessing 3 or 4 high-risk features, and revealed a significant discrimination ($p$<0.00005).

## Discussion

Although no consensus currently exists on the utility of FDG-PET/CT in the staging of primary cutaneous melanoma, the yield of 19.2% positive PET/CT scans observed in this study is clinically relevant, perhaps even surprising, albeit in a selected sample of high-risk patients. To our knowledge, the prevalence of PET/CT scan positivity observed in this cohort of primary melanoma patients has not been previously reported. In our PET/CT positive group (32 patients), PET/CT was able to provide valuable information in 18 clinically node-negative patients, helping determine accurate disease staging, and obviating the need for performing SNB to identify regional metastatic disease. We found that elevated mitotic rate, presence of lymphadenopathy, bleeding, and tumor thickness >4 mm each individually predicted a significantly higher risk of PET/CT positivity. Moreover, an

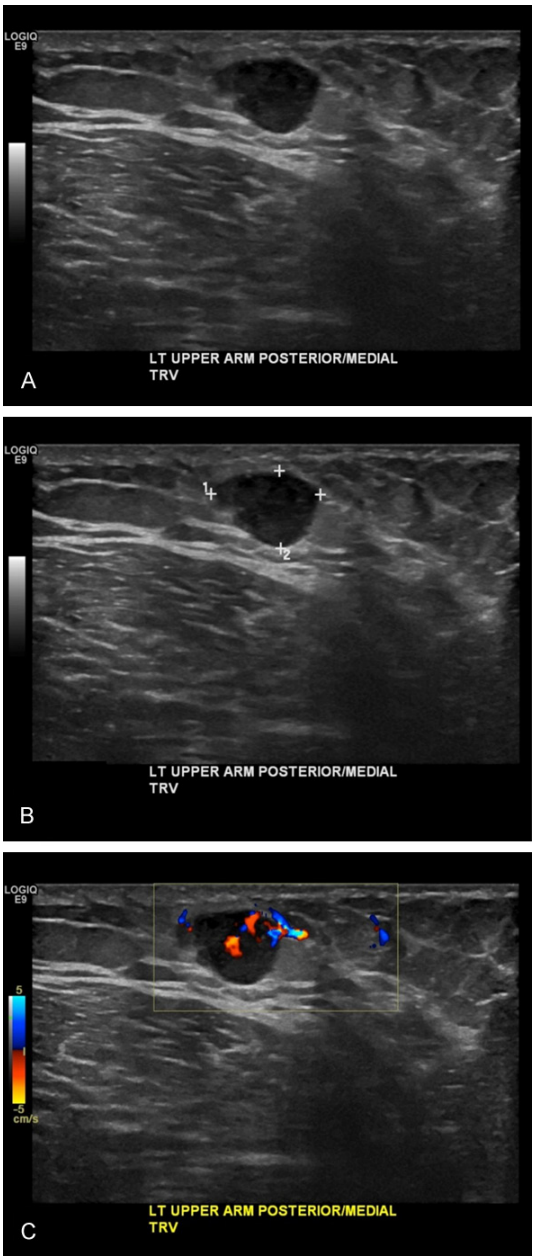


**Figure 2.** The hypermetabolic soft tissue nodule was further evaluated with (A) ultrasound on the day of surgery, immediately prior to lymphoscintigraphy. (B) The lesion measured 1.13×0.8 cm and (C) showed signs of hypervascularity. Wide local excision, sentinel lymph node excision, and excision of the left upper extremity nodule were performed in the operating room. Sentinel nodes in the left axilla were all negative. The excised nodule was found to contain metastatic melanoma.

index of these factors produced a significant association between number of high-risk features present and prevalence of PET/CT positivity.

