

Clinical added-value of ¹⁸FDG PET in neuroendocrine-Merkel cell carcinoma

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Abstract. Merkel cell carcinoma (MCC) is a rare and highly malignant skin cancer with neuroendocrine differentiation. We studied the potential value of ¹⁸FDG PET in the management of MCC. Eleven patients with MCC were examined by ¹⁸FDG PET and PET-CT for staging purpose (n=4) or for detection of recurrence (n=7). Qualitative and quantitative interpretation of PET studies was performed routinely. ¹⁸FDG PET observations were compared to clinical and radiological findings. In 6 patients, PET findings were also compared to histology. In 7 patients, the ¹⁸FDG tumor uptake was compared to the MCC proliferative activity expressed by the Ki-67 index. ¹⁸FDG PET was contributive in 10/11 MCC patients. In 7 patients, ¹⁸FDG PET detected focal lesions or a disseminated stage of the disease including dermal, nodal and visceral metastases. In 3 patients, a normal ¹⁸FDG PET confirmed complete remission of disease. Most MCC patients exhibited highly ¹⁸FDG-avid sites suggestive of increased glucose metabolism. This imaging pattern was related to a high proliferative activity (Ki-67 index >50%). In 1 patient with a weakly proliferative nodal MCC (Ki-67<10%), a false negative result was yielded by metabolic imaging. In 4/11 patients, ¹⁸FDG PET revealed an unsuspected second neoplasm in addition to MCC. It is concluded that whole-body ¹⁸FDG PET may be useful in the management of MCC patients. However, a normal ¹⁸FDG PET aspect cannot rule out MCC with low proliferative activity.

Introduction

Merkel cell carcinoma (MCC) is thought to be issued from Merkel cells (1,2). It is a highly aggressive skin cancer

exhibiting neuroendocrine differentiation (1,2). Although the neoplasm remains infrequent, its incidence is on the rise (3). MCC tends to predominantly invade the regional draining nodes. The 67% mortality of node-positive patients contrasts with 23% of patients without nodal involvement (4). At first presentation, MCC has often spread to distant sites including the liver, brain, skeleton, lungs and gastrointestinal tract (5,6). The etiology of this malignancy is still unknown. Documented cases have reported MCC after radiation and immunosuppressive therapies, or in association with other cancers (7).

To date, no standardized procedure is defined for the management of MCC patients. Conventional imaging techniques, including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), are commonly performed for pre-treatment staging as well as in post-treatment follow-up. The use of lymphatic mapping and sentinel lymphadenectomy (LM/SL) has been advocated for detecting MCC lymph node metastases (8,9). New developments for efficient staging work-up aimed at detecting regional and distant MCC metastases are welcome owing to the inherent aggressiveness of the neoplasm. Such procedures are critical for selecting the appropriate means for local therapy (surgery and/or radiotherapy) and systemic radiochemotherapy (10).

The present study was undertaken to evaluate the usefulness of ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸FDG PET) in detecting MCC. This metabolic imaging technique uses radiolabelled glucose tracer as the marker of malignancy.

Patients and methods

Patients. Eleven patients (7 women and 4 men, mean age: 63.5 years) with proven MCC were examined by ¹⁸FDG PET. Owing to the rarity of the disease, we collected cases of MCC patients from two different institutions. Patient demographics are detailed in Table I. Overall, 15 ¹⁸FDG PET examinations were performed including 4 PET scans in pre-treatment staging (4 patients), and 11 PET scans (7 patients) during post-treatment follow-up.

¹⁸FDG PET imaging. The 11 MCC patients were examined using dedicated PET devices. Eight PET assessments (6 patients) were performed on an Advance PET scanner (GEMS,

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Table I. Patient demographics.

Patients	Age (years)	Gender	Primary site	Primary therapy	Stage
1	67	F	Left thigh	WLE + chemo-radiation	I
2	46	F	Left foot	WLE + radiation	I
3	53	F	Left knee	WLE + radiation	I
4	67	F	Right buttock	WLE	I
5	60	M	Abdomen	WLE + chemotherapy	III
6	70	M	Left groin	WLE + radiation	I
7	57	M	Left shoulder	WLE + chemo-radiation	II
8	63	M	Intranodal	WLE + radiation	II
9	77	F	Left buttock	WLE	I
10	75	F	Right buttock	WLE	I
11	78	F	Left calf	WLE	I

WLE, wide local excision.

