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RESEARCH ARTICLE

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Baseline ultrasound and FDG-PET/CT imaging in Merkel cell carcinoma

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Abstract

Background: Merkel cell carcinoma (MCC) is a cutaneous tumor with a high tendency to metastasize, and a significant proportion of patients have metastases at first presentation. This study aims to determine the value of baseline ultrasound (US) and ^{18}fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) imaging in both patients with clinically localized MCC (Stage I/II) and patients who present with palpable lymph nodes (Stage III).

Methods: This retrospective cohort included 135 MCC patients who underwent baseline US (with fine needle aspiration cytology (FNAC)) and/or FDG-PET/CT imaging between 2015 and 2021.

Results: Of the 104 patients with clinically localized disease, 48% were upstaged to Stage III and 3% to Stage IV by imaging or sentinel lymph node biopsy (SLNB). FDG-PET/CT imaging identified regional metastases in 23%, while US with FNAC identified regional metastases in 19%. SLNB was performed in 56 patients, of whom 57% were upstaged to Stage III. Of the 31 patients who presented with palpable lymph nodes, 16% were upstaged to Stage IV by FDG-PET/CT imaging.

Conclusion: Baseline imaging frequently upstages Stage I/II MCC patients to Stage III, both by US and FDG-PET/CT, Stage IV disease is rarely identified. Patients who present with palpable nodes are frequently upstaged to Stage IV by FDG-PET/CT imaging.

KEYWORDS
baseline imaging, FDG-PET/CT, Merkel cell carcinoma, ultrasound

1 | INTRODUCTION

Merkel cell carcinoma (MCC) is a rare type of skin cancer with a high tendency to metastasize. At primary diagnosis, nodal metastases are present in 15%–32% of all MCC patients, and 7%–8% present with metastases at distant sites.[1–4] The overall survival (OS) decreases with increasing tumor stage, with an expected 5-year OS of 51% for localized, 35% for nodal, and 14% for distant disease according to the American Joint Committee on Cancer criteria (AJCC) eighth edition staging system.[1] Importantly, since MCC is a disease often found in elderly and frail, the disease-specific or MCC-specific survival does not correlate with overall survival.[4] A recent large cohort from Seattle described only 65% of deaths to be MCC related.[5] Because of the rarity of MCC, its treatment and staging has often been compared to that of melanoma, another type of skin cancer with a high tendency to spread. However, the incidence of MCC is rising, and the number of new diagnoses per year has more than doubled over the past 2 decades.[2,6] This rise in incidence allows adjustment of the guidelines for diagnostic work-up and treatment of MCC, based on MCC-specific data rather than an extrapolation of melanoma guidelines.

The standard of care for clinically localized MCC is complete excision with clinical safety margins and sentinel lymph node biopsy (SLNB) staging. Ultrasound (US) and fine needle aspiration cytology (FNAC) can be used to detect lymph node metastases preoperatively and are recommended for patients with clinical evidence of nodal metastases.[7] ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) imaging can be used but is not a standard part of baseline imaging for patients who present without clinical evidence for metastases.[7,8] Several retrospective studies have reported upstaging of clinical localized MCC in 13%–33% of patients by FDG-PET/CT imaging.[9–11] This high rate of upstaging is important because upstaging could potentially alter the primary treatment. Especially since immunotherapy with anti-PD(L)1 inhibitor has become available for metastatic MCC[12–14] and is currently being studied as adjuvant therapy as well.

At our national tertiary referral center, US and FDG-PET/CT imaging have been part of the standard baseline imaging for newly diagnosed MCC patients since 2015. This allows for objective evaluation of the value of US and FDG-PET/CT baseline imaging. The purpose of this retrospective study is to determine the diagnostic value of US and FDG-PET/CT imaging for newly diagnosed clinically localized (Stage I/II) MCC and for patients with clinical evidence of nodal metastases (Stage III).

2 | METHODS

2.1 | Patients

This study is a retrospective cohort analysis of MCC patients that underwent diagnostic work-up for newly diagnosed MCC in the Netherlands Cancer Institute between January 2015 and August 2021. Patients were selected from a prospective database and data was extracted from their medical records. This study was approved by the Institutional Research Board and conducted in accordance with national and local ethical guidelines.

