PRACTICAL CONSIDERATIONS WHEN INTERPRETING FDG PET/CT IMAGING FOR STAGING AND TREATMENT RESPONSE ASSESSMENT IN MELANOMA PATIENTS

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Abstract

While FDG PET/CT bears a high sensitivity and specificity for the staging of stage III and IV melanoma as well as for the purpose of melanoma recurrence detection, overall results tend to vary from one part of the body to another as well as for melanoma from cutaneous or choroidal origin. In this paper, organ or site-related differences in sensitivity and specificity in melanoma patients, both from cutaneous and choroidal origin, as well as their impact on clinical decision making are discussed. Furthermore, with the advent of immunotherapy for the treatment of malignant melanoma, post-treatment related potential false positive findings have emerged, the knowledge of which is essential for accurate treatment response assessment. These post-treatment related potential false positive findings are summarized in this paper so as to help the nuclear medicine physician in avoiding erroneous interpretation of acquired FDG PET/CT images in melanoma patients receiving immuntherapy.

Keywords: Melanoma, mucosal melanoma, FDG PET/CT, immunotherapy, immue-related adverse events

Introduction

Melanoma, predominantly arising form melanocytes in the cutis, is reported as the 19th most common cancer worldwide and its incidence is rising.[1,2] Staging of melanoma is based on the primary tumor thickness (Breslow thickness), the presence of local ulceration, lymph node and distant metastases.[1,2]

In melanoma with a Breslow-thickness < 1 mm, (stage T1) the risk of metastases is extremely low and thus imaging studies are not cost-effective in this setting.[3] In melanoma with an intermediate Breslow thickness, between 1 and 4 mm (stages T2 and T3), the risk of locoregional lymph node (LN) involvement is high but the risk for distant metastases remains relatively low, around 20%.[3,4] As tumor deposits in lymph nodes are often below the resolution of the PET-camera, around 5 mm, its use is not advocated for the purpose of detecting LN-involvement from melanoma. For instance, in a study by Crippa et al. the detection rate of melanoma-involved LNs smaller than 5 mm was only 23%. To date, for the purpose of assessing the presence of LN involvement by melanoma, the sentinel lymph node biopsy technique remains the most accurate diagnostic test.[5,6,7]

Inversely, once melanoma has spread to one or more regional LNs (stage III disease) or to distant LNs or other parts of the skin or the body, for example, lungs, liver, brain or bones (stage IV disease), because of its high diagnostic accuracy for identifying additional or unexpected sites of distant metastases, FDG/PET CT imaging is of major clinical relevance.8, 9, 10, 11[-12] In a systematic review by Krug et al. including 2150 patients with stage III and IV disease, FGD/PET proved overall 86% sensitive and 87% specific for detecting LN and distant metastases.[8] Similar results were reported by Schroër-Günther M et al.[9] In a systematic review and meta-analysis by Rodriguez-Rivera et al., including 9 eligible studies and a total of 623 patients, the overall pooled sensitivity and specificity for detecting systemic metastases was 89.42%, specificity was 88.78% and the area under the summary receiver operating curve (SROC) was 0.94.[10] Also, in a meta-analysis performed by Jiménez-Requena et al., the authors demonstrated that FDG PET is not useful for the evaluation of regional lymph node metastases, given it does not detect microscopic disease.[11] Finally, in a more recent meta-analysis by Woo Lee et al. including 11 studies, the diagnostic value of FDG PET/CT imaging for detecting recurrent disease after treatment of malignant melanoma was proven to be identical to that of initial staging in stage III and IV melanoma, with respectively a pooled sensitivity of 0.94 and pooled specificity of 0.91.[12]

Importantly, the high sensitivity and specificity of FDG/PET CT imaging in patients with stage III and IV melanoma translates into a significant change in up to 15%-64% of melanoma patients, in treatment strategy conferring amongst others survival benefits in patients with confirmed stage III disease.8, 9, 10, 11

While FDG PET/CT bears a high sensitivity and specificity in the staging of stage III and IV melanoma as well as for the purpose of recurrence detection, overall, the results tend to vary from one part of the body to another. Furthermore, with the advent of immunotherapy for the treatment of malignant melanoma, post-treatment related potential false positive treatment findings have emerged, the knowledge of which is essential for accurate treatment response assessment. Both issues will be addressed in this paper.

Organ-Dependent Variability in Sensitivity and Specificity of FDG PET/CT Imaging for Staging and Restaging of Stage III and IV Melanoma

Lymph nodes; As stated in the introduction, the detection rate of involved LNs by melanoma is size and thus resolution dependent (partial volume effect). In a study by Crippa, et al., all LNs larger than 10 mm, 83% of LN larger than 5 mm and 23% of nodal metastases smaller than 5 mm were identified.[7] In this sudy, as in several others, involvement of LN was based on visual analysis of obtained images.[10] As increased FDG metabolism in LN may also be reactive and/or inflammatory in nature, in order to avoid false positive findings, some authors investigated the value of FDG PET derived semiquantitative parameters to discern between malignant and benign LNs in melanoma patients. In a non-randomized prospective clinical trial including 144 melanoma patients scheduled for SLN-biopsy, using visual analysis and an arbitray chosen cut-off SUVmax-value > 2.5 for malignant LN involvement, a sensitivity of 21% and specificity of 97% for melanoma-involved LN-detection was found.[11] In a more recent study by Cha et al. assessing the value of semiquantitatiev FEG/PET CT imaging for the purpose of lymph node metastases detection, an SUV-max cut-off value > 2.51 and a tumour-to liver ratio > 0.91 yielded a comparable diagnostic accuracy of 80%.[13] For LN ≥ 1 cm, an SUVmax ≥ 2.4 yielded a diagnostic accuracy of 88.9% whereas for non-enlarged LNs (< 1 cm), an SUVmax cut off value of 1.4 showed the highest negative predictive value (81.3%). Other authors reported on the use of a cut-off value of three-times the bloodpool activity for differentiating malignant from benign LN-involvement in melanoma patients, but without validation against a gold standard.[14]

