# The impact of $^{18}$F-FDG PET/CT on Merkel cell carcinoma management: a retrospective study of 66 scans from a single institution

**Keywords:**

Merkel cell carcinoma

PET/CT

18F-FDG

## ABSTRACT

**Background:** Merkel cell carcinomas (MCC) are rare and aggressive neuroendocrine skin tumors for which an optimal treatment procedure remains to be defined. These extremely lymphophilic tumors are frequently responsible for lymph node recurrence and metastatic disease. The objective of this study was to evaluate the impact of $^{18}$F-FDG PET/CT on the staging and treatment of MCC patients.

**Methods:** 23 patients with a histologic diagnosis of MCC explored by $^{18}$F-FDG PET/CT between 2004 and 2012 were retrospectively included in the study. The detection of new lesions, the change in tumor staging and treatment were evaluated. For each patient, the PET/CT results were compared to histological, clinical and imaging data.

**Results:** 66 PET/CT scans were performed at initial presentation (n=18), subsequent monitoring (n=34) or in evaluation of chemotherapy response (n=14). The sensitivity, specificity, positive and negative predictive values of the PET were 97%, 89%, 94% and 94% respectively. Two false-positive results (lymphadenitis) and one false-negative result (regional metastatic lymph nodes) were also accounted for. Lesions not detected clinically or by conventional imaging techniques were found in 44% of the 52 PET/CT performed at initial presentation and subsequent monitoring, with respectively 50% and 41% of scans identifying new lesions. At initial presentation, PET/CT led to a change in tumor staging in 39% of patients. Patient management was modified by PET/CT results in one third of patients (33% of patients at initial presentation, 32% in subsequent monitoring, and 36% in evaluation of chemotherapy response). Moreover, PET/CT incidentally detected 4 additional histologically-confirmed cancers.

**Conclusion:** This retrospective study confirms the important impact of $^{18}$F-FDG PET/CT in the management of MCC patients.

## INTRODUCTION

Merkel cell carcinoma (MCC) is a rare neuroendocrine skin tumor, approximately 10 times less frequent than melanoma. MCC incidence, estimated at 0.6 cases/100,000 inhabitants in 2006, has significantly increased in the last 20 years [1]. MCC is an extremely aggressive lymphophilic tumor which is frequently responsible for lymph node recurrence and distant metastases. With a 5-year specific mortality rate of 46% when including all stages, the prognosis for MCC is globally lower than that of melanoma, although this varies depending on the disease's stage [2]. Treatment also differs depending on staging, but principally relies on surgery and sentinel lymph node biopsy at the local stage, completed with lymph node dissection and radiotherapy of the lymphatic area at the regional stage, and finally palliative radio (±chemo)-therapy at the metastatic stage. However, given the lack of large cohort studies in the literature, no standardised consensus on patient treatment has been reached to date.

Currently, optimal imaging modalities for MCC patients remain to be defined. On the basis of US recommendations (NCCN Guidelines Version 1.2012), imaging evaluation may be performed after clinical examination to better stage the patient and assure the appropriate treatment [3]. Imaging can also exclude the diagnosis of cutaneous metastasis related to a small-cell lung carcinoma which has similar histological characteristics as MCC. However, there is still no imaging algorithm for MCC, as the recommendations do not specify the priority to be given to imaging options, even if recent articles show that PET/CT is gaining more and more importance [4-5].

$^{18}$F-FDG PET/CT is a functional imaging modality with proven performance in the evaluation of malignant tumors, notably of melanoma [6]. PET/CT seems useful for MCC, particularly to detect clinically or radiologically unknown lymph node recurrence and nodal

or distant metastases [7-8]. Incidentally, PET/CT may also lead to detect unexpected primitive neoplasia. However, few studies have investigated the value of PET/CT for the management of patients with MCC [9-13]

The aim of this study was to evaluate the impact of PET/CT on the staging and the management of MCC patients.

## MATERIAL AND METHODS

*Patients*

All MCC patients addressed to our institution during the 2004-2012 period for PET/CT scan were retrospectively included in the study. The MCC diagnosis was based on an anatomopathological analysis of the primitive skin lesion or a lymph node biopsy when no primitive skin lesion was found. The required histological criteria was a proliferation of Merkel cells in the dermis or hypodermis, the presence of neural endocrine markers (principally chromogranin A, synaptophysin and Neuronal Specific Enolase) and CK20 expression in the immunohistochemistry. The histological confirmation of MCC defined the diagnosis date and the radiological or histological evidence of disease defined the recurrence date. The staging of the disease was established in accordance with the 2010 AJCC recommendations: patients presenting no lymph node involvement were considered as Stage I (primitive lesion ≤ 2cm) or II (primitive lesion >2cm); patients with regional lymph node extension were considered as Stage III, and those with distant metastasis were considered as Stage IV [2].