The association between increased tumor volume and presence of clinical node-positive disease with PET positivity has been previously evaluated [9, 10]. Accordingly, Crippa et al. [9] found that PET was able to detect lymph node metastases in all nodes larger than 10 mm, in 83% of nodes between 6-10 mm, and in 23% of nodes less than 5 mm in size. Furthermore, PET was found to have a high sensitivity for metastases with more than 50% lymph node involvement or with capsular infiltration. In a prospective study by Bastiaannet et al. [10], PET/CT was found to be indicated in staging of clinical stage III disease, supporting the findings of our study. In addition, Aukema et al. [11] found that PET/CT had a sensitivity of 87% and specificity of 98% for staging melanoma patients with palpable lymph node metastases. Reinhardt et al. [12] found an even higher diagnostic performance of PET/CT in staging of nodal involvement in melanoma, with a sensitivity and specificity of 100%. Gellen et al. [14] reported a PET/CT scan positivity of 36% in resected stage III melanoma in an analysis of 19 patients who had a total of 53 PET/CT scans. We found a similarly high performance of PET/CT in patients with palpable lymph node involvement, but observed that PET/CT was able to identify an equal proportion of patients without clinical signs of disease progression.

Interestingly, our study has identified bleeding of the primary tumor as a new and powerful factor in predicting PET/CT scan positivity. To our knowledge, bleeding of the primary tumor has not been previously reported to predict PET/CT positivity and can possibly reflect a combination of other biologic features such as tumor vascularity and/or mitotic rate.

*Sentinel node biopsy, SPECT/CT and PET/CT*

Currently, the standard of care for melanoma $\geq$ 1 mm thick is wide local excision of the primary tumor and SNB. SNB is an invasive surgical procedure requiring general anesthesia, and it is highly sensitive in determining regional nodal micro-metastasis [15]. However, in the setting of macrometastatic node-positive disease that has not been detected by physical examination, lymphoscintigraphy may identify the wrong lymph node, as the radiotracer may be diverted to non-sentinel nodes [16]. The association between sentinel lymph node dissection with

**Table 2.** Univariate logistic regression analysis of predictors of PET/CT positivity

| | $x^2$ | 2-tail *P* value | Odds ratio |
|---|---|---|---|
| Male gender | 4.02 | 0.045 | 3.13 |
| Age at diagnosis (>75 yrs.) | 1.91 | 0.167 | 1.91 |
| Tumor thickness (>4 mm) | 4.56 | 0.033 | 2.51 |
| Bleeding | 11.28 | 0.0008 | 4.63 |
| Lymphadenopathy | 22.18 | <0.00005 | 9.64 |
| SNB status | 9.50 | 0.002 | 5.19 |
| Blistering sunburns | 4.03 | 0.045 | 2.72 |
| Blue eye color | 5.01 | 0.025 | 3.20 |
| Clark level (IV or V) | 4.79 | 0.029 | 6.05 |
| Mitotic rate (>3 mitoses per $mm^2$) | 6.75 | 0.009 | 3.75 |
| Axial location | 1.03 | 0.309 | 0.66 |
| Ulceration | 1.64 | 0.200 | 1.81 |

Abbreviation: SNB stands for sentinel node biopsy.

**Table 3.** Multivariate logistic regression analysis of predictors of PET/CT positivity

| | $x^2$ | 2-tail *P* value | Odds ratio |
|---|---|---|---|
| Mitotic rate >3 per $mm^2$ | 2.50 | 0.11 | 2.58 |
| Thickness >4 mm | 2.55 | 0.11 | 2.90 |
| Lymphadenopathy | 6.41 | 0.01 | 5.44 |
| Bleeding | 5.38 | 0.02 | 4.03 |

**Table 4.** Combinatorial index of factors and prevalence of positive PET/CT scan

| | Mitotic rate >3 per $mm^2$<br>Lymphadenopathy<br>Thickness >4 mm<br>Bleeding |
|---|---|
| Factors | |
| No. of (+) factors | Positive PET/CT |
| 0-2 | 5.8% |
| 3 | 47.4% |
| 4 | 100% |