All patients had histologically proven MCC and underwent baseline imaging with nodal basin US and/or FDG-PET/CT imaging before re-excision and sentinel-node (SN) procedure. In patients who presented with MCC of the trunk or head and neck, all possible draining nodal basins were assessed by US. All SN procedures were performed within 90 days after primary diagnosis. In all patients, imaging was performed within 90 days after primary diagnosis. Patients were excluded if they presented with recurrent disease or clinical evidence of distant metastases. Furthermore, patients with insufficient data to perform staging according to the AJCC (eighth edition) were excluded. Patients with clinically localized disease (clinical stage I/II) and clinical evidence of regional metastases by palpable lymph nodes (clinical stage III) were reviewed separately. MCC of unknown primary (MUP) was included in the clinical stage III group.

2.2 | Imaging

Baseline imaging with the US of the regional lymph node station and FDG-PET/CT imaging is part of our institutional guidelines for clinical stage I and II MCC. However, because a significant part of our patients was referred from other hospitals, not all patients underwent imaging according to this protocol. Patients who underwent imaging that was performed after re-excision + SN procedure, were not included in this study.

US imaging was considered true positive if regional metastases were confirmed by FNAC. FDG-PET/CT scan findings were considered true positive when confirmed by SN procedure, FNAC or histological biopsy, or clinical follow-up. Suspect lesions on imaging that could not be confirmed by pathological examination, or that spontaneously disappeared on follow-up imaging, were considered to be false positive. FDG-avid lesions on FDG-PET/CT scan that was suspected of pathology unrelated to MCC, but required extra diagnostic procedures were also registered.

2.3 | Statistics

Discrete variables were summarized with frequencies and percentages and compared using a Fisher's exact- or χ^2 test. Continuous variables, if normally distributed, were summarized with mean and standard deviation and compared using an independent *t* test. If non-normally distributed, variables were summarized with median and interquartile range and compared using a Mann–Whitney *U* test. Sensitivity, specificity, and number needed to image were calculated using standard definitions. Statistical significance was assumed at a *p*-value of <0.05. IBM SPSS Statistics version 27 for windows was used for statistical analysis.

3 | RESULTS

3.1 | FDG-PET/CT imaging for clinically localized disease

A total of 104 patients with clinically localized diseases were included in this study (Table 1). The mean age was 76 years, 53.8% was female and 46.2% was male. All included patients were of the Caucasian race. Of the 104 included patients, 53 were upstaged to Stage III and three were upstaged to Stage IV by either imaging or SN procedure. Patients that were upstaged had a significantly larger tumor diameter (2.3 vs. 1.4 cm, $p < 0.001$) and had more frequent MCC of the extremities ($p = 0.01$). Patients with head and neck MCC were significantly less likely to be upstaged (Table 2).

FDG-PET/CT imaging was performed in 96 patients, of whom in 22 patients (23%) the PET/CT images correctly identified stage III disease and in 3 patients (3%), stage IV disease was correctly identified (Figure 1). Of the 25 PET/CT scans that were initially suspected of regionally metastatic disease, 18 patients were directly treated with lymph node dissection after confirmation of metastases by FNAC. In seven patients lymph node metastases were not confirmed by FNAC, and received the standard SN procedure with wide local excision of the primary tumor. Four patients with a positive SLNB proceeded to a completion lymph node dissection (CLND). Three patients with distant metastatic disease were treated with immunotherapy. One patient with lymph node metastases had also evidence of non-Hodgkin lymphoma and was referred to a tertiary care center for haemato-oncology. Therefore, treatment was altered in 21 patients (22%) after PET imaging.

Furthermore, PET/CT imaging found a false positive lesion in 22 patients (23%), defined as FDG-avid lesions suspect for metastases or other pathology that could not be proven by follow-up imaging or histopathological examination. There were 14 lesions initially suspected of non-MCC pathology, the remaining lesions were suspect for regional or distant MCC metastases. The sensitivity and specificity of PET/CT imaging for the detection of distant metastases were 100% and 95%, respectively. For the detection of regional lymph node metastases, sensitivity and specificity were 49% and 96%. The number of patients needed to image was 5 to identify the regional disease and 35 for distant disease.

3.2 | Detection of regional metastases by US

US was performed in 88 patients and FNAC identified regional lymph node metastases in 17 patients (19%). In 27 patients (31%), the US (with or without FNAC) was a false negative. The sensitivity and specificity of US with FNAC for the detection of regional lymph node metastases were 40% and 100%, respectively.

