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# Prospective comparison of $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma

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ABSTRACT

The aim of our study was to compare the overall and site-based accuracy and impact on patient management of positron emission tomography/computed tomography (PET/CT) and whole-body (wb) magnetic resonance imaging (MRI) in staging of advanced melanoma. In a prospective blinded study, 64 patients with American Joint Committee on Cancer (AJCC) stage III/IV melanoma underwent $^{18}$F-fluorodeoxyglucose PET/CT and wbMRI. In total 420 lesions were evaluated. The overall accuracy of PET/CT was 86.7% compared to 78.8% for wbMRI ($P = 0.0007$). PET/CT was significantly more accurate in N-staging and detecting of skin and subcutaneous metastases, whereas wbMRI was more sensitive in detecting liver, bone and brain metastases. WbMRI was less sensitive but more specific than PET/CT in classifying pulmonary lesions. In 41 patients (64%) whole-body imaging caused changes of treatment. Whole-body staging of patients with advanced melanoma is most accurate by combining wbPET/CT and organ-specific wbMRI including a brain, liver and bone marrow protocol.



## 1. Introduction

The prognosis of malignant melanoma is strongly related to the stage at which it is detected.[1,2] The 5-year survival for patients with stage III and IV melanoma according to the American Joint Committee on Cancer (AJCC) classification[2] is only about 50% and 6–10%, respectively. In stage III disease, a complete node dissection as well as in case of limited systemic disease a complete resection of metastases are probably the most effective methods in prolonging survival. Therefore, an accurate identification of all sites of metastatic spread is essential before surgery.[3–5]

So far, a complete evaluation of tumour spread in patients with advanced melanoma, necessitates various imaging procedures such as computed tomography (CT), dedicated magnetic resonance imaging (MRI), ultrasound, radiography and

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bone scan. This approach is time-consuming, cumbersome and expensive, and can miss lesions outside the fields of study. In contrast, novel whole-body technologies like dual-modality positron emission tomography/computed tomography (PET/CT) and whole-body (wb) MRI offer a complete head-to-toe coverage of the patient in a single examination with an accurate and sensitive detection of tumour spread.[6–8]

Several studies in patients with advanced melanoma revealed that PET imaging with $^{18}$F-fluorodeoxyglucose (FDG) is more sensitive than, and at least as specific as, conventional modalities such as CT and MRI, especially for metastases of more than 1 cm in diameter.[4,9–14] The combination of functional PET data with detailed anatomic information given by CT in the dual-modality PET/CT scanner provides further improvements in TNM staging.[15,16]

Recent developments in MRI technology combine the advantages of MRI with a whole-body coverage maintaining high image quality and a reasonable examination time.[6,7] A prospectively designed study comparing the accuracy of wbMRI and wbCT in patients with advanced melanoma reported the superiority of wbMRI influencing treatment decisions in 25% of patients [17].

Up to date, only single reports have evaluated the usage of wbMRI in oncologic staging or have even compared the diagnostic performance of wbMRI and PET/CT.[6,7,18] The preliminary results indicate a high diagnostic accuracy of both methods, in the correct definition of the overall TNM stage with advantages of PET/CT in lymph node detection but a higher accuracy of wbMRI in M-staging, especially with regard to brain, bone and liver.[7,18] However, these studies may be biased, as patients with various malignancies were included.

The objective of our prospective, blinded study was to determine the diagnostic accuracy of PET/CT and wbMRI for staging of patients with stage III/IV melanoma and to compare these two new imaging modalities regarding their influence on clinical management.

## 2. Material and methods

### 2.1. Patients

From September 2004 to September 2005, 100 consecutive patients with histologically proven cutaneous melanoma presenting with potential evidence of metastatic spread were referred from the Skin Cancer Unit of the Department of Dermatology for staging by PET/CT and wbMRI after being informed about the study procedures and signing an ethics-committee approved informed consent. 64 patients (41 males, 23 females, mean age 58 years, range 23–79 years) underwent both examinations, 25 patients with stage III and 39 patients with stage IV disease. In 25 patients no wbMRI could be performed due to metallic implants or claustrophobia (5 patients), refuse of a second whole-body examination on the same day (17 patients) or abortion of the examination (3 patients). The analysis was performed lesion-based. 11 patients had to be excluded because of no evidence of tumour spread (3 patients) or lack of follow-up data for lesion characterisation (8 patients). Indications for performing PET/CT and wbMRI were the exclusion of widespread diseases and confirmation of local diseases before surgical resection in 9 patients, further characterisation of abnormal radiological, clinical and laboratory (S100 protein, lactic dehydrogenase) findings in 48 patients, routine melanoma surveillance in high risk patients in 7 patients. PET/CT and wbMRI were performed within a 24–72 h time interval. For detailed patient characteristics refer to Table 1.