*PET/CT acquisition*

The PET/CT scans (n=66) were performed with General Electric Discovery ST (n=56) and Discovery 690 (n=10) PET/CT scanners, in accordance with the standard clinical protocol used in our institution. Patients fasted for at least 6 hours and presented mean blood glucose level of 1.07 ± 0.22g/l before the intravenous injection of FDG. Patients received a mean dose of 320 ± 67MBq (4.12 ± 0.64MBq/kg) and imaging was performed after an approximately uptake phase time of 68±12 minutes. The emission data were acquired in 2D on the GE

Discovery ST PET/CT scanner until July 2008, then in 3D on the GE Discovery ST and Discovery 690 PET/CT scanners. Scans went acquired from vertex to mid-thigh, finishing at the toes when the primitive tumour was found in inferior limbs. PET images were reconstructed and displayed using standard methods (OSEM iterative image reconstruction) into 3.3mm thick slices. Concurrent CT without the injection of a contrast agent (8 slices for GE Discovery ST scan or 16 slices for GE Discovery 690 scan) was performed immediately before acquisition of PET study for attenuation correction and anatomical location.

*PET/CT interpretation*

All examinations were interpreted by an experienced nuclear physician. A PET-CT study was considered positive if there was a focal abnormality with radiopharmaceutical uptake greater than background, which was not explained by physiological distribution or another benign process. The analysis was both visual and semi-quantitative. A region of interest (ROI) was delimited for every abnormal hypermetabolic area and the Standardized Uptake Value (SUV max.), which relates to the maximum pixel intensity in that area was obtained using the following formula:

SUVmax = [activity concentration in the ROI (MBq/mL) / injected dose (MBq)] / patient's weight (g)

The lesions identified by PET which had not been detected in prior clinical or imaging examinations were reported. After PET/CT, changes in tumoral staging or management were evaluated by comparing the stage and therapy described in the patient's medical records before and after PET/CT exam. The PET/CT scan results were compared to the histological data and clinical follow-up as well as to the conventional imaging examinations (US, CT, MRI) available for each patient. PET/CT performance was appraised by considering the

histological data as the standard of reference. When the histological data were not available, a combination of imaging results and clinical follow-up was considered. The incidental detection of another histologically-proven cancer was also reported.

# RESULTS

*Demography*

Between August 2004 and December 2012, 23 patients (13 men and 10 women) with MCC were scanned with FDG-PET/CT in our institution. The age of the patients at diagnosis spanned from 54 to 94 years of age (median: 74 years). None of the patients demonstrated immunodepression. Eight patients had history of previous malignancies, considered to be in remission during the study; these included 4 skin cancers (3 basocellular carcinomas, 1 squamous cell carcinoma), 2 non-Hodgkin's lymphomas, 1 colorectal adenocarcinoma, 1 prostatic adenocarcinoma, and 1 uterine cervical cancer. Primitive MCC skin lesions were found in the cervical-cephalic region (30%; n=7), lower limbs (30%; n=7), upper limbs (9%; n=2) and torso (9%; n=2). The average size of the primitive lesions was 18.7±10mm (4 to 40mm). In 5 patients (22%), no primitive skin lesion was found and lymph node biopsy led to the diagnosis. The Ki-67 cell proliferation index was obtained in 5 primitive tumors and in the lymph node biopsy of one patient without a primitive tumor. The mean Ki-67 index value was 74±16% (50 to 90%).

*Initial presentation*

Eighteen patients, five of whom had no primitive tumor, were analysed with PET/CT for assessment of stage at initial presentation. The examination was performed after surgical excision of the primitive lesion, when present. Prior to PET/CT, 5 patients were considered at Stage I (28%), 5 patients at Stage II (28%), 6 patients at Stage III (33%) and 2 patients at Stage IV (11%) with metastatic lymph node (n=2) and pancreatic (n=1) involvement.

PET detected new lesions on 50% of exams, and led to a change in disease staging in 7 patients (39%). Four patients considered at Stage I or II were redefined as Stage III. Three patients went from Stage III to Stage IV after the detection of metastatic lymph nodes (n=2), hepatic (n=1) or bone (n=1) involvement. PET detected additional lesions (metastatic lymph nodes) in two Stage IV patients.

Overall, PET results led to a change in treatment for 6 patients (33%). The surveillance recommended for 4 patients was transformed after PET/CT in lymph node dissection coupled with lymph node basin irradiation for 2 patients and chemotherapy for 1 patient (figure 1). For a patient, the inguinal lymph node dissection was extended to ileac basin after the detection of metastatic lymph nodes. In another patient where the PET revealed bone metastasis, lymph node dissection was replaced by palliative chemotherapy with an irradiation of the bone lesion (figure 2).