Skin and Subcutaneous Soft Tissue

The skin and subcutaneous soft tissue (SSST), along with the lymph nodes in the draining basin, represent the ealiest sites of regional metastases of cutaneous melanoma. SSST metastastases of cutaneous melanoma may be in the form of satellite lesion when the lesion is within 2 cm of the primary melanoma lesion or in-transit metastasis when it lies farther than 2cm from the primary lesion.[15] The presence of this regional metastases to SSST upstage the disease to stage III and has a negative implication on survival. The 10-year-survival for patients with satellite or in-transit metastases is 30-50% compared with 69%-75% for patients with lymph node micrometasis or 40-60% for patients with clinically palpable regional lymph node metastases.[16] Clinical assessment in vital in the detection of SSST metastases. FDG PET/CT may play a complementary role in assessment for SSST metastases. In a prospective evaluation of patients who presented with satellite and in-transit metastases of malignant melanoma without regional lymph node or distant metastases, Holtkamp et al. reported an FDG PET/CT sensitivity of 53% for the detection of the known sites of SSST metastases.[17] In another study with a more heterogenous patients

population (stages I-III), the sentivity, specificity, positive predictive value and negative predictive value of FDG PET/CT for the detection of SSST metastases were 50%, 0%, 88%, 0%, respectively.[18] Other authors have reported higher sensitivity (90-100%) of FDG PET/CT for the detection of SSST metastases, with a better performance for FDG PET/CT than MRI (sensitivity of 70-78%).[19]

The wide variability in the detection rate of FDG PET/CT for SSST metastases relates to the stage of disease in the patients included in the different studies. Patients with more advanced disease are more likely to have larger volume of SSST lesions while small skin or subcutaneous lesions may be seen in patients with a more limited disease. Considering the inherent limited spatial resolution of the PET system, smaller lesions may be easily missed. Improvemnet in the sensitivity and spatial resolution of the newer PET systems may improve SSST metastases detection in patients with cutaneous melanoma as the clinical use of these newer systems become more widespread.

The newer PET systems are also manufactured as hybrid systems interphased with anatomic imaging modalities, especially CT. CT, as part of PET/CT system, is useful for anatomic correlation and for attenuation correction. Due to the proximity of the skin and subcutaneous soft tissues to the PET detectors comapred with deeeper tissues, more photons emanating from positron annhilation occuring at the body surface are detected by the PET detectors compared with photons emanating from deep within the body. This phenomenum makes the skin to demosntrate more intense tracer uptake than deeper tissues on the non-attenuated corrected PET images. This difference is corrected by the application of CT data for attenuation correction. Unfortunately, attenuation correction may make skin less less apparent and easily missed on PET images. A complete interpretation of PET/CT images in patients with melanoma, therefore, includes the thorough examination of the attenuation-corrected and uncorrected images.

Eyes

Diagnosis of choroidal melanoma is made clinically with an accuracy of 99.5% and biopsy is seldom required.[20] While whole body PET/CT has proven useful for initial staging of choroidal melanoma, it is likely not very accurate in diagnosing both the primary nodular and more diffus infiltrating types of choroïdal melanoma, regardless of their size.[21] Furthermore, the degree of FDG uptake (SUVmax value) by choroïdal melanoma is also not related to the disease extent (presence of metastases). Inversely, loss of chromosome 3 by the tumor cells has been associated with a high risk of metastases and positive FDG-uptake.[22]

Brain

Approximately half of the melanoma patient population will develop brain metastases during the cours of their disease, necessitating surgery or radiotherapy.[23] Given the high level of FDG-uptake in normal brain tissue, FDG PET imaging bears a low sensitivity for detecting brain metastases and MRI imaging is the imaging modality of choice.[24,25]

Lungs

Following treatment of primary cutaneous malignant melanoma around 7%-21% of patients will develop metastatic disease to the lung.[26,27] These metastases are usuallay asymptomatic and typically detected by follow-up chest X-ray or thoracic CT-scan (Fig. 1). Older studies with less performing PET-equipment demonstrated that lung lesions smaller than 5 mm in diameter are in general PET-negative and that sensitivity for lung metastases detection progressively improves with increasing lesion size (Fig. 2); from 38.8 % to 87.5% in 5-13 mm sized lesions to 100% in lesions ≥ 14 mm.[28] As shown by Pfannenberg et al. the addition of contrast-enhanced CT to the FDG/PET examination increases its sensitivity from 26.4% to 96.2% but at the cost of a high false positive rate resulting in a specificity of only 35.3%.[25] Using more performing PET-equipment with resolution recovery slightly better but still unsatisfactory results were obtained by Mayerhoefer et al., respectively a sensitivity of 7.9% for lesions of 4-5 mm; 33.3% for lesions of 6-7 mm; 56.8% for lesions of 8-9 mm; 63.6% for lesions of 10-11 mm and 100% for lesisons of 12 mm and larger.[29] In their series, almost a quarter of patients (9 out of 38) were false negative for pulmonary involvement. These findings are in line with those reported by Bastiaannet et al. who reported that 50% of stage II melanoma patients that were false negative for the presence of distant metastases (slightly more than 6% of their entire population studied) was due to lung metastases.[30] In the series by Mayerhoefer et al. pulmonary nodules were rated as PET-negative if no focal tracer accumulation could be discerned on the acquired images whereas an SUV-max value of at least 2.5 was used as a criterion for malignancy.[29] The authors recommended that in melanoma patients with one or more PET-negative lung nodules that measure less than 12 mm on expiratory CT, additional tests should be performed. Reinhardt et al. also looked at the impact of attenuation corrected and non-attenuation corrected PET images on lung evaluation and found that out of the 174 lung lesions that were identified by FDG PET (39.7%), six were identified on the non attenuation corrected images only.[28] Bärwolf et al. studied the impact of breath-hold and free-breathing FDG PET/CT in malignant melanoma in a series of 34 patients and 117 lesions, including 33 lung lesions.[31] While breath-holding resulted in an increase in SUVmax and SUVmean of lesions, only one additional lesion, respectively a liver lesion, was identified. The authors suggested that breath-hold PET/CT is technically feasible but may only be clinically useful when fine quantitative evaluations are needed.