### 2.2. PET/CT Imaging

All patients fasted overnight. PET/CT imaging started 55–65 min after intravenous administration of 370 MBq of $^{18}$F-FDG and was performed using the Hi-Rez Biograph 16 (Siemens Medical Solutions, Knoxville, USA), consisting of a high-resolution 3D LSO PET and a state-of-the-art 16 row multi-slice CT. Emission data were acquired from the base of the skull to the lower legs with 3 min acquisition per bed position. Patients with BMI > 25 were examined 4 min per FOV. CT was operated with 120 kV, 120–160 mAs, rotation time of 0.5 s, collimation of 0.75 mm (thorax) and 1.5 mm (abdomen), respectively, table feed of 12/24 mm, and reconstructed slice thickness/increment 5/5 mm (axial) and 3/2 mm (coronal), respectively. Patients were positioned on the scanning table with their arms raised in order to reduce beam-hardening artifacts. To receive diagnostic CT data, in all patients a multi-phase CT protocol with an intravenous application of 120 ml iodinated contrast agent (Ultravist 370, Schering GmbH, Berlin, Germany) was performed. The intravenous contrast volume of 120 ml was administered with a flow of 2 ml/s. To prevent contrast-induced artefacts, we optimised

**Table 1 – Patient and tumour characteristics (N = 64)**

| Characteristics | Patients *n* (%) |
|---|---|
| Sex | |
| Male | 41 (35.9) |
| Female | 23 (64.1) |
| Age (years) | |
| Mean | 57.8 |
| Range | 23.3–79.1 |
| Histologic type of primary tumour | |
| SSM | 27 (42.2) |
| NM | 13 (20.3) |
| ALM | 4 (6.3) |
| LMM | 2 (3.1) |
| Occult melanoma | 12 (18.8) |
| Other | 6 (9.4) |
| Tumour depth (mm) | |
| Mean | 2.69 |
| Range | 0.6–12 |
| Clinical stage at time of examination | |
| III | 25 (39.1) |
| IV | 39 (60.9) |

*Note*: Patients with occult melanoma were not included in tumour depth.

*Abbreviations*: AJCC, American Joint Committee on Cancer; SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma.

the injection protocol with a 40 ml saline chaser. All patients were asked to drink 1000 ml Mannitol 2% as a negative oral contrast agent prior to scanning in order to distend the bowel. During preliminary studies, we tested different scanning and breathing protocols to optimise contrast-enhanced CT studies.[19] According to the results of our tests, patients were asked to stop breathing in normal expiration during the contrast-enhanced CT scans for optimal co-registration. The attenuation-corrected PET data were iteratively reconstructed and coregistered with the CT data by commercial software (eSoft, Siemens, Erlangen, Germany).

### 2.3. Whole-body MRI

All wbMRI examinations were performed on a whole-body 1.5 T system using multiple phased-array surface coils and receiver channels together with integrated parallel acquisition technique (Avanto, Siemens AG, Erlangen, Germany). The total examination time lasted about 1 h. The examination protocol involved state-of-the-art MRI from head to toe, including axial and coronal scans before and after intravenous contrast administration as described in Ref. [17]

### 2.4. Image evaluation

Firstly, single methods (PET, CT and wbMRI) were interpreted independently by two specialists in nuclear medicine, two CT radiologists and two MRI radiologists. The readers were aware of the clinical status of the patient, but were blinded to the results of the other imaging studies and previous tests. In the second interpretation session, after a time interval of 4–6 weeks, fused PET/CT images and the results of all modalities were evaluated in consensus, lesion-by-lesion, by the same reader team. Additionally, during this session all lesions were re-evaluated retrospectively, being aware of the results of the other modalities.

The FDG-distribution was rated visually and optionally quantified as standardised uptake values (SUV). Any focal tracer uptake exceeding normal regional tracer accumulation was assessed as a malignant lesion. The determination of malignancy in CT and MRI was based on morphological characteristics and enhancement pattern. Lymph node involvement in CT was based on region-specific nodal size criteria based on measurement of the small axis diameter.[20,21] In wbMRI detected lymph nodes smaller than 10 mm but with brighter signal on T1 sequences, due to the paramagnetic effect of melanin, also were rated as suspicious.