*Subsequent presentation*

Thirty-four PET/CT scans were performed in 16 patients for suspected recurrence (n=10), restaging after completion of surgery/radiotherapy (n=11), or ongoing surveillance (n=13). Additional lesions were found in 14 scans (41%). In all, PET detected 20 new affected areas with regional lymph nodes (n=11), metastatic lymph nodes (n=6), liver (n=1), pleura (n=1) and pancreas (n=1) involvement. PET/CT led to change management in 11 cases (32% of exams) (Table I).

*PET/CT performance*

Out of the 52 PET/CT exams performed at initial (n=18) or subsequent presentation (n=34), 17 were negative. The 35 positive exams detected 99 affected areas, including 45 regional lymph nodes areas (mean SUVmax: 9.7±4.1) and 54 metastatic areas (mean SUV max: 10.2±4.6) with metastatic lymph nodes (n=32), pancreas (n=5), brain (n=5), hepatic (n=4), bone/bone marrow (n=3), pleura and lungs (n=2), sub-cutaneous (n=2) and pharynx (n=1) involvement.

Out of the 99 involved areas visualised by PET, 18 were histologically confirmed, including 15 affected lymph nodes (11 regional and 4 metastatic), one pancreas, one pleura and one bone marrow involvement. Seventy-nine cases were confirmed through conventional imaging (CT or MRI) and/or clinical follow-up. Two false positives were found. The first patient presented a suspect cervical lymph node hypermetabolism on the PET which histology further defined as anthraco-silicosis adenitis. The second patient presented a hypermetabolism, suspected to be a recurrence in a previously-affected lymphatic area (treated by surgical dissection, without complementary irradiation), which, after a favourable clinical evolution and a normalisation during the three-month control PET scan, was finally attributed to an intertrigo. A false negative was also identified: the PET did not identify an affected regional lymph area proven by histological examination one month later.

All the lesions identified by conventional imaging examinations were found by the PET, with the exception of one patient who presented multi-focal cerebral metastases on MRI. PET detected a 4cm cerebral metastasis but did not find the other cerebral lesions which were sub-centimeter (figure 3).

The sensitivity, specificity, positive predictive value, and negative predictive value of the PET were respectively 97%, 89%, 94% and 94%.

*Evaluation of therapeutic response*

Fourteen PET/CT exams were performed to evaluate therapeutic response during or after chemotherapy. PET showed complete metabolic response in 6 patients, amongst whom 4 patients presented a regional or metastatic nodal recurrence in an average of 8 months (from 3 to 12 months) after the exam and 2 patients were still in remission after a lengthy follow-up (87 and 46 months respectively). PET showed a partial metabolic response in 5 patients, 4 of whom relapsed (3 patients died, 1 patient was still in treatment at the end of the study) and one patient (treated by the dissection of the pathological lymph node area after the exam) was in remission after a 30-month follow-up. The 3 patients who did not respond to chemotherapy (stable disease or in progression according to PET) died from the evolution of their cancer.

PET led to change management of 5 patients (36%). With one patient in partial response, an irradiation of the affected nodal area was added to chemotherapy. For a patient demonstrating metabolic progression, chemotherapy was modified, and lymph node area and brain radiotherapy initiated. For three patients, chemotherapy was interrupted and replaced by palliative nodal and cerebral radiotherapy (n=1), lymph node dissection (n=1) or the association between lymph node dissection and lymph node and bone radiotherapy (n=1).

*Second cancer*

Four additional cancers were detected by PET/CT scans performed as part of the initial presentation, suspected recurrence or ongoing surveillance. A sigmoid adenocarcinoma was discovered in 2 patients with no prior neoplasic history other than MCC. A prostatic adenocarcinoma and an epidermal squamous cell carcinoma were found in the same patient.

*Follow-up*

The mean follow-up of patients after MCC diagnosis was 37±25 months (5 to 98 months). Seven patients (30%) died during the study period and all deaths were related to the evolution of their cancers. At the end of follow-up, 11 patients were considered for remission and 5 patients showed signs of an evolving disease and/or remained in treatment.