Nxi, Milwaukee, USA) and four PET assessments (4 patients) were performed on NaI crystal-based PET scanners (UGM PENN PET 240 H or C-PET). In addition, three PET examinations (3 patients) were performed on a PET-CT device (GEMS, Discovery LS, Milwaukee, USA). In all cases, emission data were corrected for attenuation by using either a radioactive source (⁶⁸Ge or ¹³⁷Cs sources) or a CT scan for transmission purposes. All patients were prepared according to a standard protocol routinely used in oncology ¹⁸FDG PET. On average, the acquisition started 60 min after intravenous injection of glucose tracer. In the meantime, all subjects were kept at rest in a quiet environment. To improve the quality of images, some medicines were administered orally in order to reduce muscle contraction (10 mg diazepam) and bowel retention (10 mg mebeverine). Intravenous injection of 20 mg furosemide was administered to minimize the tracer stasis into the urinary tract. In all cases, standard whole-body PET was performed to cover the body from the base of the skull to mid-thigh. In two patients with a suspected local recurrence, the field of view was extended to the lower extremities. The duration of the PET procedure ranged from 45 to 75 min. Overall, the images were displayed using dedicated software in sagittal, transaxial and coronal slices for routine visual interpretation. To assess the glucose tracer intensity inside tumoral sites, semi-quantitative analysis of ¹⁸FDG uptakes was performed on all abnormal sites including MCC metastatic lesions and other malignancies. Accordingly, standardized uptake value-body weight scores (SUV-BW = decay-corrected tissue activity divided by the injected activity per patient body weight) were calculated using a conventional computerized method. Regions of interest (ROIs) were drawn on all ¹⁸FDG-avid sites on the transaxial slices. Maximum SUV-BW values (SUV-BW max) were retained for each tumor site. As a rule, ¹⁸FDG-avid sites with SUV-BW scores >3 are suggestive of malignancy.

Confirmation of ¹⁸FDG PET findings. Fifteen PET examinations were performed in 11 MCC patients. A positive PET scan was yielded in 7 patients (11 PET scans), and 4 patients (4 PET scans) had a negative PET scan. In all cases, ¹⁸FDG

PET findings were compared to the clinical follow-up and conventional imaging including CT/MRI and bone scan. In 6/7 patients with a positive PET scan (6 PET scans) histo- and immunohistochemistry were also performed (3 after surgery, 2 after biopsy, and 1 at autopsy). Three patients (3 PET scans) with negative PET findings were clinically and radiologically followed-up for 6, 20 and 24 months, respectively. In 1 patient (1 PET scan) with negative PET findings, LM/SL was performed during the week following the PET assessment and allowed the detection of regional nodal involvement.

PET correlation with the Ki-67 index. In order to correlate ¹⁸FDG uptake patterns with tumor aggressiveness, the size of the MCC germinative pool was assessed by means of the Ki-67 index using the monoclonal antibody, MIB-1 (Dako®, Glostrup, DK). The available MCC specimens (7/11 patients) corresponded to 4 primary tumors and 3 lymph node metastases. For the other 4 patients, the formalin-fixed, paraffin-embedded material was not sufficient for further analyses.

Statistical analysis. The diagnostic performance of ¹⁸FDG PET for detecting MCC and any second neoplasm was assessed in terms of sensitivity and specificity. The assessment was considered as a true positive result (TP) when the PET findings were confirmed by histology or consistent follow-up. Conversely, the PET assessment was defined as a false positive result (FP) in the absence of objective confirmation for malignancy. The assessment was considered as a true negative result (TN) when the absence of tumor by PET was confirmed after a minimum 6-month follow-up. The detection of tumors by conventional imaging or sentinel node biopsy, which were missed by ¹⁸FDG PET, was interpreted as a false negative result (FN).

