# USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

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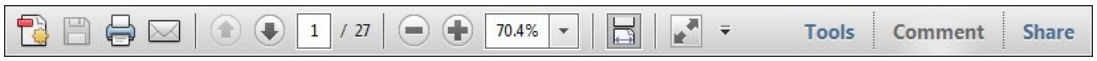


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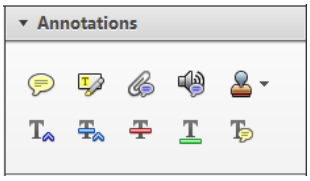


## 1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
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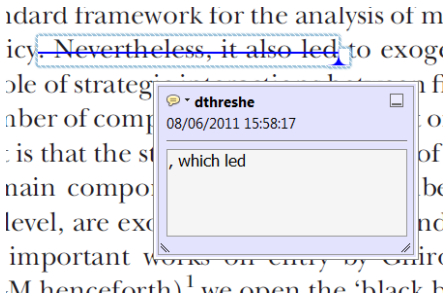


## 2. Strikethrough (Del) Tool – for deleting text.

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- Highlight a word or sentence.
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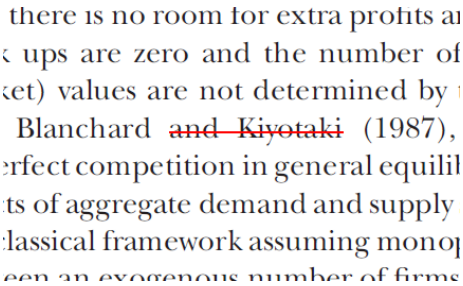

## 3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

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How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
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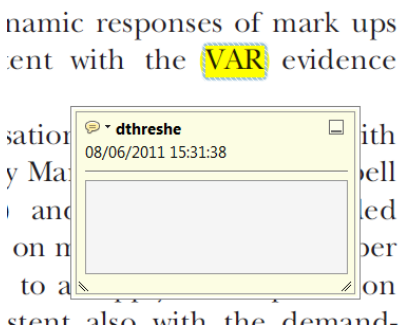


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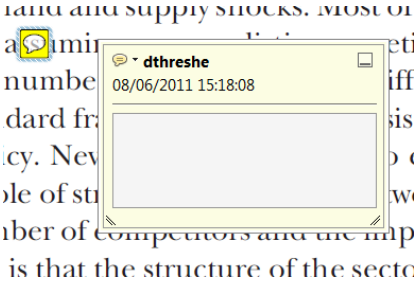

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- Click on the proof to where you'd like the attached file to be linked.
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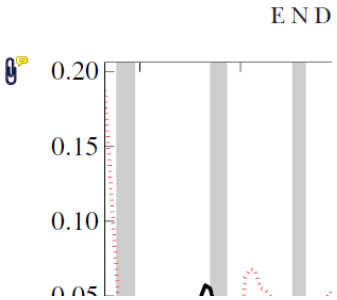


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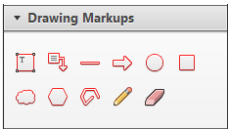


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- Click on the proof at the relevant point and draw the selected shape with the cursor.
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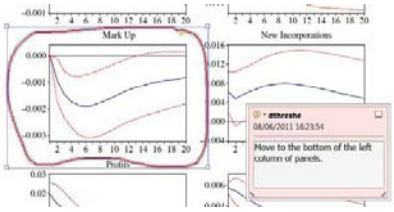

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ORIGINAL ARTICLE

# Diagnostic accuracy of $^{18}$F-FDG-PET/CT in early and late stages of high-risk cutaneous malignant melanoma

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## Abstract

**Background** The precise role of total body $^{18}$F-fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) in the clinical management of patients with cutaneous malignant melanoma (CMM) is not well established.

**Objective** The purpose of this study was to investigate the diagnostic accuracy of PET/CT in early- and late-stage patients with high-risk CMM.