## DISCUSSION

MCC is a rare skin tumor representing less than 1% of all skin cancers. Although the tumor's physiopathogenesis remains somewhat unclear since its first description by Toker in 1972 [14], it is commonly understood that MCC derives from Merkel cells, neuroendocrine cells with mechanoreceptor functions situated at the dermoepidermal junction [15]. The risk factors associated with MCC development have been identified and principally include advanced age, fair skin type, prolonged exposure to UV rays, but also immune deficiency, as witnessed by the high incidence of MCC in iatrogenic (immunosuppressants for auto-immune diseases or organ allografts) or non iatrogenic (AIDS, leukaemia, lymphoma) immune deficiency [16-17]. The role of promoting immunosuppression in the development of MCC led to suspect, and later identify, a potential oncogene virus, the Merkel Cell Polyomavirus (MCPyV). Feng *et al.*, who had already identified the implication of the HHV-8 virus in Kaposi's disease, detected MCPyV in 8 of 10 MCC cases. Feng's team suggested that viral DNA clonal integration of tumor genome preceded tumor dissemination and thereby was probably involved in the carcinogenesis [18]. Several studies have confirmed that MCPyV was present in about 80% of MCCs [19]. However, MCPyV might be more frequent according to Rodig *et al.,* who developed a new monoclonal antibody capable of detecting the antigen T (an onco-antigen necessary for the activation of MCPyV within tumor cells) in 97% of the 58 tumors studied [20]. Paulson *et al.* also found that antibodies binding to the viral T antigen were specifically associated to MCC. According to the authors, the antibody rate reflects the tumor burden and can serve as a prognosis factor as it falls rapidly in patients with no recurrence and increases in patients presenting an evolving or recurrent disease [21]. The better understanding of MCPyV involvement in pathogenesis of MCC, although incomplete and controversial, leads one to hope that new diagnosis and treatment tools will be developed to counter this aggressive tumor.

MCC is an aggressive skin tumor, with a specific 5-years survival rate at 54%, whereas that of melanoma patients is evaluated at 87% [2, 22]. Despite the current recommended treatment, locoregional recurrences and metastases remain frequent. Recurrences mainly develop in the first 2 years after diagnosis during which over 90% of MCC recurrences occur [23]. Five different classifications of the disease, based on cohorts counting a maximum of 251 patients, have been proposed in past and remain a source of confusion [2]. A new classification based on the analysis of 5,823 patients (National Cancer Data Base) and adopted by the AJCC in 2010 now serves as the reference for prognosis and optimal treatment choice [2]. Five-years survival rate is 64% in the primitive stage of the disease, 39% at the regional lymph node stage and falls to 18% for metastatic disease. Currently, there is no consensus on imaging to be performed in MCC, although the choice of a reliable examination is essential to define the staging and the optimal treatment.

The importance of using FDG-PET/CT in the management of numerous cancers, including melanoma, is well established [24]. PET/CT is particularly indicated at initial presentation for disease staging as it can detect unknown lymph nodes or distant metastases. Moreover, PET/CT is the most appropriate examination for poorly differentiated, aggressive, therefore FDG-hungry tumors, to which MCCs belong. Despite this, few authors have studied the impact of PET/CT on MCC, and even then only in retrospective and principally small cohorts because of the low prevalence of the disease.

In 2006, Belhocine *et al*. demonstrated the interest of using PET in a cohort of 11 patients examined by 15 exams for initial presentation or suspected recurrence. The sensitivity of PET was 92% (1 false negative, 11 true positives) and its specificity was 100% (3 true negatives) [7]. A voluminous cohort (97 patients, 270 examinations) was studied in 2012 by Hawryluk *et al*. The author confirmed the value of PET for staging at initial evaluation and detecting metastases at subsequent presentation, but the impact on management was not

evaluated [10]. In terms of metastatic regions, Hawryluk *et al.* described 33% lymph node areas, 18% bone, 14% skin regions, 11% hepatic and 9% pleura-lungs. Our results differed from those of Hawryluk's. On the basis of 54 metastatic regions detected at initial and subsequent presentation, the most frequently involved regions were non-regional lymph nodes (59%), pancreas (9%), brain (9%), liver (7%), and bone or bone marrow (6%).

In 2009, Concannon *et al.* showed that amongst 18 patients examined for staging at initial presentation or recurrence, PET/CT induced change in staging for 7 patients (33% of exams) and in treatment for 9 patients (43% of exams) [9]. In our study performed on a larger cohort, PET/CT led to a change in staging in 39% of patients at initial presentation, and in treatment in 33% and 30% of cases, for patients respectively at initial presentation and recurrence. These results seem comparable to those of Concannon, even though it remains difficult to compare therapeutic changes between two different centres since treatment procedures are not standardised. Moreover, PET/CT performed at recurrence detected additional lesions in 60% of our examinations, but this did not systematically result in a change of management. Siva *et al.* also proved that PET/CT provide high impact on management of MCC patients, since it changed staging in 22% and treatment in 37% of 102 patients. Furthermore they highlighted the ability of PET/CT to stratify prognosis with stage, as the exam was a strong independent prognostic factor for survival, with a 5-year overall survival at 67% for stage I/II but only 31% for stage III patients [13].

In our study, PET/CT resulted in a change in management for a third of all patients examined at subsequent presentation: the impact of PET/CT on all these patients had never been studied in literature to our knowledge. Only a few studies, principally in case-report framework, have studied the impact of PET/CT in therapeutic evaluation [25-26]. In our study, PET/CT performed for therapeutic evaluation allowed us to classify patients in chemotherapy into two categories (responders and non-responders), resulting in a change of

management in 36% of cases. However, at the metastatic stage, the interest of PET/CT can be controversial considering the current limited therapeutic resources (low efficiency of chemotherapy) and remains to be studied on larger cohorts [27].