Since suspicion of lymph node metastases on FDG-PET/CT imaging before US can influence the results, we split the analysis to look at the US that were made before FDG-PET/CT imaging only. There were 52 US performed before FDG-PET imaging, and of those 8 US (15%)

TABLE 1 a. Baseline characteristics of MCC patients who presented with localized disease and b. characteristics after baseline imaging

Variable	Mean	*n* = 104	%
1a. *Before baseline imaging*			
Sex			
Male		48	46.2%
Female		56	53.8%
Age (mean, SD)	76.06 (±8.4)		
Location primary tumor			
Extremities		40	38.5%
Trunk		8	7.7%
Head and neck		56	53.8%
Unknown primary		0	0.0%
Diameter primary tumor (median, IQR)	1.84 (0.9–2.2)		
T stage		0	0.0%
T1		74	71.2%
T2		21	20.2%
T3		4	3.8%
T4		5	4.8%
1b. *After baseline imaging*			
N stage			
N0		52	50.0%
N1a		27	26.0%
N1b		23	22.1%
N2		0	0.0%
N3		2	1.9%
M stage			
M0		101	97.1%
M1a		1	0.9%
M1b		0	0.0%
M1c		2	1.9%
SN performed			
Yes		56	53.8%
No		48	46.2%
US performed			
Yes		88	84.6%
No		16	15.4%
PET/CT performed			
Yes		96	92.3%
No		10	9.6%

(Continues)

TABLE 1 (Continued)

Variable	Mean	*n* = 104	%
Upstaged			
Yes		53	51.0%
No		51	49.0%

Abbreviations: IQR, interquartile range; MCC, Merkel cell carcinoma; PET/CT, positron emission tomography/computed tomography; SN, sentinel node; US, ultrasound.

TABLE 2 Differences in baseline characteristics between nonupstaged and upstaged patients

Variable	Nonupstaged (*n* = 51)	Upstaged (*n* = 53)	*p* Value
Sex (*n*, %)			0.562
Male	22 (43.1%)	26 (49.1%)	
Female	29 (56.9%)	27 (50.9%)	
Age (mean, SD)	77.4 (±9.4)	74.8 (±7.2)	0.119
Location			**0.011**
Head–neck	35 (68.6%)	21 (39.6%)	
Extremities	14 (27.5%)	26 (49.1%)	
Trunk	2 (3.9%)	6 (11.3%)	
Diameter (median, IQR)	1.4 (0.6–1.7)	2.3 (1.2–3.0)	<**0.001**
T-stage (*n*, %)			**0.031**
T1	43 (84.3%)	31 (58.5%)	
T2	5 (9.8%)	16 (30.2%)	
T3	1 (2.0%)	3 (5.7%)	
T4	2 (3.9%)	3 (5.7%)	

Note: *p* values shown in bold are significant
Abbreviation: IQR, interquartile range.

correctly identified lymph node metastases. In 15 patients, the US (with or without FNAC) was negative (possibly due to sampling error), but nodal metastases were proven afterward by FDG-PET/CT or SN. Sensitivity and specificity were 35% and 100% for US made before FDG-PET/CT imaging. In the 36 US that were performed after FDG-PET/CT imaging, nodal metastases were correctly identified in nine patients (25%). Of the 27 negative US (with or without FNAC) in this group, 12 missed nodal metastases which were later diagnosed by SN procedure. SN procedure was performed in 56 patients, of whom 32 patients (57%) were upstaged to stage III disease.

3.3 | FDG-PET/CT imaging for MCC patients with palpable lymph nodes

There were 31 patients who presented with palpable lymph nodes, suspected for regional MCC metastases, who underwent

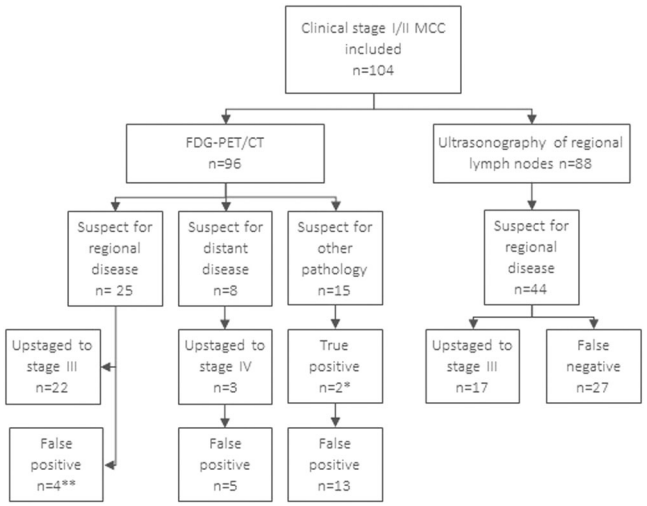

FIGURE 1 Flowchart of FDG-PET/CT scans and ultrasound performed in clinical stage I/II MCC patients. PET-CT scans are recorded as suspects for regional metastases, distant metastases, and/or other pathology. Patients with evidence of regional and distant metastases are displayed as suspects for distant disease. *One patient had treatment adjusted as a result of the positive FDG-PET/CT scan. **One PET was false positive for a suspected popliteal lymph node metastases and truly positive for inguinal lymph node metastases and therefore is counted both as upstaged and false positive. FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; MCC, Merkel cell carcinoma.

