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*Original Article*

# Evaluation of PET/CT in patients with stage III malignant cutaneous melanoma

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**Abstract:** In order to evaluate if patients with stage III-IV MCM are eligible for curative treatment PET/CT is performed. Since the diagnostic value of PET/CT is not unambiguously, a retrospective cohort study is performed to tailor optimal indication of PET/CT in patients with stage III MCM. A retrospective cohort study was conducted of all patients with stage III disease in a large oncologic teaching hospital in which PET/CT was performed from 2012 to 2016. The primary tumor- and regional lymph node characteristics were assessed to predict distant metastasis seen on PET/CT. A total of 73 patients were included of which 18% were restaged as stage IV by PET/CT. Twenty percent of the patients with a positive lymph node and 14% of patients with in transit metastasis or satellite lesions were restaged to stage IV. T-classification, ulceration and N-classification did not predict distant metastasis. Localization of the primary tumor significantly differed (P = 0.004). Localization on the head/neck resulted in a 32 greater odds of distant metastasis (P = 0.008). After a median follow-up of 36 months, 13 out of 60 (27%) stage III MCM patients were restaged as stage IV after the first performed PET/CT. This retrospective cohort study resulted in restaging of 18% of the stage III MCM patients by PET/CT, with therapeutic consequences. Patients with stage III MCM on the head/neck seem to have more distant spreading of the tumor than other localizations. Further investigation is needed, with larger sample sizes, to guide optimal indication of PET/CT.

**Keywords:** Malignant cutaneous melanoma, PET/CT, stage III, retrospective cohort

## Introduction

Skin cancer represents one third of all diagnosed types of cancer. Each year 132,000 patients are worldwide diagnosed with malignant cutaneous melanoma (MCM) and its incidence is increasing [1].

Standard practice is wide local excision of the primary tumor and staging according to the American Joint Committee on Cancer (AJCC) melanoma of the skin staging system [2]. A sentinel node procedure (SNP) is advised in case of pathological stadium 1B to provide accurate staging, ensuring regional lymph node control and improving melanoma-specific survival [3, 4]. Stage III MCM is present when metastasis to regional lymph nodes, in transit metastasis or satellite lesions is detected. In case of stage III MCM, a Positron Emission Tomography Computed Tomography (PET/CT) is performed to exclude distant metastasis [5].

PET/CT is superior to PET alone or side-by-side PET and CT in the localization and characterization of distant lesions [6], but cannot replace SNP or ultrasonography in the work-up of staging regional lymph nodes [5, 7]. In detecting distant metastasis, the specificity and sensitivity of PET/CT in patients with stage III MCM is respectively 100% and 88% [8]. Despite this, the role of PET/CT in staging of stage III MCM patients is not conclusively defined.

Therefore, the aim of this study is to evaluate the diagnostic value of PET/CT in patients with stage III MCM.

## Materials and methods

### *Patients*

From January 2012 to January 2016 all AJCC stage III MCM patients who underwent a PET/CT at the Northwest clinics, Alkmaar, The Ne-

**Table 1.** Patient- and tumor characteristics

| | PET/CT positive | PET/CT negative | *P*-value |
|---|---|---|---|
| Patients, n (%) | 13 (17.8) | 60 (82.2) | |
| Age, years (range) | 66.5 (48-88) | 64.3 (26-89) | 0.874 |
| Gender, n female (%) | 4 (30.8) | 33 (55.0) | 0.201 |
| T-stage | | | |
| Tx (%) | 0 (0) | 3 (5.0) | 0.240 |
| T1 (%) | 0 (0) | 7 (11.7) | |
| T2 (%) | 6 (46.2) | 19 (31.7) | |
| T3 (%) | 3 (23.1) | 23 (38.3) | |
| T4 (%) | 4 (30.8) | 8 (13.3) | |
| Ulceration (yes, %) | 2 (15.4) | 22 (36.7) | 0.184 |
| Regression (yes,%) | 1 (7.7) | 2 (3.3) | 0.473 |
| N-stage | | | |
| N1 (%) | 4 (30.8) | 21 (35.0) | 0.872 |
| N2 (%) | 3 (23.1) | 16 (26.7) | |
| N3 (%) | 6 (46.2) | 23 (38.3) | |
| Satellite lesion (%) | 1 (7.7) | 15 (25.0) | 0.273 |
| In transit metastasis (%) | 5 (38.5) | 19 (32.2) | 0.749 |
| Localization | | | |
| Extremities (%) | 3 (23.1) | 32 (54.2) | 0.004 |
| Torso (%) | 7 (53.8) | 26 (44.1) | |
| Head/neck (%) | 3 (23.1) | 1 (1.7) | |