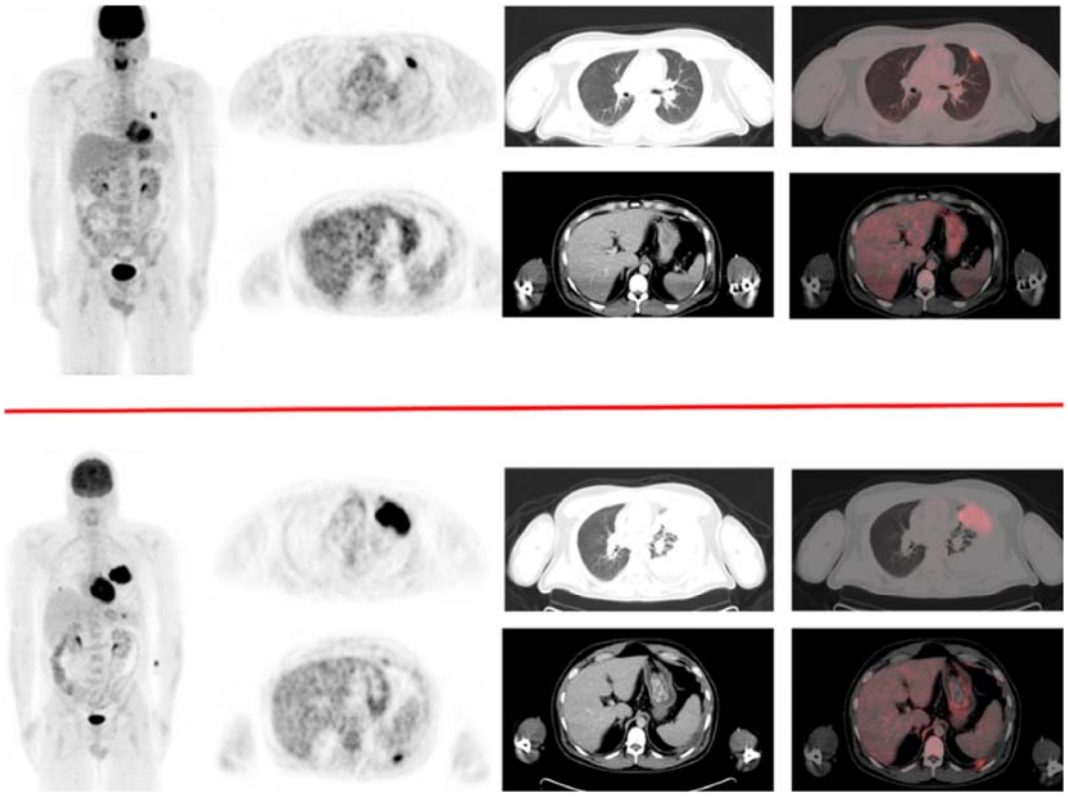

Fig 1: A 39-year-old male with a history of malignant melanoma resection from his right pinna in February 2012. Images from FDG PET/CT scan of October 2014 (top row) show a hypermetabolic pleural-based left lung nodule. No treatment was offered. A repeat FDG PET/CT scan of February 2015 (bottom row) shows progression of lung metastasis and a new focus of metastasis involving the diaphragm posterior to the spleen.

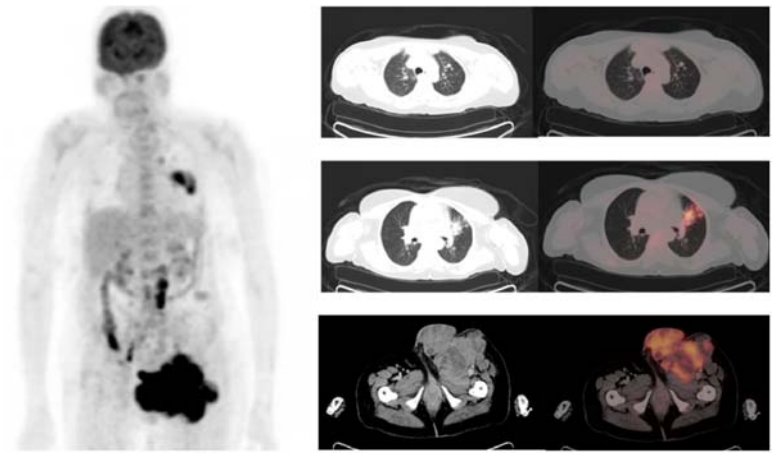

Fig 2: A 65-year-old female who presented with a fungating left inguinal mass confirmed to be metastatic melanoma on histological assessment. FDG PET/CT obtained for initial staging shows hypermetabolic nodules with associated consolidation of the lingula in favour of lung metastasis (left panel, middle row). A

sub-centimeter nodule due to lung metastasis in the left upper lobe does not demonstrate significant FDG avidity (left panel, upper row) as a result of partial volume effect.

