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18F-FDG PET/CT for post-treatment surveillance imaging of patients with stage III Merkel cell carcinoma

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Running title: Surveillance FDG PET/CT in Stage III MCC

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ABSTRACT

To investigate diagnostic and prognostic value of 18F-FDG PET/CT for surveillance imaging in patients treated for Stage III Merkel cell carcinoma (MCC). **Methods**: This retrospective study included 61 consecutive stage III MCC patients, who were clinically asymptomatic and underwent surveillance FDG-PET/CT. Findings were correlated with either pathology and/or clinical/imaging follow-up. Median follow-up period was 4.8 years. Statistical analyses were performed. **Results**: FDG-PET/CT detected unsuspected recurrences in 33% patients (20/61) with lesion-based sensitivity, specificity, and accuracy of 92%, 93%, and 93%, respectively. Mean±SD SUV for malignant and benign lesions was 7.5±3.9 and 3.8±2.0, respectively. Unknown distant metastases, as first recurrence site, were noted in 12 of 61 patients. Those with positive disease on FDG-PET/CT within one year of definitive treatment had relatively worse overall survival ($p<0.0001$). After adjustment on stage, risk of death increased with higher SUVmax (HR for one unit=1.17;$p=0.006$) and with a higher number of positive lesions on FDG-PET/CT (HR for one additional lesion=1.60;$p<0.001$). **Conclusion**: Post-definitive treatment surveillance FDG-PET/CT scan detects unsuspected recurrences and has prognostic value. Inclusion of FDG-PET/CT within the first 6 months after definitive treatment would be appropriate for surveillance and early detection of recurrence. Our data merits further studies to evaluate the prognostic implications.

Keywords: FDG PET/CT, Merkel cell carcinoma, Recurrence, Positron emission tomography, Surveillance, Prognosis

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare aggressive cutaneous malignancy of neuroendocrine origin that has shown increasing incidence in the United States with a reported increase of 95% during the years 2000-2013 (*1,2*). Patient survival depends on the stage of disease at diagnosis (*3-5*), with Stage III MCC noted for higher metastatic potential and decreased survival compared to Stage I and II (5-year cumulative incidence, CI, of death 10-15%); sub-stage IIIa having higher disease-specific survival compared to sub-stage IIIb (5-year CI of death 22% for IIIa and 53% for IIIb) (*4,6*).

Following definitive therapy, recurrences occur in approximately 25-50% patients with median-time to recurrence of about 8 months and 90% recurrences occur within 2 years (*3,6-9*). Follow-up is therefore imperative in MCC, especially in higher stage disease. National Comprehensive Cancer Network (NCCN) guidelines recommend routine follow-up visits every 3-6 months for 3 years and every 6-12 months thereafter (*3*). Complete physical examination including skin and lymph node assessment is the mainstay. Currently, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is not integrated in the routine follow-up. Imaging with contrast enhanced CT and Magnetic resonance imaging (MRI) is used, as clinically warranted on a case-by-case basis (*3,10,11*).

The overall sensitivity and specificity of FDG PET/CT for detecting primary or metastatic MCC ranges from 86-100% and 89-100%, respectively (*10,12-19*) and impact on management has been noted in up to 45% patients (*13,18-22*). Prior studies have limited data on surveillance, include small number of patients and surveillance scans, lack pathological correlation, have variable disease stage and clinical status of patients. The aim of this study is to

evaluate diagnostic and prognostic performance of surveillance FDG-PET/CT scans performed at least 1-month post-definitive treatment in asymptomatic patients with stage III MCC.

MATERIALS AND METHODS

This is an IRB approved single-institution retrospective study, performed in compliance with HIPAA regulations, and the requirement to obtain informed consent was waived. A total of 61 patients treated for stage III MCC who received surveillance FDG-PET/CT scans, as part of standard of care were included. Staging was performed at the time of diagnosis, according to American Joint Committee of Cancer guidelines, 8th edition (*23*). Patients were not on active treatment at the time of the scan, were without any evidence or suspicion of disease as per the clinical assessment of referring physicians and had a minimum interval of at least 1 month since the completion of first definitive treatment.

A total of 221 FDG-PET/CT scans were reviewed. Location, size, and SUV of 107 suspicious lesions were noted. Histopathologic correlation was available for 30 lesions as standard of reference, while clinical/imaging follow-up (≥ 6 months) was performed for remaining 77 lesions. Findings were classified as true-positive for recurrence/metastasis if confirmed by either positive histopathology from biopsies/resections or presence of detectable lesion at corresponding site on follow-up imaging showing increase in SUV or size. Comparison of findings was performed in 28 pairs of PET/CT scans and CT/MRI (limited regions/areas) acquired within one month.

Statistical Methods

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy with 95% confidence intervals (95% CI) were calculated, using pathology and

clinical/imaging follow-up as reference standard. Scan positivity, lesion SUV, number of lesions and disease sub-stage were correlated with survival. Statistical analysis was performed using R version 3.5.0 (R Core Team, Vienna, Austria).

For more details, please refer to the supplementary data.