**Methods** We retrospectively analysed various imaging, histopathological and clinical data from 97 patients also examined by PET/CT during a 5-year period (2007–2011). Three groups were assessed: stage I/II, resected stage III and unresectable stage III/stage IV.

**Results** The median follow-up time of living patients was 43.48 ± 19.67 (15–142) months. We observed a high diagnostic accuracy in all stages (91.3%, 92.5% and 96.2% respectively). PET/CT appeared to be reliable diagnostic tool even for the detection of small lymph node metastases. PET/CT was informative in 14 of 19 cases wherein another imaging examination provided inconclusive results regarding lesion dignity. However, PET/CT was less suitable for properly evaluating the dignity of a lung lesion. A true positive scan was twice as likely in clinically negative patients with resected stage III disease than in patients with stage I/II disease (35.9% and 14.5%, $P = 0.007$).

**Conclusions** These results confirm that PET/CT is an important diagnostic tool in the management of patients with high-risk CMM, but it cannot replace the standard of care examinations. More accurate clinicopathological and timing criteria must be defined to best utilize the advantages of this imaging method.

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## Conflicts of interest

The authors declare no conflict of interest.

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## Introduction

The incidence of cutaneous malignant melanoma (CMM) in fair-skinned populations is increasing worldwide.[1,2] The distant metastasis rate, which determines melanoma-associated mortality, is increased in cases with high Breslow tumour thickness, ulceration, a high mitotic rate of primary CMM and positive nodal status. These factors are considered in the current TNM staging system according to American Joint Committee on Cancer.[3] Currently, despite the use of adjuvant treatment in patients with an increased metastasis risk, disease recurrence can occur at any time or site. Early identification of metastasis and an assessment of the aggressiveness of the spread of the disease are relevant pieces of information for optimized therapeutic decisions for choices between currently available metastatic CMM treatment approaches. Thus, appropriate radiological and nuclear medicine imaging methods are of great importance. The advantages of $^{18}$F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT; hereafter referred to as PET/CT) include the ability to simultaneously provide information about the anatomic position and metabolic



 

activity of a suspicious lesion, as well as real-time whole-body imaging. The disadvantages of PET/CT include the high cost and the reduced sensitivity of detection of metastases in organs with high glucose uptake, such as the brain. Several studies have demonstrated the benefit of PET/CT in CMM, but questions concerning the adequate indication for this imaging tool remain. The diagnostic role of PET/CT has not been substantially evaluated in early CMM stages (AJCC stages I and II).[4] However, considering the high rate of PET/CT false-positive findings and the cost of whole-body imaging examinations compared with the low rate of nodal disease (less than 15%) and distant metastasis (less than 5%) at the time of primary diagnosis,[5] the standard method for initial staging (for which PET/CT is not a suitable option) remains the sentinel lymph node biopsy (SLNB).[6] Nevertheless, among high-risk melanoma patients with stage I/II disease, a high diagnostic accuracy for PET/CT in the detection of metastases has been reported in two different studies (91% and 98%).[7,8] The use of PET/CT to examine staging in patients with stage III disease is more accepted. The aim of this study was to assess the diagnostic accuracy of PET/CT in CMM at various (early and late) disease stages in a retrospective cohort study.

## Materials and methods

### Demography and PET/CT examinations

Whole-body $^{18}$F-FDG-PET/CT imaging was performed in 121 consecutive patients with CMM who were referred from the Department of Dermatology of University of Debrecen Medical Centre between January 2007 and December 2011. After the exclusion of cases without eligible follow-up data and a histopathologically unverified diagnosis of the primary CMM excised on an unknown date, 97 patients were evaluated (Table 1). Of the 97 patients, 40 (41.2%) had two, three or four PET/CT scans. Therefore, 148 PET/CT scans could be analysed with corresponding clinical and histopathological data (Tables 2–4). Patients who were still alive received follow-up for at least 12 months after PET/CT. Of the 148 PET/CT scans, 69 (46.6%) were performed in patients with stage I and stage II tumours (group 1), 53 (35.8%) in patients with resected stage III tumours (group 2) and 26 (17.6%) in patients with unresectable stage III and resected or unresectable stage IV tumours (group 3). The diagnostic accuracy of PET/CT was assessed separately in the three groups. Clinical follow-up data were reviewed carefully with regard to the influence of the PET/CT result on the clinical management, the recurrence of disease after a true negative PET/CT, and the utility of a PET/CT result after another imaging examination provided inconclusive results regarding lesion dignity.