While the problem with detecting lung metastases using FDG PET/CT imaging is predominantly a problem of low sensitivity, false positive findings may also occur and these are predominantly infectious and/or inflammatory in origine.[32,33] Of particular interest is the presence of subsolid nodules on CT findings that can be classified as pure or partially solid ground-glass nodules which are virtually always benign and mostly faintly positive on FDG PET imaging.[34] While the majority of these lesions disappear on subsequent FDG PET/CT examinations, when persistant and especially when increasing in size, also when non-FDG avid, they should be considered to represent part of the pathological spectrum of maligant melanoma as suggested by a case report by Dalpiaz et al.[35]

GI-tract

The reported incidence of symptomatic GI metastatic melanoma varies from 0.8% to 4.7% while the proportion of GI involvement in post-mortem analyses of disseminated melanoma is substantially greater, around 60%.[36,37,38] The most common GI-tract metastatic location is the small intestine (35%-97%), followed by the stomach (5%-50%) and colon (5%-32%). Average reported time-range time from initial diagnosis to intestinal metastases is 21.6-54 months. When the GI tract is the only location of metastases, complete surgical resection of the metastases can lead to a substantial survival benefit and thus careful examination of the GI-tract in melanoma patients that undergo an FDG-PET/CT examination is mandatory.[37] As shown by a number of case reports and a small series of six cases of malignant melanoma metastasized to the small bowel, FDG/PET CT may identify findings that are relevant for treatment planning in this setting that is missed during the conventional diagnostic work-up.39, 40-41 In a study by Prakoso et al. on 12 patients with positive small bowel findings on the FDG/PETexamination, capsule endoscopy confimed small-bowel metastases in only 5 of the 12 patients under study.[42] However, in their study the nature of the FDG uptake by the small bowel, focal or diffuse, was not described. In another study by Aerts et al. capsule endoscopy performed following the FDG/PET CT examination influenced the therapeutic decision making by performing or not a surgical segment resection in 2 out of 9 patients under study.[43] Based on the aforementionned findings, it has been suggested that any patient suffering from malignant melanoma presenting with abnormal increased bowel uptake should be considered for capsule endoscopy and that both investigations should be considered as complementary.[44]

Attention should be paid to the gall bladder as it may be a site of distant metastasis of malignant melanoma. Metastasis of melanoma to the gall bladder detected on FDG PET/CT has been reported in case reports.[45,46,47] The peritoneum is another rare site of intra-abdominal metastasis.[48] Figure 3, Figure 4 show FDG PET/CT images of patients with peritoneal metastases of malignant melanoma.

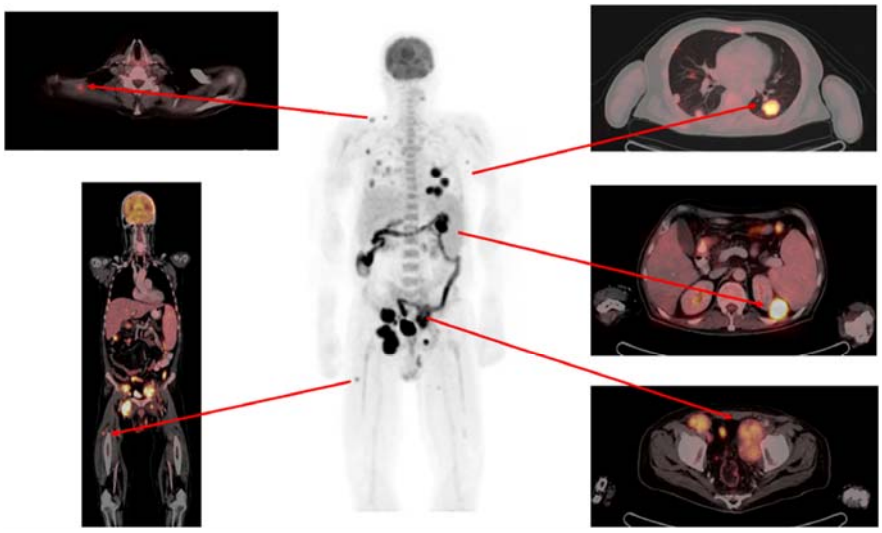

Fig 3: A 50-year-old male diagnosed with malignant melanoma from the histological evaluation of an enlarged left inguinal node. The primary site remained unknown. Images from the FDG PET/CT scan obtained for staging are shown. Middle panel shows the MIP image demonstrating multiple sites of metastases. Right panel images show foci of skeletal muscle metastases in the right trapezius muscle (upper image) and right thigh muscle (lower image). Left panel images show bilateral lung metastases (upper image), peritoneal metastasis (middle image) and bilateral inguinal nodal metastases (lower image). Diffuse large bowel FDG accumulation is because of metformin use in this patient with type II diabetes mellitus.

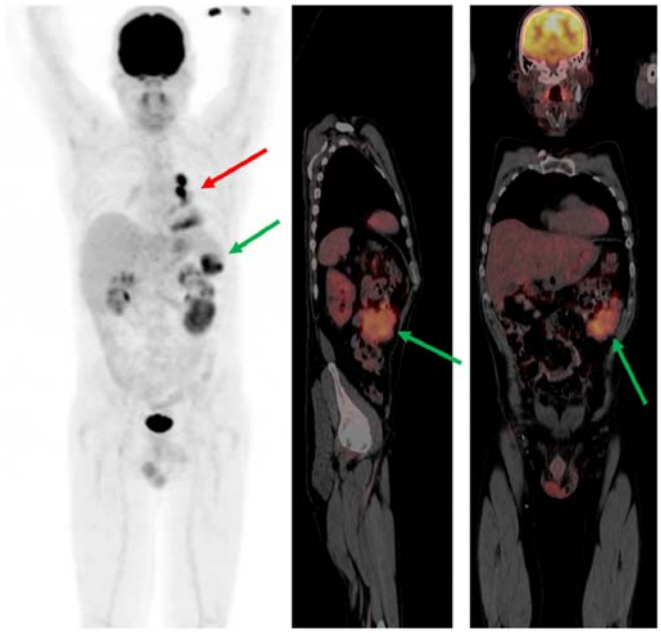

Fig 4: A 48-year-old male with a history of multiple malignant melanoma lesions resected from his right lower limb. Images from FDG PET/CT obtained on account of clinical suspicion of recurrence show large

hypermetabolic mesenteric mass (green arrows) consistent with metastasis and left pulomanry hilar lymph node metastases (red arrow).