In 2008, Peloschek *et al.* compared the performance of PET with morphological imaging (CT, MRI, Echography) in the detection of metastases in 16 patients at initial presentation or MCC follow-up. This study did not show any significant difference between PET and morphological imaging, in terms of sensitivity (respectively 85.7% vs 95.5%) or specificity (96.2% vs 89.1%) [8]. However, the fact that the study did not couple PET with CT probably lowered the performances of the examination. Today, PET coupled with CT (PET/CT), by combining functional information to precise anatomic localisation, ensures a better characterisation of anomalies. On the other hand, PET/CT can explore the whole body in a single examination, whereas classical morphological imaging exams, limited by restricted field, need to be repeated to explore all potential metastatic areas. In our study, all the lesions identified by CT and/or MRI were detected by PET, except in one case where sub-centimeter brain metastases detected by MRI did not appear on the PET images. Because the physiological glucose hypermetabolic cerebral cortex decreases PET's sensitivity in the detection of brain metastases, MRI seems more efficient for this particular indication [28].

PET/CT, as other imaging techniques, doesn't usually result in the detection of lymph node micro-metastases. In Hawryluk's study, PET only detected 14% of lymph node metastases (3/21) revealed by histological analysis of the dissected lymph node: 72% of PET's false negatives (13/18) showed lymph node micro-metastases, often only detectable through immunohistochemistry [10]. In Colgan's study comparing the performance of PET (n=33) and CT (n=69) in regional lymph node evaluation, using histological analysis as gold standard, PET showed a higher sensitivity than CT (83% vs 47% respectively) and a comparable specificity (97% vs 95%). The authors discuss some limitations of this study,

which include a recruitment bias (sub-representation of very small tumors with strong potential for nodal micro-metastases which are less-well detected by PET) [29]. The histological analysis of the drained lymphatic basin, after sentinel lymph node biopsy (SLNB) ± surgical dissection, is generally recommended in the absence of suspected nodal involvement resulting from clinical or imaging exams, in order to improve the MCC staging which orients prognosis and patients management [3-4, 30]. A negative SLNB helps avoid classical surgical dissection, which is an invasive surgical procedure resulting in high morbidity in fragile and elder MCC patients. It is recommended to carry out the SLNB during surgery on the primitive tumour, following lympho-scintigraphic mapping of the lymphatic drainage. SLNB's diagnostic accuracy and value have already been studied in detail [31]. Today, planar scintigraphy is increasingly being replaced by tomoscintigraphy coupled with CT which provides fused SPECT-CT imaging. This is particularly useful for the surgeon to guide his intervention with a precise three-dimensional mapping of lymphatic drainage. Different authors have found that approximately one third of MCC patients without clinical nodal involvement show a micro-metastatic invasion of the sentinel lymph node [32-33]. In addition, it is important to identify a positive SLNB as a factor for poor prognosis so as to associate a complementary treatment for these patients (complete surgical dissection and/or radiotherapy of the drained lymphatic basin) which could lower the risk of recurrence and improve survival. In Gupta's study, the recurrence rate was three times higher (60%) with a positive SLNB than with a negative SLNB (20%; p=0.03). Moreover, patients with a positive SLNB had a relapse-free survival rate of 51% if they received complementary treatment of the lymphatic area against 0% in the absence of additional treatment (p<0,01) [32]. In the meta-analysis conducted by Mehrany *et al.* on 60 patients, the risk of synchronous metastases or recurrence was 19 times higher in patients presenting a positive SLNB [34]. Howle's study highlighted the importance of histological nodal analysis, showing that radiotherapy of the

lymph basin in patients with a positive SLNB could improve their prognosis and that an increased number of affected lymph nodes lowered survival rates [35]. However, other authors have refuted the direct impact of SLNB results on prognosis [31, 36].

In practice, patient management is highly heterogeneous, probably due to the low incidence of MCC and its often unknown aggressiveness, and few patients (approximately 1/3 of the *National Cancer Data Base* cohort which includes more than 5,000 patients) underwent pathologic nodal evaluation [2]. In our study, out of the 5 patients without clinical nodal involvement (Stage I-II), only one patient benefited from a SLNB which was negative (the patient was in remission after 33 months of follow-up). The other four patients did not benefit from a pathologic nodal evaluation: 2 received radiotherapy of the regional lymphatic area and were still in remission after 12 and 49 months of follow-up, and 2 did not receive treatment of the lymphatic area and relapsed (regional lymph node relapse for one and bone-marrow for the other). These patients presented probably microscopic nodal involvement that was undetected by PET.