Results

The clinical characteristics and growth patterns of MCC patients explored by ¹⁸FDG PET and PET-CT are detailed in Table II. In this series, ¹⁸FDG PET was contributive in 10/11

Table II. Clinical and growth patterns in MCC patients explored by ¹⁸FDG PET.

Patient	Indications	¹⁸ FDG PET patterns	2nd neoplasms	SUV-BW max	Ki-67 indexes/ specimens	Correlation
1	Staging	Disseminated disease: skeleton (femurs, sacroiliac), right lung	NSCLC	Not available	Not available	Histology +/- CT +/-MRI +
2	Follow-up	Disseminated disease: left lung, mediastinum	NSCLC	7.70	Not available	Histology +/-CT +
3	Follow-up	Normal		Not applicable	8-38%: primary tumor	Follow-up +/- 24 months
4	Staging	Normal	NHL Breast cancer	Not applicable	4-13%: sentinel lymph nodes	LM/SL +
5	Follow-up	Disseminated disease: right lung, skeleton (ribs, spine), hilar and mediastinal lymph nodes	NSCLC	4.89-37.17	Not available	CT +/-Bone scan +
6	Staging	Normal		Not applicable	10-15%: primary tumor	Follow-up +/- 20 months
7	Follow-up	Disseminated disease: axillary lymph nodes, pleura, rib, liver		3.75-12.59	50-75%: axillary lymph nodes	Autopsy +/-CT +/- MRI +
8	Follow-up	Focal disease: left inguinal node		3.13	65-75%: inguinal lymph nodes	Histology +
	Follow-up	Normal		Not applicable		Follow-up +/- 6 months
9	Follow-up	Focal disease: left inguinal node		9.34	45-50%: primary tumor	Histology +/-CT +
	Follow-up	Focal disease: iliac lymph node		10.77		Histology +/-CT +
	Follow-up	Focal disease: mediastinal lymph node		10.89		CT +
10	Staging	Focal disease: thymus	Thymoma	7.96	Not available	CT +
	Follow-up	Disseminated disease: thymus, retroperitoneal lymph nodes		5.40-10.7		CT +
11	Follow-up	Disseminated disease: dermal nodules, inguinal and iliac lymph nodes, lungs, pleura		4.25-13.51	20-45%: primary tumor	CT +

NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; SUV-BW max, standardized uptake value-body weight max (SUV-BW max >3 is suggestive of malignancy).

MCC patients (14/15 PET scans). In 11 PET assessments, metabolic imaging showed either multiple ¹⁸FDG-avid foci (6 PET scans) or a single intense focus (5 PET scans). In all of these cases, ¹⁸FDG PET findings were confirmed as MCC metastases or as other cancers associated to MCC. Correlations were obtained by histology or by other imaging modalities including CT, MRI and bone scan. In the remaining 4 PET assessments, metabolic imaging showed no ¹⁸FDG-avid abnormality. Among them, 3 PET findings were considered as TN results with no evidence of disease after a clinical and radiological follow-up of 6, 20 and 24 months, respectively. A single PET scan led to a FN result in the case of nodal metastases. This patient had sentinel lymph node metastases larger than 1 cm with a relatively low proliferative activity (Ki-67 index: 4-13% according to the microscopic field).

Analysis by sites showed that whole-body PET detected ¹⁸FDG-avid tumors on the entire body. All of these metabolically active tumor sites had SUV-BW scores >3, including dermal metastases surrounding the primary neoplasm, regional and distant nodal disease, as well as visceral localisations including lung, pleural, liver and bone metastases (Fig. 1). Most of the sampled MCC lesions for histology exhibited a

moderate to high degree of proliferation with a Ki-67 index ranging from 10 to 75% (mean: 50%). In 4/11 patients, metabolic imaging also revealed an unsuspected second neoplasm associated to MCC at primary staging (1 non-small cell lung cancer, and 1 thymoma), as well as during the follow-up (2 non-small cell lung cancers). Most metastases arising from MCC and the second neoplasm were detected by PET examination using routine qualitative and quantitative interpretation of images. In 3 patients, PET-CT allowed a more precise anatomic localisation of ¹⁸FDG-avid tumor sites, especially for detecting retroperitoneal and mediastinal lymph nodes, and for confirming pleural involvement. However, in one patient with multiple ¹⁸FDG-avid foci, metabolic imaging missed the brain metastases detected by MRI.