Liver

On a per lesion basis, MRI has proven more sensitive for the detection of liver metastases, including those originating from malignant melanoma, with FDG PET/CT imaging being significantly less performing for lesions below 1 cm in diameter,[49,50] Figure 5. Importantly, the sensitivity of FDG PET/CT imaging appears to differ between those originating from uveal and those originating from cutaneous melanoma (Fig. 6). In a retrospective study by Strobel et al. conducted on 27 liver metastases in 13 patients with uveal melanoma and 43 liver metastases in 14 patients with cutaneous melanoma, sixteen of the uveal melanoma liver metastases (59%) proved PET-negative whereas all of the cutaneous melanoma liver metastases were FDG-positive.[51] Furthermore, liver metastases from uveal melanoma origine showed significantly lower SUVmax values when compared to those originating from cuteanous melanoma The reason for the lower FDG uptake in liver metastases originating from uveal melanoma remains unclear. While it has been demonstrated that both the proliferation rate and the cell viability of melanoma cells are likely to be key-factors for FDG uptake in melanoma, other factors than these may be responsable for the difference in FDG uptake between both types of liver metastases.[52,53] In this regard, the study by Yamada et al. looking at the impact of MDR (multidrug resistance) on FDG accumulation and efflux in malignant melanoma cell lines in vitro is of interest.[48] In their study, the SK-MEL 23 melanoma cell line which possesses a highly active function of MRP (multidrug-related protein), but not P-gp (P-glycoprotein), showed a significantly lower degree of FDG uptake and retention when compared to the SK-MEL 24 cell line that possesses weak functions of both MRP and P-gp.

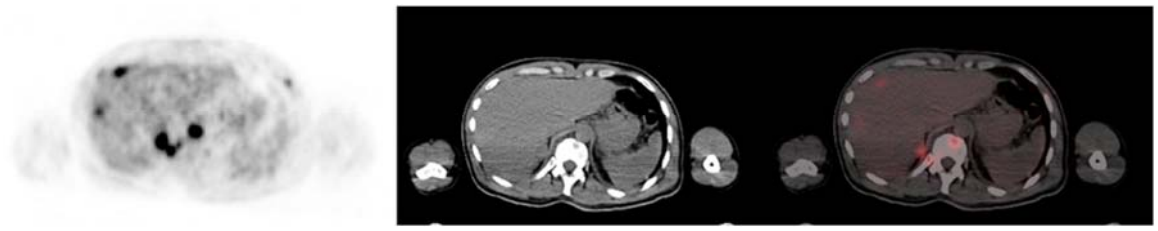

Fig 5: Axial PET, CT and fused PET/CT of a patient with advanced metastatic melanoma. Images show skeletal metastasis to a lumbar vertebra, right adrenal metastases and two foci of liver metastases. The foci of liver metastases are not apparent on this non-contrasted CT scan.

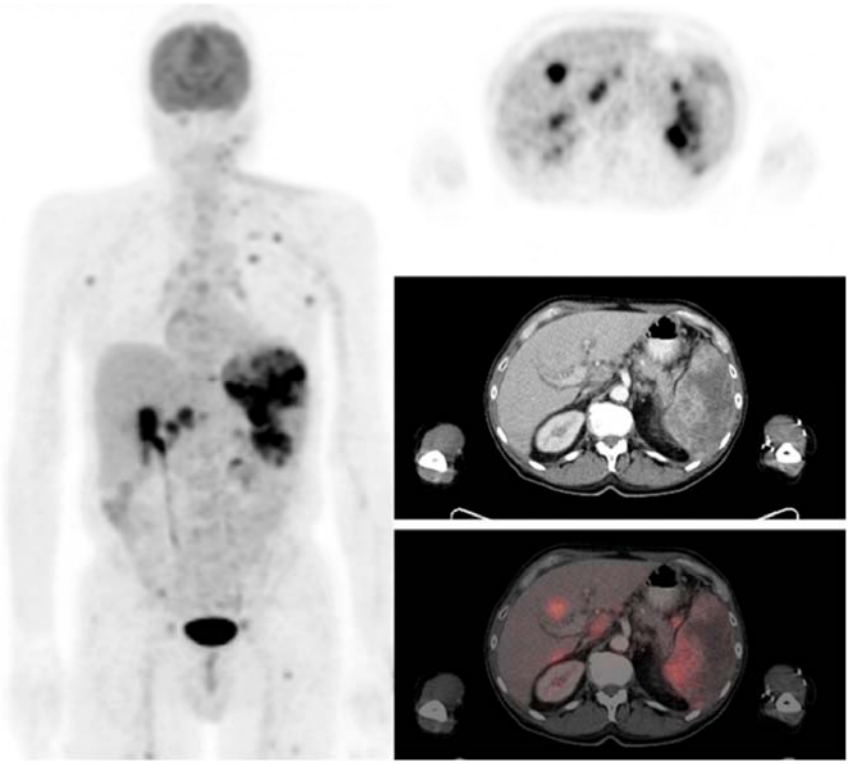

Fig 6: A 58-year-old male with a history of malignant melanoma resected from his scalp followed by left neck dissection 6 months later for the removal of metastatic cervical lymph nodes. Images of FDG PET/CT scan obtained 6 months after neck dissection are shown. Images show splenic, hepatic, and multiple lymph node metastases of malignant melanoma.