Despite its high sensitivity in detecting aggressive tumors and their metastases, PET generally presents a slightly lower specificity. FDG, a fluorinated glucose analogue, best accumulates in areas with high glucose metabolism, such as tumor cells but also inflammatory and infectious zones. If the PET does not allow to formally differentiate tumor disease from inflammatory or infectious process, the clinical context, patient history, FDG's uptake intensity and fused PET/CT analysis contribute to leading the nuclear physician towards the correct etiology. Hawryluk *et al.* counted 16 false positives relating to 11 inflammations, 2 lung carcinomas and 3 lymphomas in their study [10]. Only 2 false-positives were identified in our study. They were both cases of adenitis (silico-anthracosic on the one hand, and reactional adenitis to a regional infection on the other) found in the initially-affected and treated nodal region. This explains why the histological confirmation of the recurrence

diagnosis, suspected by clinical exam or imaging, remains essential before initiating any specific treatment.

PET/CT can also detect unexpected second cancers. This ability should not be waived as an early cancer diagnosis may have an important impact on the prognosis and treatment of the patient and the management of a patient with several neoplasia will be consequently adapted. In our study, 4 additional cancers were discovered: 2 sigmoid adenocarcinomas, a prostate adenocarcinoma and a squamous cell carcinoma. Two unknown neoplasia (basal cell and parotid gland carcinoma) were discovered in Concannon's study, and 3 neoplasia (prostate and breast carcinoma, lymphoma) in Colgan's study [9, 29]. The analysis of PET/CT imaging often guides the nuclear physician to the primitive or secondary origin of abnormalities, but does not replace the histological analysis, which is the only exam allowing to formally distinguish MCC's metastasis of other primitive cancer.

The lack of specificity of the FDG-PET has led several authors to propose other radiopharmaceuticals for functional imaging in MCC. Different exams using more specific radioactive tracers for neuro-endocrine tumors (somatostatin analogues labelled with Indium-111 or Gallium-68, F-DOPA) have been proposed [37-41]. Although the literature recognises the value of these radioactive tracers in exploring differentiated neuro-endocrine tumors, they seem to be less adequate than FDG for MCCs, probably because of the low differentiation of this tumour.

Our study presents a number of limits which call for caution in the interpretation of our results. Firstly, it is a retrospective study conducted on a limited number of patients. Secondly, the sample patients are not strictly representative of MCC patients, as many patients in Stages I and IV are not sent for PET/CT analysis. Thirdly, the lesions detected by PET were not all histologically confirmed. However, histological analysis would not have

been allowable in all situations, and all lesions without histological evidence were examined by conventional imaging and clinical follow-up.

# CONCLUSION

In our retrospective study, PET/CT had an important impact on the management of MCC patients. PET/CT changed the staging of more than a third of patients at initial presentation and led to modifying treatment in one third of all patients, explored at initial staging, subsequent assessment or therapeutic evaluation.

Even if these results need to be confirmed by prospective and larger studies, PET/CT seems to position itself as an accurate diagnosis tool to evaluate in a single examination the nodal and metastatic spread of MCC, to detect potential nodal or metastatic relapse, and to appraise therapeutic responses. The prescription of PET appears to us particularly justified in patients with clinical or histological lymph node involvement, who have a high risk of metastases and recurrence, and during the two-year period following diagnosis, the period at which recurrence is most likely.

# LIST OF ABBREVIATIONS

MCC: Merkel cell carcinoma

PET: Positron emission tomography

FDG: Fluorodeoxyglucose

AJCC: American Joint Committee on Cancer

SUV: Standardised Uptake Value

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

MIP: Maximum Intensity Projection

MCPyV: Merkel Cell Polyomavirus

SLNB: Sentinel Lymph node Biopsy

SPECT: Single Photon Emission Computed Tomography

F-DOPA: Fluoro-dihydroxyphenylalanine

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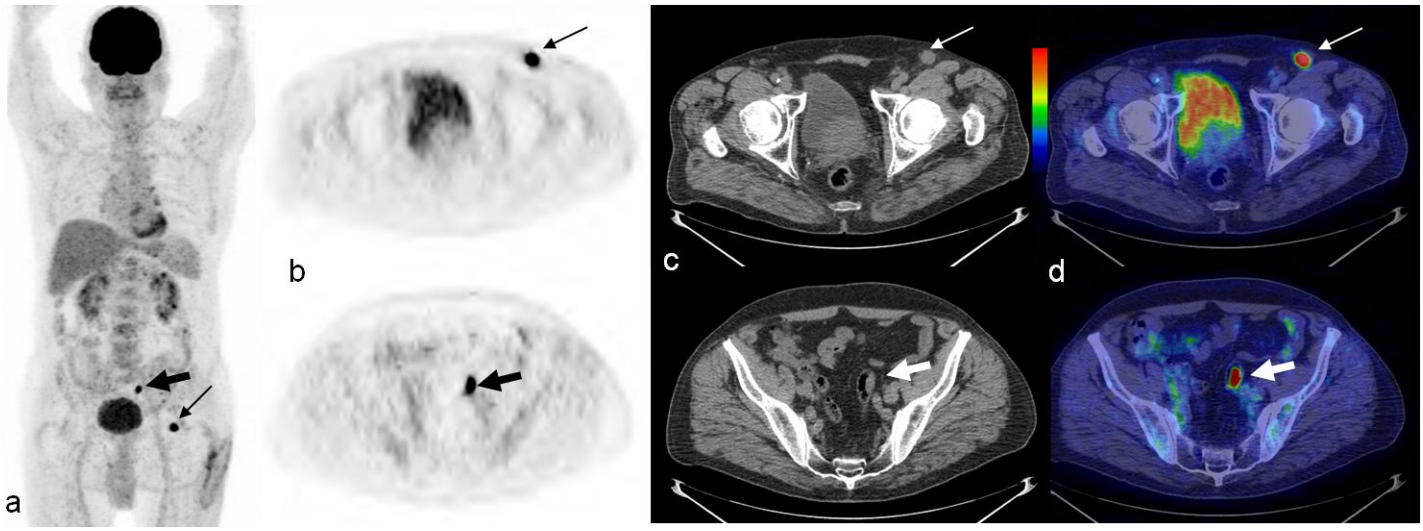
# FIGURES AND TABLES