therlands were retrospectively analyzed. All patients had histologically proven MCM including regional lymph node metastasis, in transit metastasis or satellites lesions. Positive regional lymph nodes were observed by sentinel node procedure (SNP), lymph node dissection (LND) or lymph node biopsy (LNB). Additional parameters such as patient characteristics, localization of the primary tumor, Breslow thickness, ulceration, pathological TNM classification according to the AJCC staging system and PET/CT characteristics were included in a database [2]. Distant metastases seen on PET/CT were histologically proven.

This study did not needed approval by a Medical Ethical Committee, because of the retrospective nature of this study in which anonymous data was used.

*PET/CT protocol*

A standardized PET/CT protocol was performed in all patients. Patients were scanned by a Siemens Biograph-16 TruePoint PET/CT (Siemens Healthcare, Knoxville, USA). Patients were in a fasted state of at least 6 hours and drank one liter of water before the examination. In the case of diabetes mellitus, non-insulin dependent patients were in a fasted state of 6 hours and insulin dependent patients were at least 4 hours in a fasted state. Blood glucose was checked before the examination and had to be < 10 mmol/L. 274 ± 47 MBq of $^{18}$F-FDG is injected and the patient was instructed to lie still in a warm bed for 40 minutes before the examination.

If the lesion was above the umbilicus, a PET/CT was performed from the skull to the groin, otherwise a whole-body PET/CT was executed. Reconstruction was done by means of an iterative OSEM3D algorithm using 4 iterations and 8 subsets and a 5 mm Gaussian filter. Reconstructed images had an image matrix size of 256 × 256, a pixel spacing of 2.67 × 2.67 mm and a slice thickness of 4 mm. A low-dose CT scan was acquired for localization and attenuation correction purposes using a tube current of 25 mAs at 130 kV, collimation 16 × 1.2 mm and a pitch of 0.95. For some patients a diagnostic CT total body scan was acquired with 110 ref. mAs and 110 or 130 kV with 4D Care Dose, and in these patients intravenous contrast was used. CT images were reconstructed using a slice thickness of 4 mm (2 mm for diagnostic CT) and a matrix size of 512 × 512.

*Statistical analysis*

Data was analyzed using SPSS Statistics, version 20 (IBM, Washington, DC). Continuous variables were expressed as means and standard deviations for normal distributions and medians and interquartile ranges for non-normal distributions. Comparisons of PET/CT negative and PET/CT positive for distant metastasis was performed with a Student's T-test or Mann-Whitney-U test as was deemed appropriate. Frequencies were expressed as percentages and analyzed using the Chi-square test. Data was considered statistically significant when a *P*-value of < 0.05 was present.

## Results

Seventy-three consecutive patients were included in this retrospective cohort study (see **Ta-**