Muscle and Bone

Metastases to muscle tissue from melanoma, a late event in the progression of the disease, are rare (Fig. 3), occuring in 0.8% of patients[54] inspite of the fact that the abundantly blood supplied skeletal muscle tissue represents nearly 50% of the total body weight.[55]

Inversely, bone is a common site of melanoma metastatic spread usually occurring in patients who already have wide-spread metastases (Figs. 7 & 8). While the reported incidence in clinical series varies from 11%-17%, autopsy series have shown that skeletal metastases are much more common, ranging from 23%-49%.56, 57, 58 Of interest, isolated metastases to the bone from melanoma is rare, accounting for approximately 3.7%-6.9% of patients presenting with melanoma. As shown by Nocuri et al. using FDG PET/CT imaging, while the prevalence of solitary skeletal metastases was highest in malignant melanoma patients (6.9%), they are usually associated with the presence of other metastases and do not affect tumor staging.[59] Over 80% of metastases to the bone from melanoma are found in the axial skeleton. and 20% in the appendicular skeleton.[60] FDG PET/CT imaging has been previously shown to outperform contrast-enhanced CT for the detection of bone metastases, with less than 40% of the bone lesions identified on FDG PET/CT being picked up by contrast-

enhanced CT.[61] Inversely, FDG PET/CT imaging and MRI were shown to be equally suited for the detection of skeletal metastases in melanoma patients.[62]

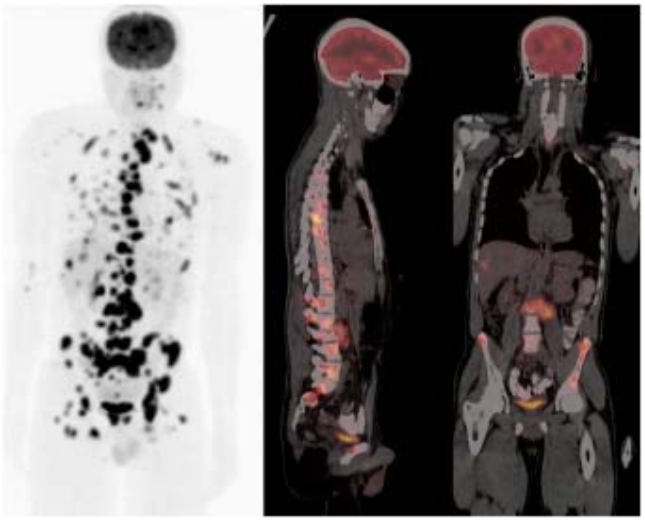

Fig 7: A 30-year-old male with melanoma of the head and neck region. He had surgical resection of the primary lesion with cervical dissection for removal of metastatic nodes. An FDG PET/CT scan was obtained due to complain of bone pain in the back and hips with numbness in the lower limbs. Images show liver, para-aortic lymph nodes and widespread skeletal metastases of malignant melanoma.

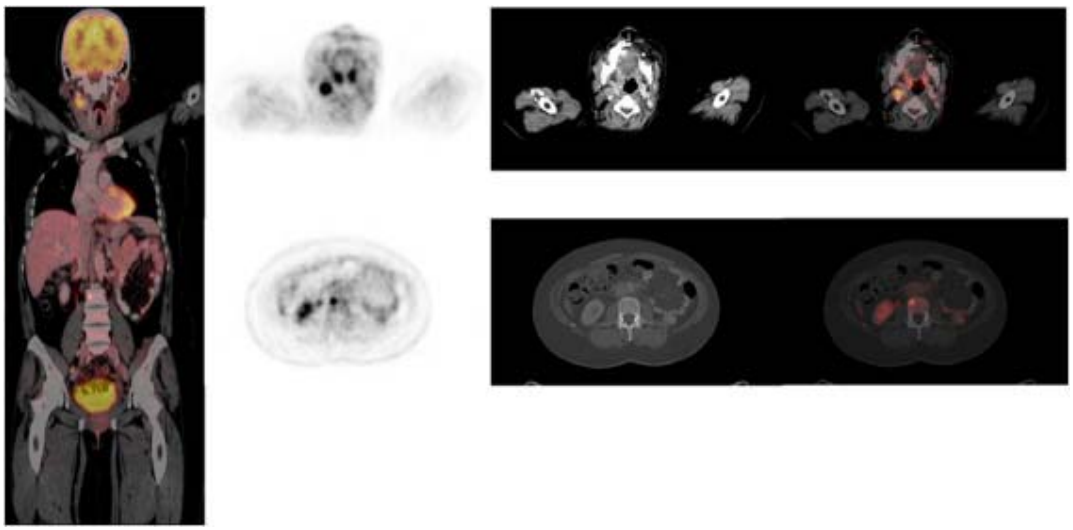

Fig 8: A 51-year-old female with a history of surgical resection of malignant melanoma from the uvula. FDG PET/CT obtained for re-staging showed right-sided cervical lymph node metastasis and a solitary skeletal metastasis to L3 lumbar vertebra.

Given muscle and skeletal metastases may occur throughout the body, the clinical relevance of including the lower-limbs in the FDG/PET CT whole body examination was addressed by a number of authors. Löfller et al. assessed 213 consecutive PET studies of 153 patients with suspected or newly diagnosed melanoma and found pathologic tracer

uptake in the limbs of 53 patients on 76 occasions.[63] However, with the exception of one patient in whom an isolated manifestation at the legs was identified, including the legs in the whole body examination did not yield relevant additional information. Similar findings were observed in a series of 200 malignant cutaneous melanoma patients by Lazaga et al.[64] Three patients in this series had positive findings in the lower extremities, and only one of these lesions, respectively loctated proximally in the femur (so included in the standard whole body examination), proved to be a melanoma-related metastases. Plouznoff et al. analyzed 461 full-body scans performed on melanoma patients, including the legs and identified unusual tracer accumulation in the lower limbs in 109 scans.[65] However, out of the 21 scans identifying lower-limb lesions attributed to melanoma, in no case did imaging of the lower limbs resulted in upstaging. Furthermore, in only one patient a treatment adjustment was made based on the data from the lower limbs. The authors concluded that imaging the lower extremities offers little additional clinical information and that stopping the scan at the proximal thigh has essentially no clinical impact. Of interest, in the series above, lesions below the mid-thigh on FDG PET/CT were only true positive in patients with the primary melanoma on the lower extremities.