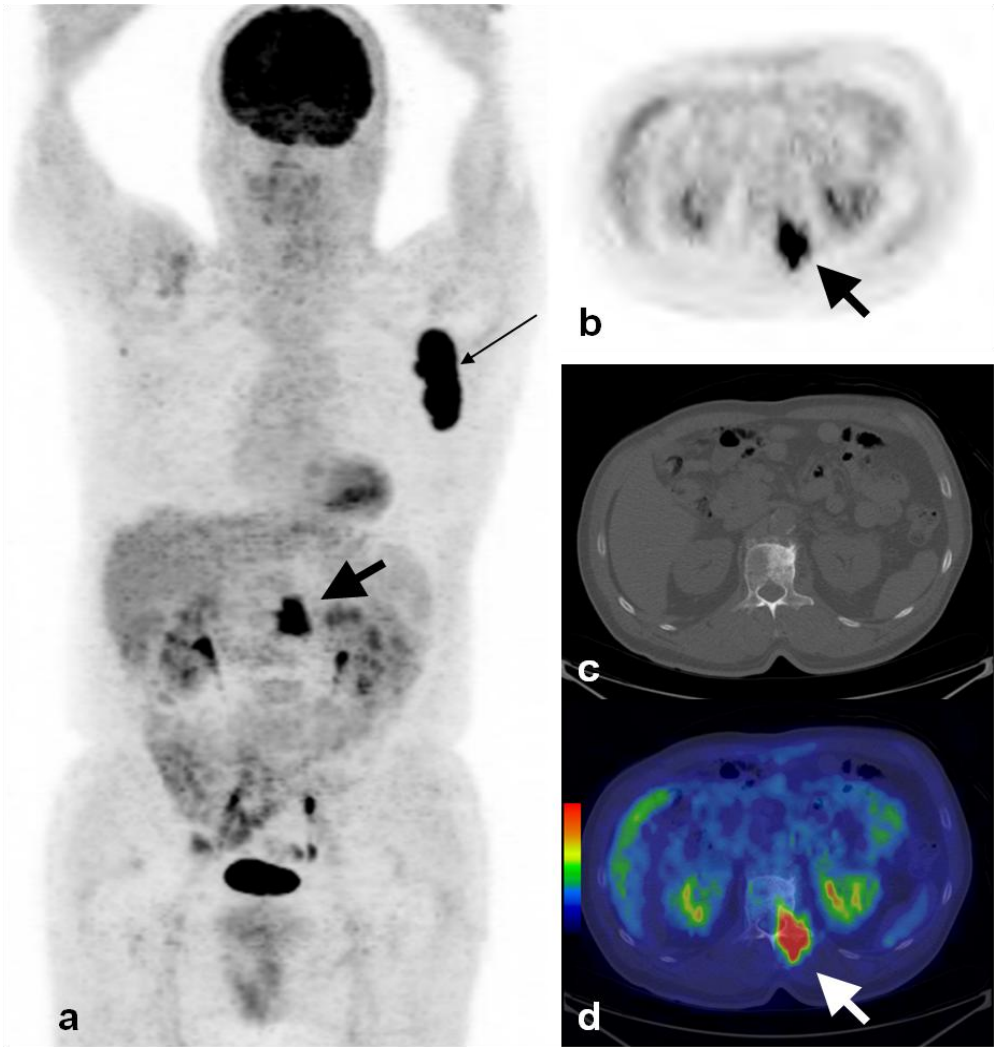
*Figure 1: PET/CT performed for staging of MCC*




MIP (a) and axial slices of PET (b), CT (c) and PET/CT (d) of MCC patient after surgical excision of the left thigh primitive skin lesion.