### $^{18}$F-FDG-PET/CT imaging procedure

The PET/CT examinations were performed at the ScanoMed Debrecen Centre according to their melanoma PET/CT protocol using a Philips Gemini TF 64 PET/CT scanner. Total body images were obtained from the top of the head to the toes. Patients fasted for at least 6 h prior to the examination. Glucose levels were measured prior to the FDG injection to ensure that the value was not greater than 12 mmol/L. $^{18}$F-FDG [4.4 MBq (0.12 mCi)/kg] was intravenously administered to each patient 1 h before PET image acquisition. During this uptake time, each patient consumed 1000 mL water. Low-dose CT (120 KV and 100–200 mAS depending on the patient's bodyweight) was performed over the entire range for attenuation correction and anatomical localisation. PET acquisition was subsequently performed over the entire range (50% overlap, 18 cm axial field of view, 3D time of flight technique). The acquisition times were 60–150 s/frame from the top of the head to the upper thigh based on the patient's bodyweight and 60 s/frame from the upper thigh to the toes in each case. Images were reconstructed using the 3D-RAMLA iterative technique. Images were interpreted by experienced nuclear medicine and radiology specialists working at the ScanoMed Centre who were familiar with previous PET/CT results (if available).

### Assessment of diagnostic accuracy

Interpretation of PET/CT was accepted as true positive or true negative if the presence or absence of metastases revealed by the examination were consistent with histopathological and/or clinical data during the follow-up. The diagnosis was defined as false positive in the following cases: when the histopathological examination of the indicated lesion was negative or when a suspicious lesion became undetectable by other imaging modalities during the minimum 12-month clinical follow-up. PET/CT results were evaluated as false negative in cases of histopathologically verified disease recurrence within 3 months of a negative scan. By definition, the diagnostic accuracy is calculated from the following equation: (number of true positive cases + number of true negative cases) / (number of true positive cases + number of true negative cases + number of false negative cases + number of false positive cases).

### Statistical analysis

The data were statistically analysed using the independent *t*-test, Mann–Whitney *U*-test, and the Pearson Chi-squared test (SPSS for Windows, version 19.0, SPSS Inc., Chicago, IL, USA). Test results were defined as significant if $P < 0.05$.

## Results

### Clinical benefits of PET/CT examinations

The demographic and clinicopathological data from patients undergoing PET/CT examination during a 5-year period (2007–2011) are summarized in Table 1. Based on their clinicopathological parameters (Breslow tumour thickness, ulceration and lymph node status), these patients were at high risk of disease