RESULTS

Patient Characteristics

Patient, scan, and tumor characteristics are described in Table 1. The median interval between end of treatment and first surveillance FDG-PET/CT scan was 3.7 months (range, 1.1–23.3). The time interval between consecutive scans predominantly ranged between 1.5 months to 1.6 years, usually based on the clinician's discretion.

FDG-PET/CT Scan-based Analysis

Of 221 FDG-PET/CT scans, 39 showed FDG positive foci. Pathology confirmed recurrent MCC in 15 of 39 scans while clinical/imaging follow-up confirmed recurrence in another 11 scans. Incidental second malignancy was detected in 1 scan. Overall, true positive (TP) findings were seen in 27 scans (12%, 27/221). False positive findings were seen in 12 scans (5%, 12/221), confirmed on pathology in 2 and on clinical/imaging follow-up in 10 scans. One hundred and eighty-two FDG-PET/CT scans were negative for recurrent disease of which 4 (2%, 4/221) were falsely negative, all confirmed on pathology. Remaining 178 scans (81%, 178/221) were true negative based on clinical/imaging follow-up.

Lesion-based Analysis

A total of 107 sites of abnormal FDG avidity were noted (Figure 1), of which pathology confirmed disease in 24 sites, while clinical/imaging follow-up confirmed in 68 sites. False positive FDG uptake was seen in 15 sites, including nasal and axillary cutaneous sites (confirmed on pathology), pelvic fracture, rib fracture, nine reactive neck and mediastinal nodes, and cutaneous sites in thigh and foot (confirmed on clinical/imaging follow-up). Two lesions were thought to be benign but were later confirmed as recurrent disease on pathology - lung infiltrates and neck node. Two in-transit metastases in thigh and arm were also missed on FDG-PET/CT that were below PET resolution and too small to characterize.

Overall SUVmean±SD (range) for FDG avid malignant and benign lesions was 7.5±3.9(1.7–18.9) and 3.8±2.0(1.6-6.0), respectively; for local recurrence 6.5±4.1(1.7–18.9) and for distant metastases 8.0±3.7(2.3–18.0). Mean SUV(range) for FDG avid distant nodes was 7.1(2.3–12.7) and for osseous lesions was 8.2(4.0–13.4). Mean size of FDG avid distant nodal metastases was 1.3 cm in short axis (range, 0.6–2.1 cm). SUVmean±SD (range) for false positive findings was 3.7±1.2(1.6-6.0). Based on ROC curve, the optimal cut-off SUV of 5.4 was associated with a low sensitivity of 54.9%, but high specificity of 91.4% (Figure 2).

Lesion-based sensitivity, specificity, PPV, NPV and accuracy of PET/CT scan, calculated based on correlation either with pathology or clinical/imaging follow-up was 92%, 93%, 86%, 96%, and 93%, respectively while scan-based sensitivity, specificity, PPV, NPV and accuracy was calculated to be 90%, 94%, 69%, 98%, and 93%, respectively.

Patient-based Evaluation

Overall, 20 patients had relapse detected on FDG-PET/CT. The cumulative rate of detecting recurrences was 8.2% (95%CI:1.3, 15.1%) within 3 months, 16.4% (95%CI:7.1, 25.7%) within 6

months and 26.2% (95%CI:15.2, 37.3%) within 12 months post-definitive treatment. Local or locoregional relapse at/or adjacent to the site of primary was seen in 8 patients with a median interval of 4.5 months (range,1.1–14.7 months) from the end of treatment; disease sites included cutaneous/subcutaneous lesions in extremities (number of patients, n=4), nodal disease in posterior auricular, inguinal, and axillary region (n=3) and cutaneous lesion in leg with inguinal node (n=1). Four of these 8 patients subsequently developed distant metastases. Distant metastasis, as first site of recurrence, was seen in 12 of the total 61 patients, with median interval of 7.2 months from the end of treatment (range,3.0–41.9).

FDG-PET/CT findings led to implementation of treatment in 20 patients (33%, 20/61). Surgery only was performed in 4 patients including excision of cutaneous/subcutaneous lesions in extremities (number of patients, n=3) and bilateral salpingo-oophorectomy (n=1). Radiation only was performed in 7 patients, sites including retroperitoneal/pelvic nodes (n=4), pancreas (n=1), vertebrae (n=1), mediastinal node and subcutaneous thigh lesion (n=1). Chemotherapy only was administered in 3 patients, while 2 patients received both chemotherapy and radiation therapy to osseous sites, and 1 patient received chemotherapy and radiation therapy to subcutaneous/skin lesions in lower extremities in two different settings. Two patients received surgery followed by radiation therapy in axilla and groin, while 1 patient received immunotherapy.