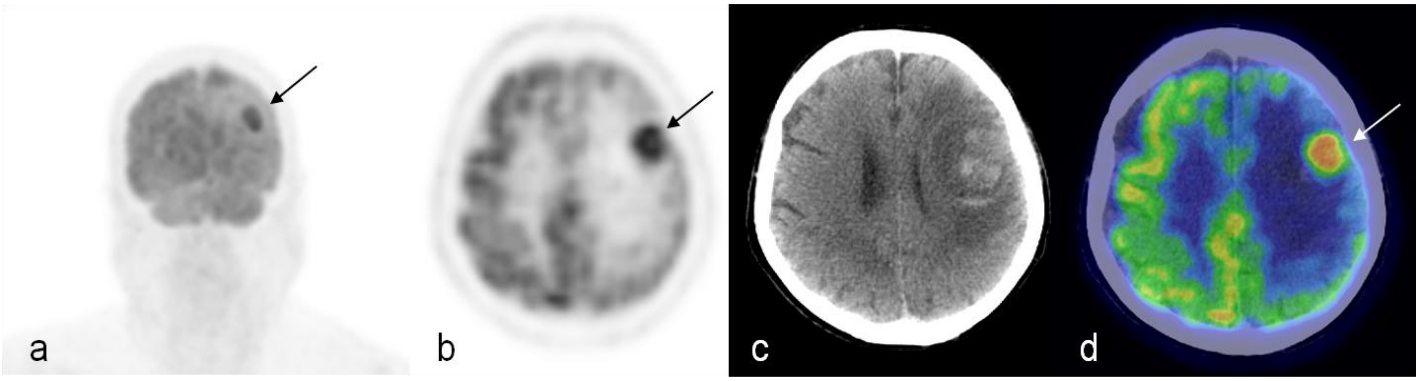
Detection of a left-hand side inguinal adenopathy (fine arrow), leading to a change in staging (II → III) and treatment (monitoring →lymph node dissection and radiotherapy of nodal area). Fortuitous detection of a histologically confirmed sigmoid adenocarcinoma (bold arrow).

*Figure 2: PET/CT performed at initial presentation of MCC*




MIP (a) and axial slices of PET (b), CT (c) and PET/CT (d) of MCC patient with left axillary lymph node involvement and without primitive lesion associated.
In addition to the left-hand side axillary adenopathy (fine arrow), detection of a bone metastasis in L1 vertebra (bold arrow) leading to a change in staging (III → IV) and treatment (curative surgery → palliative chemotherapy and bone radiotherapy).

*Figure 3: PET/CT performed for recurrence*




MIP (a) and axial slices of PET (b), CT (c) and PET/CT (d) of patient with Stage III MCC of the nose.

Detection of a 4cm frontal-parietal brain metastasis (arrow). Other cerebral lesions of less than a centimetre visualised by MRI were not detected by PET.

*Table I: Impact of PET/CT on MCC in subsequent presentation*

| Indication | Number of exams | Number of exams with supplementary lesions | Number of new sites detected | Number of therapy changes | Type |
|---|---|---|---|---|---|
| Suspected recurrence | 10 | 6 (60%) | 8 | 3 (30%) | 2 LND→CT<br>1CT→RT |
| Restaging after completion of surgery/radiotherapy | 11 | 5 (45%) | 8 | 6 (55%) | 3S→CT<br>1CT+RT→RT<br>1RT→S<br>1RT+CT→S |
| Ongoing surveillance | 13 | 3 (23%) | 4 | 2 (15%) | 1S→CT<br>1S→CT+ LND |
| Total | 34 | 14 (41%) | 20 | 11 (32%) | |

LND = lymph node dissection, CT = chemotherapy, RT = radiotherapy, S= surveillance

# ANNEXE

*American Joint Committee on Cancer TNM Staging of Merkel Cell Carcinoma, 2010 :*

| Category and Stage | Characteristic |
|---|---|
| **Primary Tumor (T)** | |
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | In situ primary tumor |
| T1 | ≤ 2 cm in greatest dimension |
| T2 | > 2 cm but < 5 cm in greatest dimension |
| T3 | > 5 cm tumor |
| T4 | Primary tumor invades bones, muscle, cartilage, or fascia |
| **Regional lymph node (N)** | |
| Nx | Regional lymph node cannot be assessed |
| N0 | No regional nodal metastasis either by clinical examination (cN0) or pathologic examination (pN0) |
| N1 | Metastasis in regional nodes either micrometastasis (N1a) or macrometastasis (N1b) |
| N2 | In transit metastasis |
| **Distant metastasis (M)** | |
| M0 | No distant metastasis |
| M1 | Metastasis beyond regional lymph nodes |
| **Stage** | |
| I | T1N0M0 |
| II | T2-4N0M0 |
| III | Any T N1-2 M0 |
| IV | Any T any N M1 |