FDG-PET/CT scanning. Most patients were male (68%), the mean age was 69 years, and 17 (55%) patients had an MUP (Table 3). Of the included patients, five (16%) were upstaged to stage IV disease by FDG-PET/CT imaging. In this group of clinically stage III disease, treatment was altered in seven patients (23%) who received FDG-PET/CT imaging, five because of distant MCC metastases, one patient was diagnosed with metastasized melanoma, and one patient had a Warthin tumor in the parotid gland. There were five patients (16%) with false positive lesions that required additional investigation. The number of patients needed to image to upstage disease in this group was 5.

4 | DISCUSSION

This study shows that baseline imaging of clinically localized MCC patients with FDG-PET/CT upstages a significant proportion (23%) to stage III disease. In 3% of patients were upstaged to stage IV disease. Therapeutic management was altered by 22% due to FDG-PET/CT imaging. US imaging of the regional nodal basin combined with FNAC in case of suspicion of lymph node metastases detected lymph node metastases in 19%, with or without preprocedural PET/CT information. Approximately 25% of the clinical stage I/II MCC patients that underwent baseline imaging with US and PET/CT were upstaged, additionally another 25% with negative imaging preoperatively were upstaged by SLNB.

TABLE 3 a. Baseline characteristics of MCC patients with palpable lymph nodes at first presentation and b. characteristics after baseline imaging

Variable	Mean	N = 31	%
3a. *Before baseline imaging*			
Sex			
Male		21	68%
Female		10	32%
Age (mean, SD)	68.68		
Location primary tumor			
Extremities		6	19.4%
Trunk		0	0.0%
Head and neck		8	25.8%
Unknown primary		17	54.8%
Diameter primary tumor (median, IQR)	3.1		
T stage			
T0		17	54.8%
T1		4	12.9%
T2		5	16.1%
T3		4	12.9%
T4		1	3.2%
N stage			
N0		0	0.0%
N1a		0	0.0%
N1b		29	93.5%
N2		1	3.2%
N3		1	3.2%
3b. *After baseline imaging*			
M stage			
M0		26	83.9%
M1a		3	9.7%
M1b		0	0.0%
M1c		2	6.5%
Ultrasonography evidence of metastases			
Negative		0	0%
Positive		27	100%
PET/CT evidence of metastases			
Negative		0	0.0%
Positive		31	100.0%
Upstaged to Stage IV			
No		26	83.9%
Yes		5	16.1%

Abbreviations: IQR, interquartile range; MCC, Merkel cell carcinoma; PET/CT, positron emission tomography/computed tomography.

There is currently no consensus on the use of FDG-PET/CT as part of the baseline imaging of clinically localized MCC. However, in recent years, several studies have described high rates of upstaging of disease by FDG-PET/CT imaging. In the largest study to date, Singh et al.[10] describe overall upstaging by FDG-PET/CT of this patient group in 16.8%. Other smaller studies describe rates of upstaging ranging from 16% to 33%.[11,15,16] The majority of patients were upstaged to Stage III. Of the 71 patients in our cohort with FDG-PET/CT scan that were not suspect for regional metastases, 23 patients (32%) were upstaged to Stage IIIA by SLNB. This data indicates that baseline FDG-PET/CT imaging does not replace SLNB for the detection of regional metastases. Interestingly, even though our cohort had a high rate of regional nodal metastases (56%), distant metastases at baseline were rare (3%). This is slightly less than the extent of disease at baseline described in the largest cohort to date of 5823 patients enrolled in the National Cancer Data Base, of whom 7.3% had distant metastatic disease at presentation.[1] However, even if more patients would present with distant metastatic disease, the number needed to image to identify distant metastases would remain considerably high.