**Table 1** Patient demographics

| | Patients | | |
|---|---|---|---|
| | **Male** | **Female** | **Total** |
| N (%) | 47 (48.5) | 50 (51.5) | 97 (100) |
| Age, mean ± SD, min–max (years) | 52.55 ± 12.80, 28–81 | 50.72 ± 13.23, 23–77 | 51.61 ± 12.99, 23–81 |
| Clinicopathological type | *N* (%) | | |
| Superficial spreading melanoma | 21 (44.7) | 23 (46.0) | 44 (45.4) |
| Nodular melanoma | 21 (44.7) | 22 (44.0) | 43 (44.3) |
| Not classified | 4 (8.4) | 4 (8.0) | 8 (8.2) |
| Occult | 1 (2.1) | 1 (2.0) | 2 (2.1) |
| Ulceration, *N* (%) | 18 (38.3) | 18 (36.0) | 36 (37.1) |
| Breslow, mean ± SD, median (mm) | 4.57 ± 6.54, 2.28 | 4.07 ± 3.57, 2.86 | 4.32 ± 5.23, 2.70 |
| Breslow (mm) | *N* (%) | | |
| ≤1.00 | 9 (19.1) | 6 (12.0) | 15 (15.5) |
| 1.01–2.00 | 10 (21.3) | 13 (26.0) | 23 (23.7) |
| 2.01–4.00 | 11 (23.4) | 10 (20.0) | 21 (21.6) |
| ≥4.01 | 15 (31.9) | 17 (34.0) | 32 (33.0) |
| Occult | 1 (2.1) | 1 (2.0) | 2 (2.1) |
| Unknown | 1 (2.1) | 3 (6.0) | 4 (4.1) |
| Localisation | *N* (%) | | |
| Trunk | 25 (53.2) | 21 (42.0) | 46 (47.4) |
| Lower extremities | 9 (19.1) | 12 (24.0) | 21 (21.6) |
| Upper extremities | 7 (14.9) | 5 (10.0) | 12 (12.4) |
| Head-neck | 5 (10.6) | 11 (22.0) | 16 (16.5) |
| Occult | 1 (2.1) | 1 (2.0) | 2 (2.1) |
| AJCC stage at diagnosis | *N* (%) | | |
| IA–IB | 17 (36.2) | 13 (26.0) | 30 (30.9) |
| IIA–IIC | 22 (46.8) | 25 (50.0) | 47 (48.5) |
| IIIA–IIIC | 8 (17.0) | 11 (22.0) | 19 (19.6) |
| IV | 0 (0.0) | 1 (2.0) | 1 (1.0) |
| Follow-up time of living patients, mean ± SD, min–max (months) | 42.34 ± 18.97, 15–96 | 42.25 ± 20.26, 18–142 | 43.48 ± 19.67, 15–142 |

recurrence. The proportions presented are not consistent with the characteristics of the entire population with CMM cared for in the department (these data are beyond the scope of this study). In 97 patients, 148 PET/CT scans were performed (Table 2), primarily for (re-)staging (Table 3). After PET/CT examination, the mean follow-up time of patients alive was 43.48 ± 19.67 months. The rate of the change in stage due to the PET/CT result was increased in resected stage III patients (14 of 53) compared with stage I/II patients (eight of 69). PET/CT was informative in 14 of 19 cases wherein another imaging examination provided inconclusive results regarding lesion dignity (equivocal lymph node enlargement; lung and subcutaneous nodule). Metastasis was confirmed in six of 14 cases and excluded in eight of 14 cases. Reviewing the clinical follow-up data, we found that the PET/CT result influenced the clinical management of 28.4% of patients. The surgical removal of lymph node, subcutaneous, lung, brain and mesenteric metastasis was noted in 10.8% of patients. In addition, 21.6% of patients were administered systemic treatment, and surgical excision and systemic therapy was provided to 8.8% of patients. Of note, we observed disease recurrence in 22.6% of patients with stage I/II tumours within 4–15 months after a true negative PET/CT. This rate was slightly lower (16.7% within 4–12 months) in resected stage III tumours. The sites of recurrences included regional lymph nodes (8/12 in stage I/II and 3/5 in resected stage III respectively) or distant organs (4/12 in stage I/II and 2/5 in resected stage III respectively).