Some caution is warranted when interpreting musculoskeletal FDG-avid lesions in the extremities of melanoma patients given the low positive predictive value of only 31% identified by Mansour et al. in a retrospective study in 342 patients suffering from stage IIB-IV melanoma.[66] The relative risk for false positive musculo-skeletal uptake was higher when no other metastases were present (5.33%) whereas the relative risk of an FDG-avid site seen in the appendicular region not being melanoma was 1.78 that of a site seen in the axial region. False-positive findings were more common in musculoskeletal soft tissue (63.6%) than in bone (36.4%), with the most common location for false positive findings being the knee (7 out of 26 cases) (Fig. 9).

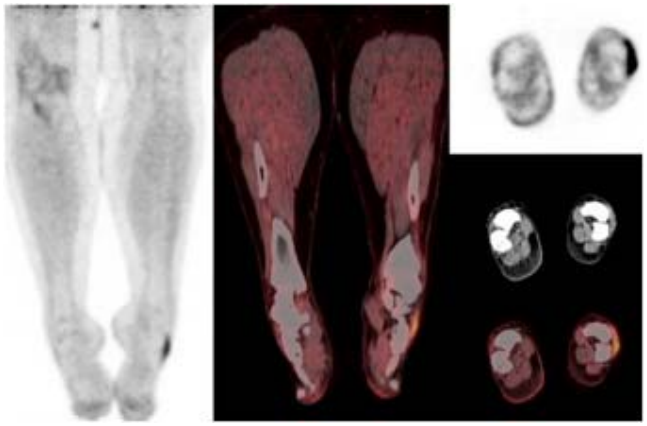

Fig 9: A 30-year-old male with a history of wide local excision of a melanoma lesion from his upper back and excision of a metastatic axillary lymph node. FDG PET/CT was obtained for re-staging. Skin thickening with increased metabolic activity is seen in the lateral aspect of left foot raising a suspicion of another malignant skin lesion. Without any further treatment, FDG PET/CT repeated 6 months after showed complete resolution of the

left foot lesion (not shown). The left foot finding on the first FDG PET/CT was interpreted as false positive for malignant skin lesion in retrospect.

Mucosal Melanoma

Malignant melanoma is predominantly a cutaneous disease. Melanoma, in rare instances, may originate in the mucosal lining of the aero-digestive and genito-urinary tracts. Mucosal melanoma accounts for about 0.8%-3.7% of all cases of melanomas.[67] Because metastatic spread of melanoma to the mucosal surface can occur, primary cutaneous site of melanoma must be excluded before a diagnosis of mucosal melanoma is made. Despite its low contribution to the overall incidence of melanoma, mucosal melanoma has attracted a lot of interest due to its poor prognossis, most likely related to delay in diagnosis and unique genetic alterations that drive an aggressive biology.[68]

Studies dedicated to the assessment of the diagnostic performance of FDG PET/CT in patients with mucosal melanoma are limited to small series and case reports.69, 70, 71 In a small series by Haerle et al., FDG PET demonstrated the primary tumours, regional and distant metastases in all patients with sinonasal mucosal melonoma. Brain metastasis was missed in one patient.[72] Another small study has reported a similar high diagnostic performance of FDG PET in the staging and re-staging of mucosal melanoma of the head and neck region.[73] In the series by Agrawal and colleagues, FDG PET/CT detected more sites of disease leading to upstaging of disease in 32% of patients with a change in therapy plan in 25% of patients imaged for initial staging and 43% of patients imaged for disease re-staging.[74] Despite the difference in the clinical variables and genetic alterations between cutaneous and mucosal melanomas, the limited available evidence does not suggest a difference in the performance of FDG PET/CT between the two.

Treatment Response Assessment

Treatment response of melanoma to conventional treatment modalities using FDG PET/CT imaging has been mostly straightforward. However, monitoring response to immunotherapy with immune checkpoint inhibitors (ICIs) for melanoma treatmen when using FDG PET/CT imaging requires a more careful and detailed analysis of post-treatment FDG PET/CT images than was previously the case. First, a number of hypermetabolic immuno-therapy related adverse events (irAEs) may occur that may decrease the specificity of the examination and second, immunotherapy (especially with ipilimumab) is characterized by some more atypical patterns of treatment response that may be misinterpreted as disease progression. Given both topics have been recently extensively reviewed in a recent issue of this journal as will as in a recent meta-analysis, they will only be briefly addressed below.[75,76]

Observed patterns of hypermetabolic irAEs on FDG PET/CT imaging in melanoma include (1) symmetrical hilar and mediastinal lymph node FDG uptake comparable to that observed in sarcoïdosis, estimated to occur in approximately 10% of treated melanoma patients, (2) nodal FDG uptake in the lymphatic drainage basin of metastatic lesions and (3) diffuse splenic uptake. The overall incidence of irAEs in patients treated with ICIs varies based on the mode of assessment. Findings suggestive of irAEs may be seen on FDG PET/CT without clinical symptoms, which may make incidence determined

by imaging to be higher than incidence assessed by clinical symptoms. Dermatological irAEs such as pruritus, burning sensation, rash, alopecia, etc. appear to be one of the earliest and commest irAEs detectable by clinical assessment. Since dermatological evaluation is rarely the focus of whole-body imaging modalities like FDG PET/CT, this category of irAEs may be underestimated when their prevalence is determined by imaging alone. The time of occurence of irAEs is quite variable[77] and may occur after one or two cycles of treatment with ICIs. The time of onset of irAEs may range from 2 to 26 months since commencement of therapy.[78,79] Imaging evidence of irAEs may resolve within 6 months of onset despite contineued treatment with ICIs in some patients while in others, slow resolution occurs only after completion of treatment.[78]