FDG-PET/CT imaging found a high number of false positive lesions suspect for MCC and incidental findings, in both the clinical stage I/II and stage III groups (23% and 16%). This rate is significantly higher than in the study of Singh et al.[10] (<2%), and can be partly explained by the fact that they did not take incidental findings into account. All of these false positive findings required additional imaging or pathological examination and is one of the known disadvantages of extensive use of FDG-PET/CT imaging.

US imaging with FNAC detected lymph node metastases in 17 (19%) of all 88 patients who underwent US imaging. These patients were all directly treated with a therapeutic lymph node dissection instead of SLNB. In 36 patients, FDG-PET/CT imaging was performed before the US and found an FDG-avid lymph node suspected for MCC metastases. This prior knowledge of anatomy and metabolic state influences the sensitivity of the US, and therefore US performed before FDG-PET/CT scanning were reviewed separately. The lower rate of identification of nodal metastases in US made prior compared to after FDG-PET/CT imaging (15% vs. 25%) supports this. A study by Righi et al.[17] described to have correctly identified lymph node metastases by US with FNAC in 19% of patients with localized MCC in a smaller number of patients. The authors even suggest that in a certain patient group SLNB could be replaced by US with FNAC. However, SLNB is generally considered to be the most accurate modality of detecting lymph node metastases, as was also demonstrated in our cohort, where in approximately 25% of the patients who underwent SLNB clinically occult lymph node metastases were found. The data of our cohort, therefore, does not provide support for the notion that SLNB can be replaced by US with FNAC for patients with clinically localized MCC.

These numbers show that FDG-PET/CT imaging had a slightly higher sensitivity for the detection of lymph node metastases compared to US with FNAC (49% vs. 40%); however, the clinical benefit can be questioned. Although these sensitivity percentages

might seem moderate, this means that nearly half of the patients with lymph node metastases are detected preoperatively. A higher rate of preoperative detection of lymph node metastases could spare patients an unnecessary (SLNB) operation, and allow them to immediately proceed to a lymph node dissection. However, due to the lack of randomized controlled trials, since MCC is rare cancer, there is debate on the most appropriate management of SLNB-positive disease. Either CLND, radiotherapy, a combination of these, and even observation have been suggested as management of SLNB-positive disease. Therefore, one can question the usefulness of imaging to detect stage III disease before a SLNB. At least for those centers that would offer routine CLND, this preoperative imaging of stage I/II MCC patients can reduce unnecessary surgery, that is, SLNB and the associated anesthetics. A recent study by Cramer et al.[18] did suggest that the best outcomes were seen for the combination of CLND + adjuvant radiotherapy for SLNB-positive disease.

Also, the rate of detection of lymph node metastases by US is only slightly lower than that of FDG-PET/CT, with US being a more affordable imaging modality without the high rate of false positive findings and without additional irradiation risk that comes with computed tomography.

Patients with clinical evidence of lymph node metastases were upstaged by FDG-PET/CT imaging to stage IV disease in 16%. This is even higher than the study by Singh et al.,[10] who described upstaging in 10.8% of patients with palpable lymph nodes. With a number needed to image of 5 to upstage clinical stage III MCC patients and alteration of treatment in 23%, this data supports the current recommendation of performing baseline FDG-PET/CT imaging for this patient category.[7]

There are some limitations to our study. First, not all patients received both US and FDG-PET/CT imaging with SLNB afterward. This was caused by the referral of patients from other hospitals where other guidelines are in place. Second, this study included only a small number of patients, which is inevitable in MCC research because of the low incidence of this type of tumor. In comparison to other imaging studies concerning MCC, this study is one of the larger ones performed to date. Furthermore, this study was performed retrospectively and imaging was not reassessed by radiologists, which could lead to biased results. However, at our center FDG-PET/CT and US imaging were part of the standard work-up, and data was prospectively collected since 2015. Therefore, our cohort reliably shows the added value of FDG-PET/CT and US imaging for clinically localized MCC patients, as the majority of the recently published studies on this subject suggest.

5 | CONCLUSION

This study shows that patients with clinically localized MCC are frequently upstaged by both baseline US and FDG-PET/CT imaging, predominantly for stage III disease. FDG-PET/CT imaging before US enhances the sensitivity of US with FNAC to diagnose lymph node metastases; however, it rarely identifies distant metastases at baseline. Despite the high rate of upstaging by baseline imaging, SLNB remains an essential staging tool for patients with negative preoperative imaging. Patients with palpable lymph nodes are frequently upstaged to Stage IV by FDG-PET/CT imaging, and therefore benefit from baseline FDG-PET/CT imaging.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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