### PET/CT exhibits a high diagnostic accuracy

*Group 1: patients with resected stage I and stage II disease* Of the 69 PET/CT scans, 54 were negative, 53 (76.8%) were true negative and one was false negative (Table 4). In the latter case, a histopathologically confirmed subcutaneous recurrence of CMM at the primary site was removed within 3 months of the examination. Of the 69 PET/CT examinations, ten (14.5%) were true positive, and five were false positive. Most of the true positive PET/CT examinations were performed in the first year, and

**Table 2** PET/CT examinations

| | Patients | | |
|---|---|---|---|
| | **Male** | **Female** | **Total** |
| Number of PET/CT, *N* (%) | 65 (43.9) | 83 (56.1) | 148 (100) |
| Number of PET-CT per patient | *N* (%) | | |
| 1 | 34 (72.3) | 23 (46.0) | 57 (58.8) |
| 2 | 9 (19.2) | 21 (42.0) | 30 (30.9) |
| 3 | 3 (6.4) | 6 (12.0) | 9 (9.3) |
| 4 | 1 (2.1) | 0 (0.0) | 1 (1.0) |
| AJCC stage at PET-CT | *N* (%) | | |
| I/II | 27 (41.5) | 42 (50.6) | 69 (46.6) |
| resected III | 23 (35.4) | 30 (36.1) | 53 (35.8) |
| unresectable III/IV | 15 (23.1) | 11 (13.3) | 26 (17.6) |
| AJCC stage at PET-CT | Relapse after a true negative PET/CT*, *N* (%) | | |
| I/II | 5 (62.5) | 7 (63.6) | 12 (22.6) |
| resected III | 2 (25) | 3 (27.3) | 5 (16.7) |
| unresectable III/IV | 1 (12.5) | 1 (9.1) | 2 (50.0) |

*Disease recurrence was detected >3 months after the PET/CT scan.

**Table 3** PET/CT indications and the rate of the change in stage

| **Indication** | ***N* (%)** | **PET/CT result** |
|---|---|---|
| (Re-)staging | 129 (87.2) | 99 unchanged status<br>18 change in stage<br>9 progression<br>3 complete remission |
| Results of other imaging examinations were uncertain | 19 (12.8) | 6 verified recurrence/progression<br>8 progression excluded<br>5 remained uncertain |
| AJCC stage at the change in stage | | |
| I/II | 8 (11.6) | 4 regional lymph node metastasis<br>4 distant lymph node, lung, or bone metastases |
| resected III | 14 (26.4) | 5 distant lymph node, or subcutaneous metastases<br>9 lung, bone, brain, or liver metastases |

**Table 4** Diagnostic accuracy of PET/CT

| | **True positive** | **True negative** | **False positive** | **False negative** | **Total** | **Sensitivity** | **Specificity** | **Diagnostic accuracy** | **PPV** | **NPV** |
|---|---|---|---|---|---|---|---|---|---|---|
| *N* | 50 | 87 | 10 | 1 | 148 | 98.0 | 89.7 | 92.6 | 83.3 | 98.9 |
| AJCC stage at PET/CT | *N* (%) | | | | | | | | | |
| I/II | 10 (14.5) | 53 (76.8) | 5 (7.3) | 1 (1.4) | 69 (46.6) | 90.9 | 91.4 | 91.3 | 66.6 | 98.1 |
| resected III | 19 (35.9) | 30 (56.6) | 4 (7.5) | 0 (0) | 53 (35.8) | 100 | 88.2 | 92.5 | 82.6 | 100 |
| unresectable III/IV | 21 (80.7) | 4 (15.4) | 1 (3.8) | 0 (0) | 26 (17.6) | 100 | 80.0 | 96.2 | 95.45 | 100 |

PPV, positive predictive value; NPV, negative predictive value.

metastatic lymph nodes (8–20 mm in diameter) were detected in half of the scans. This finding indicates that these cases would have been SLN-positive melanomas, but SLNB was not performed initially due to head/neck localization, multidirectional lymphatic drainage detected by lymphoscintigraphy, or patient-related reasons. It should be mentioned that despite the early detection of metastases by PET/CT and subsequent therapeutic interventions, the rate of rapid disease progression was increased in this patient group (70%). One of the false-positive cases involved an enlarged distant lymph node in the left parailiacal region with increased