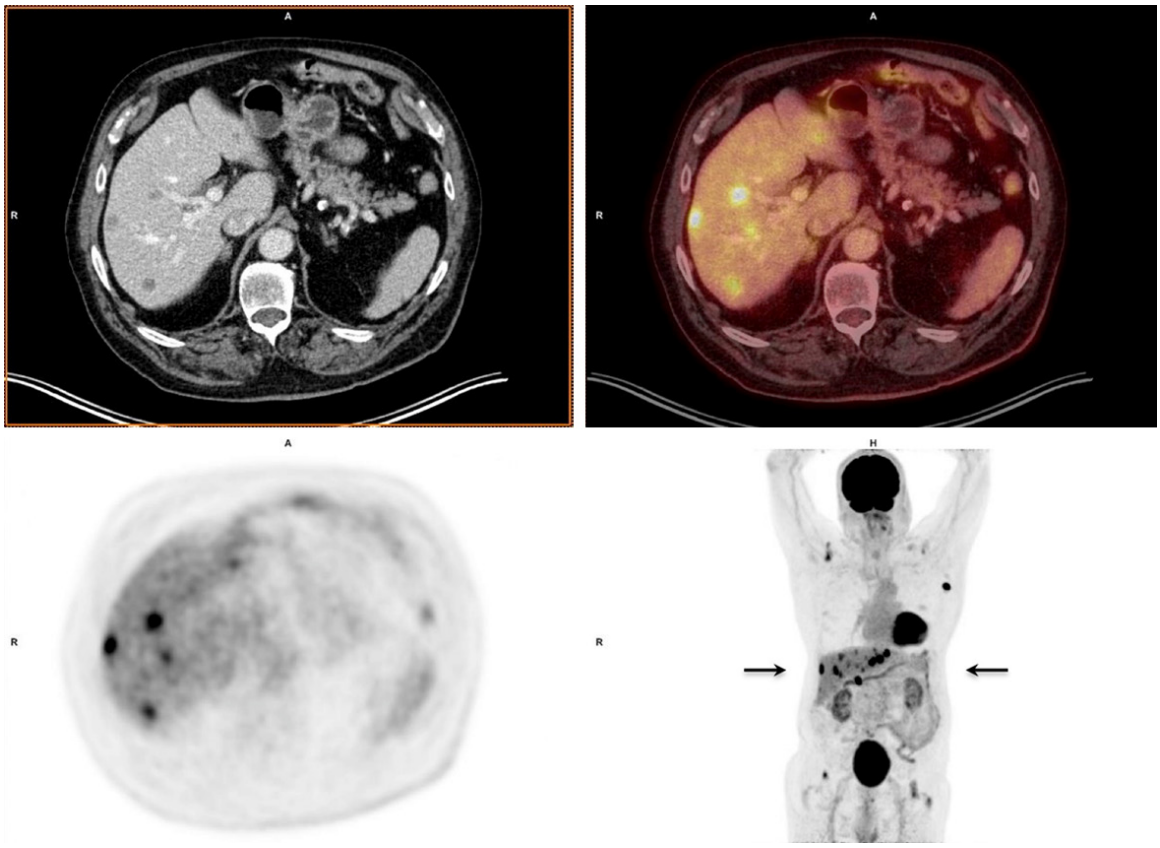

**Figure 1.** A 65-year old male with distant metastasis seen on PET/CT. This patient is diagnosed with a pT4a MCM frontotemporal. Pathological positive lymph nodes preauricular were observed. PET/CT revealed lymphatic and hepatic metastasis.

**Table 2.** Individual predictor of distant metastasis

| | PET/CT positive | PET/CT negative | Odds ratio (*p*-value) |
|---|---|---|---|
| Localization | | | |
| Extremities (%) | 3 (23.1) | 32 (54.2) | |
| Torso (%) | 7 (53.8) | 26 (44.1) | 2.87 (0.153) |
| Head/neck (%) | 3 (23.1) | 1 (1.7) | 32.00 (0.008) |

ble 1). Of these patients, thirteen (18%) patients who were primarily staged as stage III MCM, were restaged as stage IV based on distant metastasis seen on PET/CT (see **Figure 1**). Patient characteristics, tumor (T) and nodes (N)-classification, ulceration and regression did not significantly differ between patients with or without distant metastasis. None of the patients with a Tx- or T1-tumour had distant metastasis. In transit metastasis or satellite lesions were not identified as predictors of distant metastasis. However, the localization of the primary tumor differed significantly (P = 0.004) between patients with or without distant metastasis. Patients with a MCM on the torso had a 2.87 greater odd of distant metastasis compared to patients with a MCM on the extremities (P = 0.153). In patients with a head or neck MCM the odds was 32 times greater of developing distant metastasis compared to patients with MCM on the extremities (see **Table 2**).

*PET/CT characteristics*

The median time from diagnosis of the primary tumor to the indication of performing a PET/CT (stage III MCM), when nodal disease became present (direct or in the follow-up), was 42.2 months in stage IV MCM patients and 34.0 months in stage III MCM patients (P = 0.184). Distant metastasis was seen in 14% of the patients who had satellite lesions or in transit metastasis. In patients who had a positive lymph node, 20% had distant metastasis on PET/CT imaging (see **Table 3**).