For each lesion suspicious for malignancy in PET, CT, PET/CT or wbMRI, the site-based localisation (skin, soft tissue, lymph node, lung, liver, other viscera and bone) and the degree of suspicion (malignant, benign, probably malignant, probably benign) were recorded. On the basis of this scale, the lesions rated malignant or probably malignant were considered to be malignant, and the lesions rated benign and probably benign were considered to be benign. In addition, the largest and smallest diameter of lesions in CT and wbMRI, and the average SUV of lesions in PET were evaluated. Cerebral lesions in wbMRI were recorded, but excluded from the analysis because of the lack of comparable PET data. More than 5 lesions per site (lung, liver, bone) were numbered as 'multiple'. PET/CT and wbMRI were compared regarding their overall and site-based accuracy and by M1-subcategory according to AJCC (M1a: metastases in the skin, subcutaneous tissue, and lymph nodes, M1b: lung metastases, M1c: other visceral sites).

The impact of PET/CT and wbMRI on patient management was evaluated on the basis of treatment changes. For each patient an individual treatment plan was prepared on the basis of disease history, current clinical situation and tumour stage according to recent therapy and follow-up guidelines. The treatment concept was re-evaluated after performing PET/CT and wbMRI and changes of the primary plan caused by the whole-body imaging were recorded. The following treatment changes by PET/CT and wbMRI were considered: (i) change of the surgical field of curative intended metastasectomy, (ii) change from curative resection to palliative treatment, (iii) change of palliative treatment protocol (first-line to second-line), (iv) establishment of indications for palliative surgery, (v) exclusion of metastatic spread. Changes in treatment schedule were evaluated retrospectively by professionals from the Skin Cancer Program of the Department of Dermatology on the basis of the imaging findings.

### 2.5. Standard of reference

The standard of reference for suspicious lesions was classified into three categories: (i) histology obtained by metastasectomy, (ii) imaging follow-up by PET/CT, CT, dedicated MRI, ultrasound, bone scan or radiography, (iii) clinical follow-up including tumour marker (S100, lactic dehydrogenase) and other laboratory and clinical tests. True positive (TP) means that a lesion was rated as malignant or probably malignant and malignancy was confirmed by histology or progression on follow-up. True negative (TN) was defined when a lesion was rated as benign or probably benign and was found to be benign on histology or failed to show progression on follow-up. False negative (FN) occurred either when one of the modalities failed to detect a lesion or when a lesion was falsely classified as benign or probably benign and the lesion was found to be malignant at histology or showed progression on follow-up. False positive (FP) occurred when a modality classified a lesion as malignant or probably malignant and the lesion was found to be benign on histology or failed to show progression on follow-up. Patients were observed in a regular three-month interval follow-up schedule for a mean follow-up time of 252.5 days (range, 99–474 days). The data of the reference standard were collected by a physician unaware of the results of PET/CT and MRI imaging.

### 2.6. Statistical analysis

Sensitivity, specificity, including their 95%-confidence intervals (CI), positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. The differences between the accuracies of PET, CT, PET/CT and wbMRI in lesion classification were tested for significance by sign test. A $P$-value $< 0.05$ was considered statistically significant. All statistical analyses were performed using the statistical software package JMP® IN 5.1 (SAS Institute, USA).

The selection of inclusion criteria led to underestimated calculated specificity, because only the lesions suspicious of malignancy in one of the different methods were included in the study and compared by different methods.

## 3. Results

### 3.1. Overall N- and M-staging analysis

The evaluable cohort of 64 patients presented a total number of 420 lesions, suspicious for malignancy in at least one of the modalities. All lesions were validated by a standard of reference, 65 (15%) lesions were confirmed by histology after resection, 267 (64%) lesions by imaging follow-up, 88 (21%) lesions by clinical follow-up. According to the reference standard, 297 (70.7%) of the 420 lesions proved to be melanoma metastases. The overall accuracy of PET/CT in the lesion-based evaluation was 86.7% compared with 78.8% for wbMRI, 75.0% for CT and 74.3% for PET alone. The differences between PET/CT and wbMRI ($P = 0.0007$) as well as between PET/CT and PET alone ($P < 0.0001$) were significant. While the results of PET and PET/CT changed only marginally by retrospective re-evaluation, the sensitivity of wbMRI improved from 79.8% to 86.9% by reducing the rate of false negative (FN) classifications in this manner. A detailed staging analysis is presented in Table 2.

### 3.2. Staging analysis of specific metastatic sites

The lesion-based evaluation of diagnostic accuracy in various metastatic sites showed a different performance of PET/CT and wbMRI (Fig. 1). The details of the site-based lesion analysis are presented in Table 3. PET/CT was more sensitive than wbMRI in detecting skin and subcutaneous metastases, the specificity was equal for both modalities. In N-staging, PET/CT showed a significantly higher accuracy than wbMRI (86.7% and 69.6%, respectively, $P < 0.0001$). WbMRI was less sensitive than PET/CT in detecting pulmonary metastases, but more specific by reducing the high number of false positive (FP) results produced by CT. All hepatic lesions were correctly determined by wbMRI, while PET/CT missed two malignant lesions. The most accurate method to classify bone lesions was wbMRI, but without a significant difference to PET/CT. All other visceral metastases were correctly detected by PET/CT in comparison to 61.5% sensitivity of wbMRI ($P = 0.12$). 15 patients (23.4%) developed cerebral metastases, exclusively diagnosed by wbMRI.