Overall, ¹⁸FDG PET exhibited a 92% sensitivity (11 TP and 1 FN) and a 100% specificity (3 TN and 0 FP) in the detection of MCC tumors and associated malignancies.

Discussion

MC is a highly malignant neoplasm that may represent the most aggressive skin cancer (1,10). Owing to the rarity of the

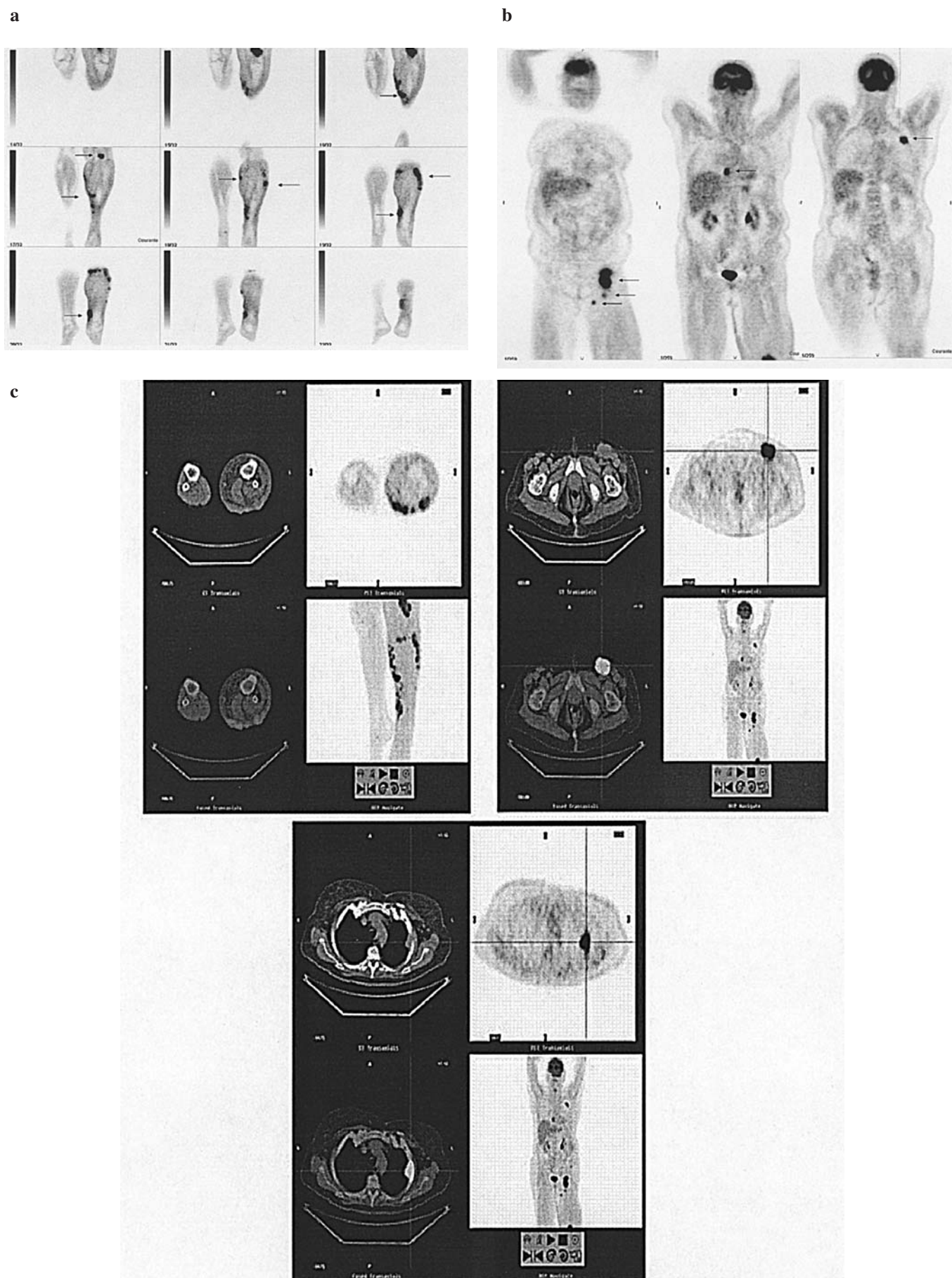


Figure 1. A 78-year-old woman with MCC of the left calf was explored for re-staging purposes. Whole-body ^{18}F FDG PET-CT revealed (arrows) dermo-lymphatic metastases at the level of the primary tumor (a) as well as regional lymph nodes and distant lung metastases (b). Combined PET-CT images allowed precise anatomometabolic localization of the tumor sites (c).

Table III. ¹⁸FDG PET and Merkel cell carcinoma: review of the literature.

Authors	Year	No. of patients	Clinical indications	Comments
Lampreave <i>et al</i>	1998	1	Staging-restaging	¹⁸ FDG PET>CT
Wong <i>et al</i>	2000	1	Staging	¹⁸ FDG PET>SRS
Nguyen <i>et al</i>	2002	1	Restaging	¹⁸ FDG PET>CT
Lin <i>et al</i>	2004	1	Staging-restaging	¹⁸ FDG PET>CT/MRI
Scanga <i>et al</i>	2004	2	Staging-restaging	¹⁸ FDG PET>CT/MRI
Min <i>et al</i>	2005	2	Staging-restaging	PET>CT
Belhocine <i>et al</i>	2005	11	Staging-restaging	¹⁸ FDG PET (PET/CT)>CT
Grewal <i>et al</i>	2005	23	Staging-restaging	¹⁸ FDG PET alone
Talbot <i>et al</i>	2005	3	Staging-restaging	¹⁸ FDG PET>SRS
				Tumor uptake: ¹⁸ FDG> ¹⁸ FDOPA
				Specificity: ¹⁸ FDOPA> ¹⁸ FDG
Golan <i>et al</i>	2005	1	Restaging	¹⁸ FDG PET>CT

¹⁸FDG, ¹⁸F-fluoro-2-deoxy-D-glucose; ¹⁸FDOPA, ¹⁸F-fluoro-L-dihydroxyphenylalanine; SRS, somatostatin receptors scintigraphy; PET, positron emission tomography; CT, computed tomography; CI, conventional imaging.