Abbreviation: PET/CT stands for positron emission tomography/computed tomography.

or without preoperative SPECT/CT and metastatic node detection has been studied [17]. SPECT/CT-aided sentinel lymph node dissection has been shown to not only reduce the false negative results but also give the surgeons a more precise 3D localization of sentinel lymph nodes and identify sentinel lymph nodes and interval nodes missed on planar images. Also, the CT scan identifies unexpected macroscopic nodal involvement, and better direct surgical approach. Stoffels et al. [18] found a significant cost reduction by using preoperative SPECT/CT-aided sentinel lymph node dissection for staging of microscopic disease in melanoma patients. An important limitation of lymphoscintigraphy and SPECT/CT is the reasonably big flare of activity around the edge of the injection site, which can mask sentinel nodes. Furthermore, macroscopically replaced lymph nodes consisting of cancer cells will not light up on the lymphoscintigraphy or SPECT/CT, and another reliable diagnostic tool is necessary to detect these lesions.

PET/CT is a non-invasive imaging tool that enables simultaneous assessment of both local and distant sites and, as a result of avid uptake of the FDG-tracer, may potentially identify and confirm a clinically positive lymph node. If PET/CT identifies clinical node-positive disease in melanoma patients, one can proceed directly to fine needle aspiration and therapeutic lymphadenectomy, thereby sparing the patient at least one invasive procedure requiring general anesthesia. However, it is important to note that routine screening for patients with clinically negative nodes by PET/CT is not indicated, as it is much less sensitive than SNB in identifying microscopic nodal involvement.

*PET/CT in initial staging of melanoma*

At the current time, there are no specific guidelines identifying which melanoma patients should have staging PET. Medicare covered the use of FDG-PET/CT in the pre-operative evaluation of recurrent melanoma in 1999, and two years later, PET/CT became a reimbursable test for the diagnosis, staging, and restaging of malignant melanoma. Medicare does not cover PET/CT for the evaluation of regional nodes in initial diagnosis of primary melanoma (www.cms.gov). For initial diagnosis, PET is only covered in three settings: 1) when PET may assist in avoiding an invasive diagnostic procedure; 2) when PET may assist in determining the optimal anatomical location to perform an invasive diagnostic procedure; or 3) if treatment will differ depending on the stage of cancer identified.

Despite significant research on the diagnostic value of radiologic imaging in staging/restaging of CMM patients [19-26], currently, the recommendations for or against PET lack level 1 evidence support. The results reported in this study are promising, but will need to be validated in larger cohorts of high-risk melanoma patients to accurately determine which patients should have PET/CT scans at initial staging. There is also a disagreement on the cost-effectiveness of PET/CT as a part of the diagnostic workup, underscoring the limited utility of PET/CT in early-stage melanoma [23, 27-30] and in clinically node-negative head and neck cutaneous melanoma [31]. A recent meta-analysis by Rivera et al. [32] concluded that PET has a high sensitivity, specificity, and performance in stage IIIb/IIIc melanoma, and indicated that a subgroup of high-risk melanoma patients will benefit from a staging PET scan. Our study extends these results by identifying factors predictive of PET/CT positivity, resulting in the development of an index to identify those patients with the highest risk of PET/CT positivity.

There are some limitations of our study. The study design is retrospective, the PET/CT-positive sub-sample is rather small (n=32), and, as such, selection and information bias cannot be excluded. In addition, a proportion of the patients were referred to our clinic after being diagnosed elsewhere and may have had PET/CT already performed at the time of presentation, resulting in potentially different PET protocols and inter-observer variability.

In conclusion, our analysis demonstrated a clinically relevant (19.2%) rate of PET/CT positivity in high-risk primary melanoma, and identified four factors predictive of an increased risk of PET/CT positivity. If replicated in independent cohorts, these factors may be used to identify those patients most likely to benefit from an initial staging PET/CT in a selected group of patients.

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