### 3.3. Staging analysis related to AJCC M1-subcategories

The details of lesion-based analysis of the different M1-categories are presented in Table 4.

Diagnostic accuracy in defining the M1a-category was significantly higher for PET/CT than for wbMRI ($P < 0.0001$). The results of the M1b-category were identical to the site-based analysis showing no significant difference between both modalities. The M1c-category was correctly determined by PET/CT and wbMRI with a similar accuracy of 92.0% and 91.1%, respectively.

### 3.4. Impact on patient management

The overall change of treatment according to the results of whole-body staging was recorded in 41 patients (64.1%). In 12 patients the therapy concept changed from curative (metastasectomy) to palliative (immunochemotherapy), in 10 patients the surgical field of curative intended resection was modified, in 10 patients tumour progression was recognised and the protocol of palliative treatment was altered from first-line to second-line chemotherapy, in 7 patients the indication for palliative surgery was established; in 2 patients with suspicious lesions in CT, tumour spread could be excluded. When changes in the treatment schedule were analysed for the influence of different imaging procedures, PET/CT performed best; 90.2% of the changes could be motivated by PET/CT alone, 87.8% by wbMRI alone (cerebral metastases excluded), 75.6% by PET alone and 73.2% by CT alone. In 15 patients with cerebral metastases changes of management were prompted exclusively by wbMRI.

## 4. Discussion

The results of our prospective study demonstrate the potential of whole-body imaging techniques such as PET/CT and wbMRI for staging of metastatic melanoma. Whole-body staging modalities simplify and shorten the work-up of

**Table 2 – Overall assessment of N- and M-stage with PET, CT, PET/CT and wbMRI according to lesion-based analysis**

| Imaging modality | Number of lesions | | | | Sensitivity | | Specificity | | PPV (%) | NPV (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | TP | FP | TN | FN | % | 95% CI | % | 95% CI | | | |
| PET | 209 | 20 | 103 | 88 | 70.4 | 64.8–75.5 | 83.7 | 76.0–89.8 | 91.3 | 53.9 | 74.3 |
| CT | 229 | 37 | 86 | 68 | 77.1 | 71.9–81.8 | 69.9 | 61.0–77.9 | 86.1 | 55.8 | 75.0 |
| *PET/CT* | *269* | *28* | *95* | *28* | *90.6* | *86.7–93.6* | *77.2* | *68.8–84.3* | *90.6* | *77.2* | *86.7* |
| *wbMRI* | *237* | *29* | *94* | *60* | *79.8* | *74.8–84.2* | *76.4* | *67.9–83.6* | *89.1* | *61.0* | *78.8* |
| All | 275 | 27 | 96 | 22 | 92.6 | 89.0–95.3 | 78.0 | 69.7–85.0 | 91.1 | 81.4 | 88.3 |

*Note*: The table includes 64 patients presenting a total number of 420 lesions suspicious for malignancy in at least one of the modalities. The standard of reference defined 297 lesions as malignant and 123 lesions as benign. Brain metastases were excluded. Overall accuracy PET/CT *versus* wbMRI $P = 0.0007$, PET *versus* PET/CT $P < 0.0001$.

*Abbreviations*: PET, positron emission tomography; CT, computed tomography; wbMRI, whole-body magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value; TP, true positive; TN, true negative; FP, false positive; FN, false negative.