disease, however, no standardized approach is currently defined to optimally manage MCC patients, both in the pre-treatment set-up and in the post-treatment follow-up (11). In recent years, functional imaging methods using LM/SL and somatostatin receptor scintigraphy (SRS) have been shown to efficiently complement morphological imaging (8,11,12). This holds particularly true in stage I and II MCC patients with local and regional involvement, respectively (11). So far, LM/SL cannot assess the full extent of the disease, especially in stage III patients with disseminated disease to nodal and visceral sites. Similarly, SRS is often of limited value for detecting metastases in organs such as liver, kidneys and spleen showing a physiological uptake of radiolabelled octreotide (12).

Because the ¹⁸FDG tracer is avidly taken up in highly aggressive malignancies including cutaneous melanoma, we investigated the potential benefit of metabolic imaging to detect ¹⁸FDG-avid sites from MCC. Additionally, in many types of cancer, whole-body ¹⁸FDG PET appears to be more sensitive and more specific than conventional imaging including US, CT and MRI (13). Until now, only a few case reports have suggested the clinical feasibility of ¹⁸FDG PET in MCC patients [(14-20); Scanga D, *et al*, J Nucl Med 46 (Suppl 2): abs. 137, 2005]. Although limited, these findings highlighted the added-value of metabolic imaging for detecting metastases from MCC as well as for localizing local and distant recurrences, which were missed by conventional imaging including CT and SRS (Table III).