 

FDG uptake, which was surgically removed; the histopathological examination indicated reactive lymphadenopathy. Another case involved a solitary regional lymph node in the right axillary region that was not detected by subsequent follow-up ultrasound (US) examinations. There were five uncertain results, which were counted as positive scans. In three of the five uncertain cases, non-calcified nodules with uncertain dignity were visualized in the lungs by PET/CT. During the clinical follow-up, thorax CT indicated nodule disappearance in two cases (false positive), whereas pulmonary metastases were observed in the third case (true positive). In the fourth case, the mediastinal lymph nodes were interpreted as uncertain positive lesions that were not detected either by thorax CT 3 months later or by PET/CT 1 year later (false positive). In the fifth case, an axillary regional lymph node was described with uncertain dignity, and both the fine needle aspiration biopsy (FNAB) and the histopathological examination of block-dissection confirmed lymph node metastasis (true positive). Overall, the sensitivity of PET/CT in stage I/II tumours was 90.9%, the specificity was 91.4% and the diagnostic accuracy was 91.3%.

*Group 2: patients with resected stage III disease* Of the 53 PET/CT examinations, 30 (56.6%) were true negative, and 19 (35.9%) were true positive. No false-negative results were obtained. Of these 53 PET/CT scans, four (7.5%) were false positive. A regional lymph node in one case and a distant lymph node in another case, both with increased FDG uptake, were identified as metastatic lesions. However, FNAB was negative in both cases, and the lymph nodes subsequently became undetectable in follow-up US examinations. In the third case, a subcutaneous nodule was detected in an in-transit location but was undetectable in the next follow-up US examination as well as by a subsequent PET/CT scan 6 months later. The fourth false-positive case involved a pelvic mass with increased FDG uptake that was undetectable by US either at that time or during subsequent follow-up. Only one case was noted wherein a subcutaneous mass with moderate FDG uptake in the left inguinal region was depicted as a lesion with uncertain dignity. We decided to remove this lesion because it was close to the surgical scar of the previous block dissection. Histopathological examination revealed that the lesion was a subcutaneous in-transit metastasis. Overall, in resected stage III tumours, the sensitivity of PET/CT was 100%, the specificity was 88.2% and the diagnostic accuracy was 92.5%.

*Group 3: patients with unresectable stage III and resected or unresectable stage IV disease* Of the 26 examinations, 21 (80.7%) were true positive, and four (15.4%) were true negative. The indication for PET/CT at this stage primarily involved the assessment of therapeutic efficacy. One false-positive case proved to be a submandibular lymph node. In one case, FDG-positive nodules were detected in the apex of both lungs by PET/CT. Based on the localization of the nodules and the distribution of FDG uptake, the scan was interpreted to be uncertain with the possibility of reactivation of pulmonary tuberculosis. Neither thorax CT nor bronchoscopy with cytological examination and mycobacterial culturing led to a diagnosis. We considered the case to be a lung metastasis; however, lymph node and in-transit metastases progressed without deterioration of the pulmonary status. Overall, in this advanced stage, the sensitivity of PET/CT was 100%, the specificity was 80% and the diagnostic accuracy was 96.2%.

## Discussion

The early detection and appropriate treatment of lymph node or distant metastases are important factors in the overall survival of CMM patients. The diagnostic sensitivity of FDG-PET in this disease is 90% for metastatic nodules ≥78 $mm^3$ in volume (approximately ≥5.3 mm in diameter).[9,10] Thus, FDG-PET is unable to detect micrometastases in patients with clinically localized CMM; therefore, it was concluded that FDG-PET scanning is not of use in the initial staging of these patients.[11] FDG-PET combined with CT increased the diagnostic accuracy,[12] and several studies have demonstrated that PET/CT is superior to PET or CT alone as well as other conventional imaging methods.[13–15] Several studies have been conducted to determine the role of PET/CT in primary staging and restaging in early-stage and high-risk melanoma patients.[10,16–29] From these, the reported ranges for diagnostic sensitivity were 0 to 100% in AJCC stages I and II and 68 to 87% in AJCC stages III and IV.[18]