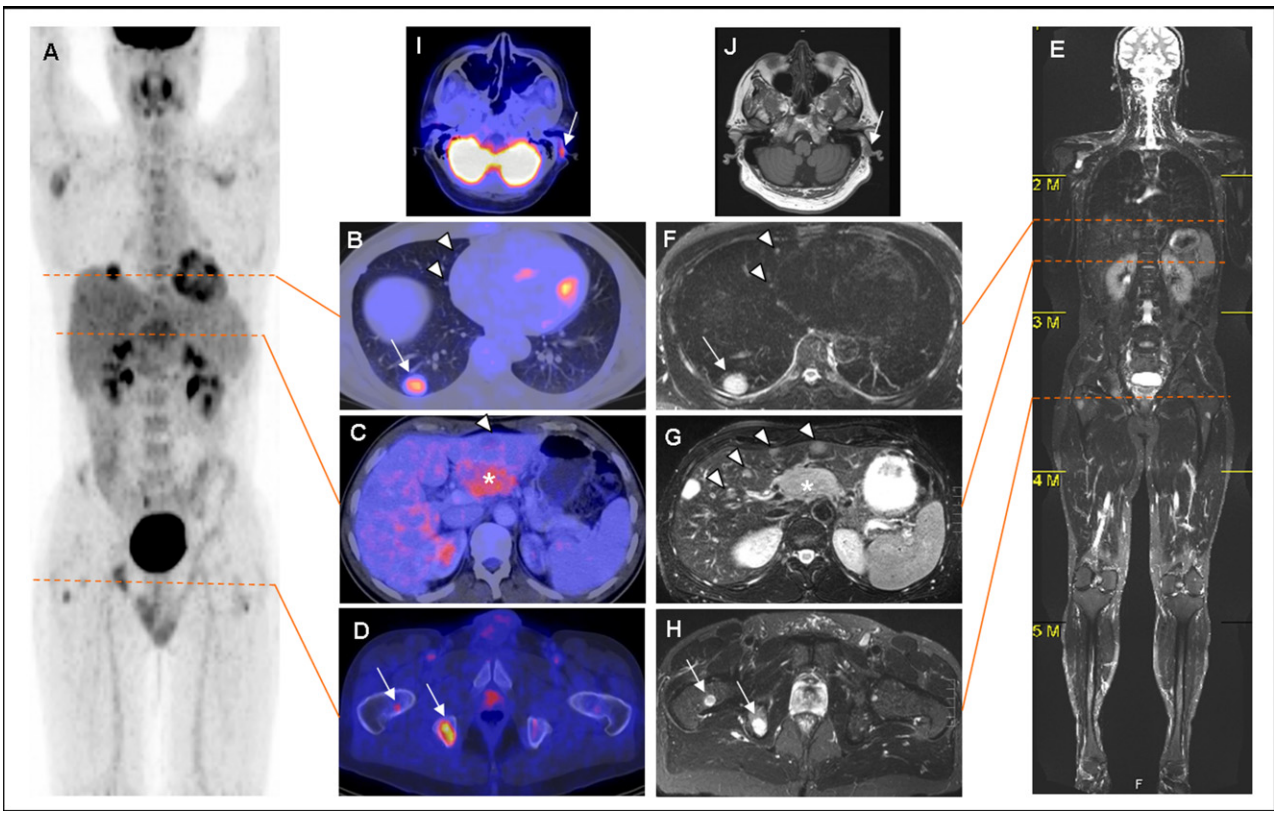


**Fig. 1 – PET/CT (A–D) and wbMRI (E–H) of a 37-year-old male with metastatic melanoma. CT and MRI found more lung metastases than PET (B/F, arrowheads) and MRI found more liver lesions than PET/CT (C/G, arrowheads). Bone metastases were equally detected (D/H, arrows). The nodal metastasis behind the left auricle (I/J, arrows) was detected by PET only.**

melanoma patients by replacing the conventional multimodality imaging approach. However, to further increase the acceptance of the whole-body staging examinations, the two examinations should be scheduled for separate days.

In our patient cohort PET/CT was significantly more accurate than wbMRI in the overall detection of malignant lesions, except brain metastases. But the more detailed analysis of the metastatic sites underlines that sensitivity and specificity of PET/CT and WbMRI notably differ between sites. WbMRI proved to be more sensitive for tumour detection in the central nervous system, liver and bone marrow, while PET/CT was superior for the detection of lymph node metastases and metastases to all other organs. Regarding specificity, the strengths of PET/CT were mainly apparent in the more accurate classification of lymph nodes and bone metastases.

The diagnostic performance of PET/CT and wbMRI in patients with melanoma has not been extensively studied so far. In a prospective evaluation of our own institution comparing the diagnostic accuracy of wbMRI and wbCT in 41 patients with advanced melanoma, Mueller-Horvat and colleagues[17] demonstrated the superiority of wbMRI, which detected 41% more metastases than CT (except lung metastases) and influenced treatment decisions in 25% of patients. A recently published study by Reinhardt and colleagues[16] evaluating 250 patients with melanoma (AJCC stage I–IV) by comparing PET/CT with PET and CT alone, found PET/CT to be superior to single modalities in N- and M-staging (accuracy 97%, 93% and 79%, respectively) influencing the therapeutic management in 48% of patients. So far, only two groups compared the diagnostic performance of wbMRI and PET/CT for oncological staging of various malignancies systematically, including only a small number of melanomas.[7,18] In both studies PET/CT proved to be superior to wbMRI in N-staging. The reported accuracies in N-staging were 93% and 91%, respectively, for PET/CT, and 79% and 78%, respectively, for wbMRI. Our study, evaluating exclusively patients with advanced melanoma, showed comparable results. The difference in diagnostic performance between PET/CT and wbMRI was most significant in the assessment of lymph nodes with a clear superiority of PET/CT. The advantages of functional PET information compared to general limitations in mainly size-based assessment of lymphatic spread by MRI (and CT) are well-known.[22–24] The accuracy of wbMRI may be improved by the introduction of novel contrast agents based on superparamagnetic iron oxide particles.[25,26]