In the present study on MCC cases, all ¹⁸FDG PET findings were confirmed histologically or by clinical and radiological follow-up. Regardless to PET model, our findings indicate that MCC sites exhibit increased ¹⁸FDG uptake according to routine qualitative and quantitative interpretation. In an attempt to correlate glucose metabolism with MCC biology, we assessed the Ki-67 index as a marker of cycling cells, bearing in mind that neuroendocrine tumors (NETs) with a rapid growth or aggressive behavior were found to be highly ¹⁸FDG-avid, while

slow-growing NETs usually showed no or low FDG uptake (21-23). In the present series, all MCC specimens expressed a large germinative compartment, thereby confirming the importance of cell proliferation as a key factor in the biologic behavior of MCC (24). Nonetheless, the heterogeneity in the MCC tumor samples prevented any firm conclusion as to the biological significance of ¹⁸FDG uptake in primary tumors and nodal metastases.

In the management of MCC patients, ¹⁸FDG PET may offer several advantages in pre-treatment staging as well as in post-treatment follow-up. A single, whole-body PET procedure helps to avoid repeated and time-consuming conventional imaging assessments. In addition, metabolic characterization may precede some imaging expression. ¹⁸FDG PET may also be useful to reliably rule out recurrence from MCC, especially when conventional work-up cannot distinguish between post-treatment changes and tumor recurrence. The strength of metabolic imaging relies on its capability to detect malignancy sites over the entire body, including lymphatic lesions (dermal and nodal sites) or haematogenous metastases. As such, whole-body ¹⁸FDG PET may significantly impact the treatment options in terms of loco-regional disease versus disseminated disease. In the present series, most of the patients had standard whole-body PET from the base of the skull to mid-thigh. Some of them had an extended field of view to cover the lower extremities and the brain. Owing to the aggressiveness of MCC, a true total body scan from the top of the head to the tip of the toes may be warranted, especially with faster PET-CT devices (20). So far, metabolic imaging remains suboptimal for the detection of brain metastases due to the high cerebral background (25). Therefore, brain MRI should complement standard whole-body ¹⁸FDG PET as routinely performed in malignant melanoma. The present findings also highlight the added-value of combined PET-CT device for better anatomic localization of ¹⁸FDG-avid tumor sites. This may be particularly relevant for a precisely targeted radiation

treatment. Despite the heterogeneity of the study group, ¹⁸FDG PET was able to detect other cancers in 4/11 MCC patients. Second neoplasms are frequently associated to primary MCC, including skin carcinomas and non-cutaneous solid tumors as well as haematological diseases (26,27). This provides a strong argument for the performance of whole-body ¹⁸FDG PET in the staging and re-staging of MCC.

Recently, the feasibility of ¹⁸F-FDOPA was reported in three patients with proven MCC-neuroendocrine tumors (28). MCC tumor sites exhibited a more intense uptake with ¹⁸FDG compared to ¹⁸F-FDOPA. In this case report, ¹⁸F-FDOPA PET did not show more extra-cranial metastases from MCC than ¹⁸FDG PET. So far, ¹⁸F-FDOPA may be of particular interest for detection of brain metastases that are often missed with ¹⁸FDG PET. Additionally, the high specificity of ¹⁸F-FDOPA for neuroendocrine tumors may help to rule out FP results and equivocal findings obtained with ¹⁸F-FDG and SRS (28). Although our study group included only 11 MCC patients who underwent 15 ¹⁸FDG PET evaluations, this low number is in line with most published series owing to the rarity of the disease (29). So far, the retrospective nature of the study limits the possibility of more sophisticated analysis in terms of patient survival and treatment impact. Further studies appear warranted to confirm the promising findings, and to address other key-issues in the management of MCC patients.

Based on the present findings, the use of whole-body ¹⁸FDG imaging may be clinically contributive in the management of MCC patients. However, a normal ¹⁸FDG PET distribution cannot exclude the possibility of MCC with a low proliferative activity. Prospective multicenter studies will help collect more data to refine the role of ¹⁸FDG PET along with LM/SL and ¹⁸F-DOPA PET in various stages of MCC.

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