In terms of treatment response, two novel response patterns have been identified following effective treatment of melanoma with immunotherapy that may be misniterpreted as disease progression. The first pattern, termed pseudoprogression, is characterized by an initial increase in tumor dimensions followed by a subsequent response. Hypothetically, pseudoprogression might be attributed to an initial immuno-therapy induced massive infiltration of the tumor tissue by activated T-lymphocytes. In order to discern pseudoprogression form true progression, consecutive scans at least 4 weeks apart have been proposed as a discrimation method. The second novel pattern involves regression of the baseline lesion in addition to the appearance of new lesions.

Discussion and Conclusion

The detection rate of involved LNs by melanoma is size and thus resolution dependent (partial volume effect) with the majority of involved LNs larger than I cm and only 20% of involved LNs smaller than 5 cm being accurately identified on the FDG-PET/CT examination. While some authors have suggested the use of semiquantitative parameters for example, different SUVmax cut-off values, or LN tracer uptake greater than three-times the blood-pool activity to discern involved from non-involved LNs, their added value as opposed to visual analyses warrants a more large-scale validation prior to their routine clinical implementation.

While cutaneosu melanoma are usually highly metabolic active, choroïdal primary melanoma are significantly less active and may be missed on the FDG-PET examination, thus a careful anaysis of the CT-part of the FDG/PET CT examination of the eyes is mandatory in these patients.

GIven the high level of FDG_uptake in the normal brain, FDG PET imaging bears a low sensitivity for detecting brain metastases. MRI imaging is the imaging modality of choice for this purpose and should be performed when evaluation of the brain in melanoma patients is deemed clinically relevant.

FDG-PET/CT positivity of lung metastases originating from melanoma is size-depedent with virtually all lesions larger than 12 mm in diameter in size being accurately identified on the FDG PET examination and fewer than 40% of those smaller than 5 mm in diameter. Accordingly, it is recommendable that in those patients with one or more PET-negative lung nodules that measure less than 12 mm on expiratory CT, additional tests to exclude lung involvement, when judged clinically relevant, should be performed. Furtehrmore, limited available data in melanoma patients suggest that neither breath-

holding techniques, although increasing overall SUV-max and mean values of the lesions, nor the use of non-attenuation corrected images has any significant clinical added value. While most of false positive lung findings, predominantly inflammatory or infectious in nature, are mostly straightforward identified, caution is warranted with ground glass lesions that progressively increase in size on follow FDG/PET CT examinations. These should be considered to represent a part of the pathological spectrum of malignant melanoma.

Melanoma metastases to the bowel are relatively frequent and any patient suffering from malignant melanoma presenting with focal abnormal uptake in small bowel tissue on the FDG/PET CT examination should be considered for capsule endoscopy, given both examinations have proven complementary to rule out isolated small bowel metastases from melanoma, this esepcially given a subset of these patients have a better ouctome.

Similar to primary uveal melanoma, liver metastases originating from uveal melanoma are significantly less frequenetly FDG-positive when compared to those originating from cutaneous melanoma. Furthermore, those liver metastases from uveal melanoma that are FDG-positive show a significantly lower SUVmax values when compared to those originating from cutaenous melanoma.

While the bone is a common site of melanoma metastatic spread, available data suggest that including the lower extremities in the FDG/PET CT examination offers little additional clinical information and that stopping the scan at the proximal thigh has essentially no clinical impact on patient management. Furthermore, caution is warranted when interpreting musculoskeletal FDG-avid lesions in the extremities of melanoma patients given their overall low positive predictive value of only 31%, the most common location for false positive findings being the knee.

The skin and subcutaneous soft tissues are one of the organs involved in the regional spread of melanoma. Their presence uptstage disease and portends poor prognosis. The inherent limited spatial resolution of PET compromises its sensitivity for small skin and subcutaneous lesions causing an under-estimation of disease extent. Attenuation correction may also contribute to the reduced sensitivity of FDG PET/CT for cutaneous lesions. In view of this, both attenuation-corrected and uncorrected images should be examined in interpreation of PET/CT imaging of melanoma.

Mucosal melanoma is a distinct sub-group of melanoma with a different biology compared with cutaneous melanoma. It is rare but aggressive. There are very limited published studies on FDG PET/CT utilization in mucosal melanoma. The limited available evidence does not suggest a different diagnostic performance of FDG PET/CT between cutaneous and mucosal melanomas.

Following immunotherapy typical patterns of hypermetabolic treatment-related adverse events include symmetrical hilar and mediastinal lymph node FDG uptake comparable to that observed in sarcoïdosis, nodal FDG uptake in the lymphatic drainage basin of metastatic lesions and diffuse splenic uptake. These findings should not be falsely interpreted as disease-progression. Also, following immunotherapy for malignant melanoma, pseudoprogression characterized by an initial increase in tumor

dimensions followed by a subsequent response and regression of the baseline lesion in addition to the appearance of new lesions should also not be interpreted as disease progression given their documented favorable clinical outcome. In order to discern pseudoprogression from true progression, consecutive scans at least 4 weeks apart have been proposed as a discrimation method.

Conflict of Interest

The authors declare no conflcit of interest with regard to this paper.

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