Our study demonstrates the high diagnostic accuracy (92.6%) of PET/CT. The reduced accuracy observed in cases of lymph node, pulmonary and subcutaneous metastases is consistent with previous reports.[7] For example, pulmonary nodules smaller than 12 mm in diameter may be FDG negative despite their metastatic origin, and additional examinations, such as a follow-up CT of the thorax 3 months later, are required.[7,30] PET/CT also exhibits a disadvantage in the detection of central nervous system metastases. The accuracy of PET/CT to detect metastases in the central nervous system is also reduced given the increased glucose uptake of grey matter and variations in the pattern of the FDG uptake of melanoma brain metastases (hypermetabolic, hypometabolic or ring like).[31,32] There is no doubt that MRI is the most appropriate imaging technique to investigate the central nervous system and to exclude its involvement in metastatic disease. Nevertheless, given the high prevalence of brain metastasis in metastatic melanoma and the likelihood of detecting a brain metastasis by PET/CT even in an asymptomatic patient, as observed in three of 97 patients in this study, PET/CT imaging must include the investigation of head in melanoma patients.[32]

By comparing the diagnostic accuracy of PET/CT in various disease stages, we observed reduced specificity in resected stage III tumours compared with stage I/II tumours, where the technique exhibits reduced sensitivity. However, the diagnostic accuracy was high in both stages (91.3% and 92.5% respectively).

As expected, most of the true positive PET/CT scans were obtained from advanced stage patients, and most of the true negative PET/CT examinations were obtained from stage I/II patients. In this study population, a true positive scan was twice as likely in patients with resected stage III disease than in patients with stage I and stage II disease ($P = 0.007$). No significant difference was noted between the clinicopathological features of patients with true negative and true positive PET/CT scans (data not shown). In terms of prognosis, based on clinical follow-up data, the rate of disease progression was increased after a true positive PET/CT in all stages (70.0%, 73.7% and 81%) despite treatment. Nevertheless, a relatively high rate of disease recurrence (22.6%) was obvious in stage I/II patients soon (within 4–15 months) after a true negative PET/CT. This rate was slightly lower (16.7% within 4–12 months) in resected stage III tumours. If we consider a PET/CT scan to be a false negative when the disease recurs at any time during the observation period after a negative PET/CT, the diagnostic accuracy of PET/CT is reduced. However, the accuracy remains high, with rates of 91.3% in stage I/II, 92.5% in resected stage III and 96.2% in unresectable stage III/stage IV tumours.

The high diagnostic accuracy of PET/CT makes this imaging technique an appropriate tool for use in CMM staging; however, the optimum timing of the PET/CT scan to ensure cost-related and patient-related benefits remains unclear. PET/CT does not appear to be useful for initial staging or during regular follow-up of low-risk CMM patients (stage I), who comprise the majority of melanoma cases.[5] In the initial staging of high-risk patients with stage IB/II tumours, the SLND must be the first choice. Our results justify the utility of PET/CT in the (re)staging of CMM patients with diagnosed stage III but suggest that PET/CT may also be beneficial for stage I/II patients in a selected high-risk population where SLND is negative or could not be performed. Which of the clinicopathological and/or immunohistochemical parameters of the primary tumour can be used for selection requires clarification.[33] Most of the PET/CT-positive cases in stage I/II were associated with the aggressive clinical behaviour of CMM; however, in general, only lymph nodes were initially detected by PET/CT.

In conclusion, PET/CT is an important diagnostic method in the management of patients with high-risk CMM; however, the technique cannot replace close clinical follow-up. Optimized stage-related patient selection and the optimum timing of the PET/CT scan must be established by further studies to best utilize the advantages of this imaging method. This study provides additional information.

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