**Table 3.** PET/CT characteristics, stratified by indication

| | PET/CT positive | PET/CT negative | *P*-value |
|---|---|---|---|
| Months to PET/CT | 42.2 | 34.0 | 0.184 |
| Indication of PET/CT | | | |
| Positive lymph nodes (%) | 9 (69.2) | 36 (60.0) | 0.535 |
| Satellite lesions or in transit metastasis (%) | 4 (30.8) | 24 (40.0) | |

**Table 4.** Follow-up of the 60 PET/CT negative patients, in which 30 received a second, third or fourth PET/CT

| | PET/CT positive | PET/CT negative | *P*-value |
|---|---|---|---|
| Patients, total (%) | 16 (53.3%) | 14 (46.7%) | |
| Indication of second PET/CT | | | |
| Positive lymph nodes, n (%) | 6 (60.0) | 14 (70.0) | 0.440 |
| Satellite lesions or in transit metastasis, n (%) | 4 (40.0) | 6 (30.0) | |
| Indication of third PET/CT | | | |
| Positive lymph nodes, n (%) | 2 (50.0) | 1 (25.0) | 0.500 |
| Satellite lesions or in transit metastasis, n (%) | 2 (50.0) | 3 (75.0) | |
| Indication of fourth PET/CT | | | |
| Positive lymph nodes, n (%) | 2 (100) | 0 (0) | 0.333 |
| Satellite lesions or in transit metastasis, n (%) | 0 (0) | 1 (100) | |

*Follow-up*

Thirteen of the 73 (18%) stage IV MCM patients were additionally treated with immunotherapy. The other 60 patients received clinical follow-up, whereby in 30 patients (50%) additional PET/CT's were performed for possible distant metastasis. Sixteen of the 60 patients (27%) were restaged as stage IV by PET/CT after a median follow-up of 36 months (see **Table 4**). Distant metastasis was seen after a median of 12 months after the first performed PET/CT (see **Figures 2** and **3**).

*Diagnostic accuracy of PET/CT*

Of the 73 stage III MCM patients included in this study, 13 patients were initially staged to stage IV based on PET/CT. In the follow-up at a median of 36 months an additional 16 patients were identified with distant metastasis seen on PET/CT after the first performed PET/CT. An additional PET/CT was indicated when recurrent regional disease or clinical suspicion of distant metastasis was present. This results in a diagnostic accuracy of PET/CT in this serie of 80%.

## Discussion

This study shows that 18% of the stage III MCM patients were restaged to stage IV based on the first performed PET/CT. Distant metastasis was present on PET/CT in 20% of patients with a positive lymph node and 14% of patients with satellite lesions or in transit metastasis. Localization of MCM is identified as a possible predictor of metastasis, as localization on the head/neck had a 32 greater odd of distant metastasis compared to the extremities. The results are in line with other studies, in which 22-26% of the patients were restaged from stadium III MCM to stadium IV by PET/CT [8, 9]. Since patients with stage IV MCM can be treated with immunotherapy with promising results, it is essential to identify this patient group as soon as possible [10-13].

As shown by this study, 16 of 60 patients (27%) were detected with distant metastasis by PET/CT after a median of 36 months after the first performed PET/CT. This high incidence of patients with distant metastasis in the follow-up could be the result of the limitations of PET/CT. Since PET/CT depends on the $^{18}$F-FDG avidity of the tumor, the volume of vital tumor cells, movement during acquisition and physiological uptake in the adjacent background factors such as small tumor lesion (partial volume effect), resolution of PET/CT, and the body composition (obesity) of the patient influence the detection of metastasis [14, 15].