Assessing the M-stage, the performance of PET/CT and wbMRI in our cohort notably differs between metastatic sites. PET/CT was more accurate than wbMRI in detecting skin and soft tissue lesions in spite of the inherent excellent soft tissue contrast in MRI. Obviously, the coronal image orientation of the legs led to missing or misinterpretation of lesions localised superficially in the skin and subcutaneous tissue. Accordingly, the legs should also be scanned in axial orientation in further studies. As expected, the high sensitivity of PET/CT in the detection of lung metastases could not be reached by wbMRI as already reported by other groups.[7,17,18]

**Table 3 – Assessment of N- and M-stage with PET, CT, PET/CT and wbMRI for the different sites of metastases**

| Site of metastases | Number of lesions | Imaging modality | Number of lesions | | | | Sensitivity | | Specificity | | PPV (%) | NPV (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TP | FP | TN | FN | % | 95% CI | % | 95% CI | | | |
| Skin and subcutaneous tissue | 80 | PET | 50 | 8 | 13 | 9 | 82.6 | 73.0–92.8 | 64.7 | 38.4–81.9 | 86.4 | 57.9 | 77.8 |
| | | CT | 38 | 6 | 15 | 21 | 73.9 | 50.9–76.4 | 70.6 | 47.8–88.7 | 87.2 | 50.0 | 73.0 |
| | | *PET/CT* | 53 | 7 | 14 | 6 | 89.1 | 79.2–96.2 | 70.6 | 43.0–85.4 | 89.1 | 70.6 | 84.1 |
| | | *wbMRI* | 46 | 7 | 14 | 13 | 76.1 | 65.3–87.7 | 70.6 | 43.0–85.4 | 87.5 | 52.2 | 74.6 |
| | | All | 55 | 6 | 15 | 4 | 91.3 | 83.5–98.1 | 70.6 | 47.8–88.7 | 89.4 | 75.0 | 85.7 |
| Lymph nodes | 158 | PET | 86 | 4 | 52 | 16 | 84.3 | 75.8–90.8 | 92.9 | 82.7–98.0 | 95.6 | 76.5 | 87.3 |
| | | CT | 78 | 13 | 43 | 24 | 76.5 | 67.0–84.3 | 76.8 | 63.6–87.0 | 85.7 | 64.2 | 76.5 |
| | | *PET/CT* | 87 | 6 | 50 | 15 | 85.3 | 76.9–91.5 | 89.3 | 78.1–96.0 | 93.6 | 67.9 | 86.7 |
| | | *wbMRI* | 67 | 13 | 43 | 35 | 65.7 | 55.6–74.8 | 76.8 | 63.6–87.0 | 83.8 | 55.1 | 69.6 |
| | | All | 86 | 5 | 51 | 16 | 84.3 | 75.8–90.8 | 91.1 | 80.4–97.0 | 94.5 | 76.1 | 86.7 |
| Lung | 70 | PET | 14 | 1 | 16 | 39 | 26.4 | 15.3–40.3 | 94.1 | 71.3–99.9 | 93.3 | 29.1 | 42.8 |
| | | CT | 51 | 12 | 5 | 2 | 96.2 | 87.0–99.5 | 29.4 | 10.3–56.0 | 80.9 | 71.4 | 80.0 |
| | | *PET/CT* | 51 | 11 | 6 | 2 | 96.2 | 87.0–99.5 | 35.3 | 14.2–61.7 | 82.3 | 75.0 | 81.4 |
| | | *wbMRI* | 46 | 4 | 13 | 7 | 86.8 | 74.7–94.5 | 76.5 | 50.1–93.2 | 92.0 | 65.0 | 84.3 |
| | | All | 51 | 11 | 6 | 2 | 96.2 | 87.0–99.5 | 35.3 | 14.2–61.7 | 82.3 | 75.0 | 81.4 |
| Liver | 37 | PET | 22 | 0 | 2 | 13 | 62.9 | 44.9–78.5 | 100.0 | 15.8–100.0 | 100.0 | 13.3 | 64.9 |
| | | CT | 28 | 1 | 1 | 7 | 80.0 | 63.1–91.6 | 50.0 | 1.3–98.7 | 96.6 | 12.5 | 78.3 |
| | | *PET/CT* | 33 | 0 | 2 | 2 | 94.3 | 80.8–99.3 | 100.0 | 15.8–100.0 | 100.0 | 50.0 | 94.5 |
| | | *wbMRI* | 35 | 0 | 2 | 0 | 100.0 | 90.0–100.0 | 100.0 | 15.8–100.0 | 100.0 | 100.0 | 100.0 |
| | | All | 35 | 0 | 2 | 0 | 100.0 | 90.0–100.0 | 100.0 | 15.8–100.0 | 100.0 | 100.0 | 100.0 |
| Bone | 50 | PET | 25 | 4 | 11 | 10 | 71.4 | 53.7–85.4 | 73.3 | 44.9–92.2 | 86.2 | 52.4 | 72.0 |
| | | CT | 22 | 3 | 12 | 13 | 62.9 | 44.9–78.5 | 80.0 | 51.9–95.7 | 88.0 | 48.0 | 68.0 |
| | | *PET/CT* | 32 | 3 | 12 | 3 | 91.4 | 76.9–98.2 | 80.0 | 51.9–95.7 | 91.4 | 80.0 | 88.0 |
| | | *wbMRI* | 35 | 4 | 11 | 0 | 100.0 | 90.0–100.0 | 73.3 | 44.9–92.2 | 89.7 | 100.0 | 92.0 |
| | | All | 35 | 4 | 11 | 0 | 100.0 | 90.0–100.0 | 73.3 | 44.9–92.2 | 89.7 | 100.0 | 92.0 |
| Other viscera | 25 | PET | 12 | 3 | 9 | 1 | 92.3 | 64.0–99.8 | 75.0 | 42.8–94.5 | 80.0 | 90.0 | 84.0 |
| | | CT | 12 | 2 | 10 | 1 | 92.3 | 64.0–99.8 | 83.3 | 51.6–97.9 | 85.7 | 90.9 | 88.0 |
| | | *PET/CT* | 13 | 1 | 11 | 0 | 100.0 | 75.3–100.0 | 91.7 | 61.5–99.8 | 92.9 | 100.0 | 96.0 |
| | | *wbMRI* | 8 | 1 | 11 | 5 | 61.5 | 31.6–86.1 | 91.7 | 61.5–99.8 | 88.9 | 68.7 | 76.0 |
| | | All | 13 | 1 | 11 | 0 | 100.0 | 75.3–100.0 | 91.7 | 61.5–99.8 | 92.9 | 100.0 | 96.0 |

*Note*: The table includes 64 patients presenting a total number of 420 lesions suspicious for malignancy in at least one of the modalities. Brain metastases were excluded. Accuracy in N-staging: PET/CT *versus* wbMRI $P < 0.0001$, PET *versus* CT $P = 0.0023$, PET *versus* wbMRI $P < 0.0001$, accuracy in lung staging: CT *versus* PET $P = 0.0002$, wbMRI *versus* PET $P < 0.0001$, accuracy in liver staging wbMRI *versus* PET $P = 0.0002$.
*Abbreviations*: PET, positron mission omography; CT, computed tomography; wbMRI, whole-body magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value; TP, true positive; TN, true negative; FP, false positive; FN, false negative.

Regarding the accuracy, however, PET/CT and wbMRI did not differ substantially due to the higher specificity provided by the applied wbMRI technique using 3D high-resolution T1-weighted gradient-echo sequences. Regarding liver and bone metastases, our results confirmed the observations of other groups indicating a higher accuracy of wbMRI in comparison to PET/CT.[7,18,27] In case of hepatic metastases this is particularly true for small (<8–10 mm) melanin containing lesions which are better displayed by their bright signal on T1-weighted MRI.[17,28] Neither liver nor bone metastases were missed in our cohort with wbMRI. The two liver metastases missed on PET/CT measured <10 mm in diameter. In the detection of other visceral metastases such as bowel or peritoneal lesions, PET/CT proved to be more reliable than wbMRI. It is important to note that the detection of tumour involvement of the central nervous system is most accurate only with wbMRI.[29,30] A limitation of PET is the normal uptake of FDG into the brain, leading to an uncertainty in the detection of cerebral metastases.[11]

Changes in treatment were recorded in a substantial part of our patients (64%), which is higher than 48% and 32% reported by other groups.[16,31] The differences may be explained, at least in part, by the variable patient cohorts. In contrast to the patient population of Reinhardt[16] and Harris,[31] our cohort involved only patients with stage III and IV melanoma that require changes in the palliative treatment towards second-line and third-line protocols more often. The global analysis of the different whole-body modalities in providing the accurate basis for treatment changes suggests a slight advantage for PET/CT compared to wbMRI. But none of the modalities ensured 100% staging accuracy to perform the sole basis for all modifications of treatment. In 15 patients (23%) with cerebral metastases the treatment changes were prompted exclusively by wbMRI.