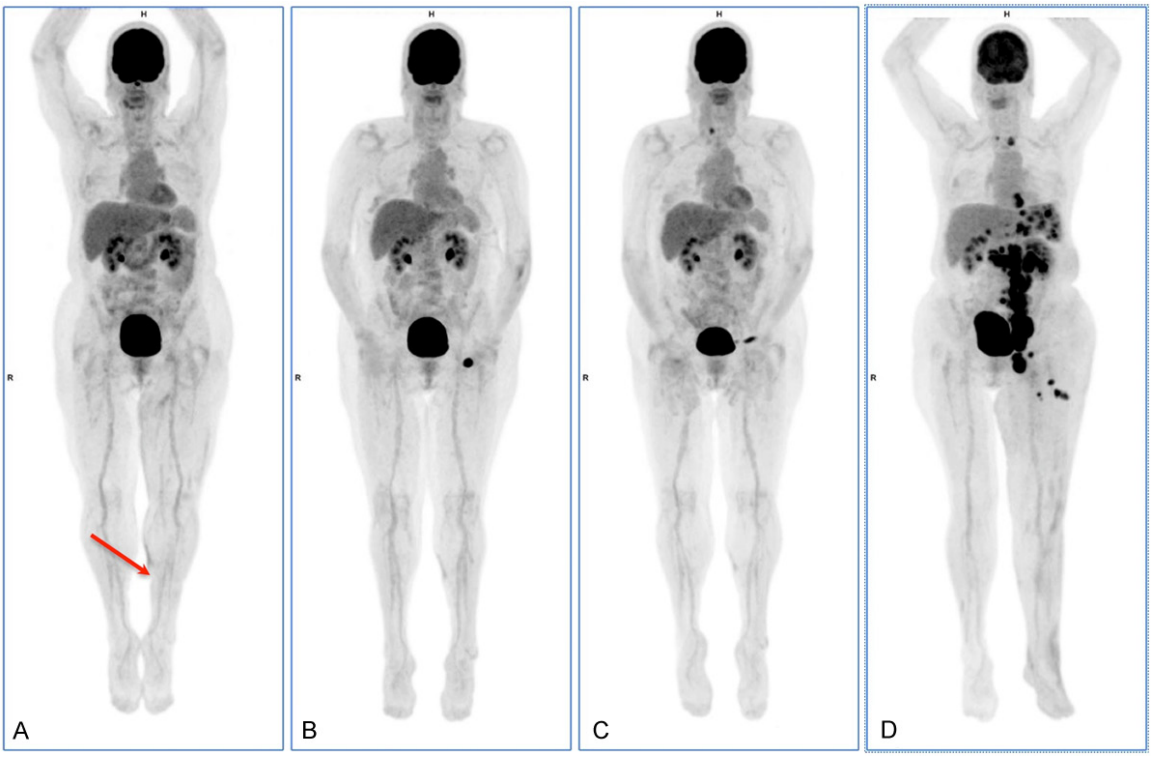


**Figure 2.** A 69-year old patient with distant metastasis in the follow-up after the first performed PET/CT. A patient with a pT3b superficial spreading melanoma on the left lower extremity. The pathological results of the therapeutic re-excision and sentinel node showed macrometastasis in two of the two lymph nodes. A superficial lymph node dissection was performed which showed micrometastasis in 3 of the 5 lymph nodes. A: PET/CT after a superficial lymph node dissection. No signs of regional- or distant metastasis was seen. B: After 7 months a solitaire FDG-avid pathological inguinal lymph node on the left side was observed. This lymph node was resected and showed regional metastasis without extra nodal growth. No distant metastasis was seen. C: 1 year after the first performed PET/CT regional lymph node metastasis was seen, with signs of distant metastasis in the thyroid gland (pathological proven). A thyroidectomy and inguinal lymphadenectomy was performed. D: 1.5 year after the first performed PET/CT extensive distant metastasis was seen and patient was referred for immunotherapy to a tertiary referral center.

Regarding surveillance of stage III MCM patients there is no consensus. As stated in a national guideline in The Netherlands, patients are screened in the follow-up by physical symptoms and -examination, which guides further diagnostics. If regional pathologic proven regional metastasis or clinical suspicion of regional metastasis by physical symptoms or -examination is present, a PET/CT is performed. Only few studies examined the optimal follow-up strategy in stage III MCM after the primary work-up also consisting a PET/CT. In one study in sentinel lymph node-positive stage IIIA-B MCM patients, patients were clinically examined every three months and received annually a PET/CT. Within one year six patients (9%) developed distant metastasis, of which one asymptomatic diagnosed by PET/CT. In the following median follow-up of 27.5 months, four patients (11%) developed distant metastasis of which two (50%) were detected by PET/CT, one by brain MRI and one by physical examination [16]. In another study of patients with stage IIIA-B MCM, patients received physical examination every 3-6 months and a PET/CT was performed only when clinical suspicion was present. In this study 19 out of 67 patients (28%) were restaged as stage IV after a median follow-up of 58 months after the first performed PET/CT [17].

As described before, follow-up strategies vary widely and varying results are reported. Although more research is needed to point out the optimal follow-up strategy in stage III MCM patients the current study indicates that PET/CT should be performed with a low threshold. As 25-45% of the recurrences in the follow-up are distant metastasis, it is important to identify

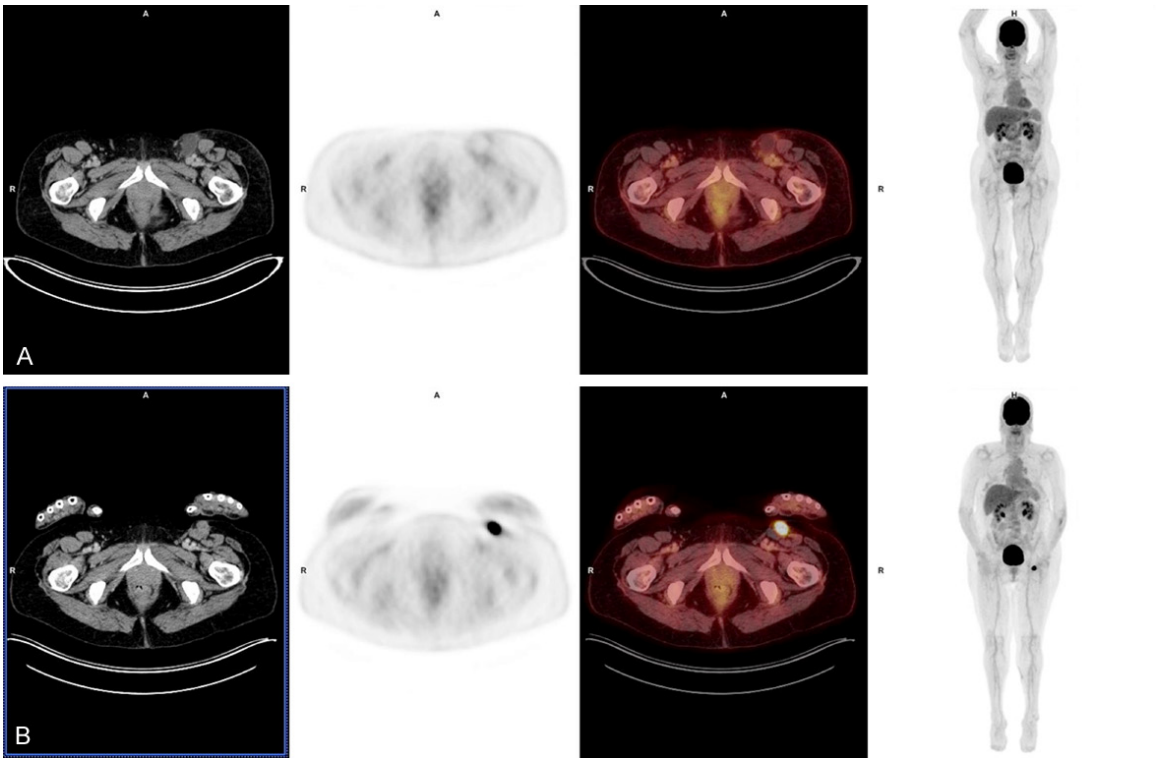


**Figure 3.** Characterization of PET/CT in a 69-year old patient. A: The initial PET/CT after a superficial lymph node dissection showed no signs of regional- or distant metastasis. B: In further detail, in a PET/CT after 7 months a solitaire FDG-avid pathological inguinal lymph node on the left side was observed. This lymph node was resected and showed regional metastasis without extra nodal growth. No distant metastasis was seen.

these stage IV MCM patients as early as possible [18, 19]. These patients can be selected to be treated with immunotherapy, as this leads better overall survival, overall response rate and progression free survival compared to chemotherapeutics [13, 20-22].

There were also a number of limitations in our study. The study was retrospective and is also limited by a small cohort of patients with stage III MCM. Potential other predictors of distant metastasis could possibly be detected if a larger sample size is present.

## Conclusions

Taking the limitations into consideration, this study in stage III MCM patients shows a considerable number of patients with metastatic disease identified by PET/CT, at the primary diagnosis, as well as during follow-up. PET/CT resulted in restaging 18% of the patients at diagnosis of stage III MCM. Localization on the head/neck resulted in a 32 higher odds of distant metastasis. At a median of 12 months in the follow-up after the first performed PET/CT an addition of 27% patients were restaged as stage IV. More research is needed, with larger sample sizes, to further tailor optimal indication of PET/CT in stage III MCM patients.

## Disclosure of conflict of interest

None.

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