In summary, our data suggest that whole-body staging of patients with advanced melanoma is most accurate by combining PET/CT and organ-specific wbMRI including a brain, liver and bone marrow protocol. Depending on the individual treatment plan, PET/CT may be recommended as a first-line modality. However, in patients with equivocal results organ-specific wbMRI protocols should complement the PET/CT, particularly when the detection or exclusion of distant tumour spread to the brain, liver and bones is deemed crucial.

**Table 4 – Assessment of N- and M-stage with PET, CT, PET/CT and wbMRI by M1-category**

| M1 category | Number of lesions | Imaging modality | Number of lesions | | | | Sensitivity | | Specificity | | PPV (%) | NPV (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TP | FN | TN | FP | % | 95% CI | % | 95% CI | | | |
| M1a (skin, subcutaneous tissue and distant LN) | 238 | PET | 136 | 25 | 65 | 12 | 84.5 | 77.9–89.7 | 84.4 | 74.4–91.7 | 91.9 | 72.2 | 84.5 |
| | | CT | 116 | 45 | 58 | 19 | 72.1 | 64.4–78.8 | 75.3 | 64.2–84.4 | 85.9 | 56.3 | 73.1 |
| | | *PET/CT* | *140* | *21* | *64* | *13* | 87.0 | 80.8–91.7 | 83.1 | 72.9–90.7 | 91.5 | *75.3* | 85.7 |
| | | *wbMRI* | *113* | 48 | 57 | 20 | 70.2 | 62.5–77.1 | 74.0 | 62.8–83.4 | 85.0 | 54.3 | 71.4 |
| | | All | 141 | 20 | 66 | 11 | 87.6 | 81.5–92.2 | 85.7 | 75.9–92.6 | 92.8 | 76.7 | 87.0 |
| M1b (lung) | 70 | PET | 14 | 39 | 16 | 1 | 26.4 | 15.3–40.3 | 94.1 | 71.3–99.9 | 93.3 | 29.1 | 42.8 |
| | | CT | 51 | 2 | 5 | 12 | 96.2 | 87.0–99.5 | 29.4 | 10.3–56.0 | 80.9 | 71.4 | 80.0 |
| | | *PET/CT* | *51* | *2* | *6* | *11* | 96.2 | 87.0–99.5 | 35.3 | 14.2–61.7 | 82.3 | *75.0* | 81.4 |
| | | *wbMRI* | *46* | *7* | *13* | *4* | *86.8* | *74.7–94.5* | *76.5* | 50.1–93.2 | 92.0 | *65.0* | *84.3* |
| | | All | 51 | 2 | 6 | 11 | 96.2 | 87.0–99.5 | 35.3 | 14.2–61.7 | 82.3 | 75.0 | 81.4 |
| M1c (other viscera) | 112 | PET | 62 | 21 | 23 | 6 | 74.7 | 64.0–83.6 | 79.3 | 60.3–92.0 | 91.2 | 52.3 | 75.9 |
| | | CT | 62 | 21 | 23 | 6 | 74.7 | 64.0–83.6 | 79.3 | 60.3–92.0 | 91.2 | 52.3 | 75.9 |
| | | *PET/CT* | *78* | 5 | 25 | 4 | 94.0 | 86.5–98.0 | 86.2 | 68.3–96.1 | 95.1 | *83.3* | 92.0 |
| | | *wbMRI* | *78* | 5 | 24 | 5 | 94.0 | 86.5–98.0 | *82.8* | *64.2–94.2* | *94.0* | *82.8* | *91.1* |
| | | All | 83 | 0 | 24 | 5 | 100.0 | 95.7–100.0 | 82.8 | 64.2–94.2 | 94.3 | 100.0 | 95.6 |

*Note*: All patients were classified to different M1-categories according to the AJCC staging system. Brain metastases were excluded. Accuracy in defining M1a: PET/CT *versus* wbMRI $P < 0.0001$, PET *versus* CT $P = 0.001$, PET *versus* wbMRI $P < 0.0001$, accuracy in defining M1b: CT *versus* PET $P = 0.0002$, accuracy in defining M1b: PET/CT *versus* PET $P < 0.0001$, wbMRI *versus* PET $P < 0.0001$, accuracy in defining M1c: PET *versus* wbMRI $P = 0.0015$, PET/CT *versus* PET $P < 0.0001$.

*Abbreviations*: PET, positron emission tomography; CT, computed tomography; wbMRI, whole-body magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value; TP, true positive; TN, true negative; FP, false positive; FN, false negative; LN, lymph nodes; AJCC, American Joint Committee on Cancer.

## Conflict of interest statement

None declared.

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