Comparison with CT/MRI Imaging

Comparison with 28 CT/MRI scans and PET/CT was available in 17 of 61 patients (28%). Of 28 CT/MRI scans, 7 showed suspicious findings. Of 7 scans, 6 were true positives as confirmed by histology in 4 and clinical follow up in 2. False positive finding was seen in 1 CT scan confirmed

on clinical follow up that demonstrated a borderline enlarged inguinal node (non FDG avid) in patient with primary disease in groin. Two findings were falsely negative on CT, including biopsy proven in-transit metastases in thigh (non-FDG avid) and inguinal node (FDG avid) positive for recurrence in imaging follow up. Two findings including a lung nodule and bone lesion, suspicious on FDG-PET/CT and positive for recurrent disease on clinical/imaging follow up, were outside the regional field of view of CT/MRI.

Prognostic Analyses

Mean follow-up duration was 4.8 years (range, 8months-18years) post-first surveillance FDG-PET/CT. Among the 43 patients with negative scans at 3 months, 7 had a positive scan later, i.e., 16%. Among the 41 patients with negative scans at 6 months, 5 had a positive scan later, i.e., 12%. Among the 39 patients with negative scans at 12 months, 3 had a positive scan later, i.e., 8%. Surveillance of patients is represented in the swimmer plot demonstrating the time points of FDG-PET/CT scan positivity and the follow up duration (Figure 3). Most of the recurrences developed within 1.5 years after the end of primary treatment. Based on the timing of the scan, statistical analysis revealed better overall survival in patients with negative FDG-PET/CT scan, as compared to patients with positive scan, within 3 months (<0.0001), 6 months (<0.0001) and 12 months post-treatment (<0.0001) (Figure 4).

Univariable statistical analysis showed that the risk of death increases with a positive surveillance FDG-PET/CT scan, higher SUV and with higher number of FDG avid lesions (Table 2). Multivariable analysis showed that risk of death was increased with higher SUV (HR for one unit=1.17; 95%CI 1.05 to 1.31;p=0.006), and number of FDG avid lesions (HR for one additional lesion=1.60; 95%CI 1.25 to 2.04;p<0.001); and was decreased for patients with Stage

IIIA(UP) compared to Stage IIIA(KP) (HR = 0.09; 95%CI 0.01 to 0.99, Table 2). FDG PET/CT scan positivity was not evaluated in the multivariable model as we used a summary of the number of positive lesions.

DISCUSSION

In this study, FDG-PET/CT showed high sensitivity and specificity of 92% and 93%, respectively, to detect recurrent MCC lesions in local as well as distant sites. Overall, 12% (27/221) of surveillance FDG-PET/CT scans were true-positive for recurrence, while 81% were true-negative. FDG-PET/CT results contributed to implementation of treatments in 33% (20/61) patients. We also assessed the prognostic significance of FDG-PET/CT, specifically in patients treated for stage III disease, which has never been reported before.

Based on our results, early inclusion of FDG-PET/CT within the first 6 months after definitive treatment is suitable to initiate imaging surveillance in stage III MCC patients. Although none of our patients had clinically evident disease after receiving definitive treatment, unexpected true-positive FDG-PET/CT findings were detected in local or locoregional nodes in 13%(8/61) patients at median interval of 4.5 months post-treatment; all patients had normal-appearing skin and negative clinical nodal exam. Additionally, unexpected findings were seen in distant organs including ovaries, pancreas, bone, and distant lymph nodes in 20% (12/61) of patients; median interval of 7.2 months post-treatment. Only a few prior studies have partly evaluated follow-up FDG-PET/CT in MCC, with relapse noted in 7-15% scans and overall impact on management seen in 20-32% patients (*10,12-13,16,18,20-21*). However, these studies were limited due to small patient cohort, small number of surveillance PET/CT scans included, variable disease stage, unclear patient's clinical status at the time of scan and varying indications

for including FDG-PET/CT scans e.g., monitoring treatment response, clinically suspected recurrence, or ongoing surveillance (*16,18,20,22*).

We also observed that most recurrences developed within 1.5 years after definitive treatment and FDG-PET/CT enabled identification of unsuspected disease relapse leading to appropriate treatment planning. This invites further studies, preferably of prospective nature, to evaluate the appropriate time intervals of performing surveillance imaging in the initial post-treatment years. Based on our data, surveillance FDG-PET/CT scans obtained within first 6 months of end of definitive treatment and follow up scans, spaced at intervals of 6-9 months for at least 2 years may be beneficial, considering that most recurrences are detected within the first 2 years of diagnosis (*3,6,7-9*). Currently, there is no consensus on follow-up surveillance imaging of asymptomatic patients after treatment completion. Another study has shown slightly different results with longer mean time to recurrence of 15.3 months, which may have been due to variable disease stage of included patients (*18*). A few studies that demonstrated median time to recurrence of 6-9 months, have not clearly explained the imaging modality used to detect recurrence (*3,24-27*).

The OS of patients with recurrence detected on FDG-PET/CT was significantly reduced compared to patients with negative FDG-PET/CT scans. It is of interest to note that the chances of developing recurrence decreased with increasing elapsed time from the end of treatment. In our cohort, 16%, 12% and 8% of patients who had negative FDG-PET/CT scans at 3-, 6- and 12-months post-treatment, respectively, developed recurrences. In addition, the overall survival of patients was negatively impacted by higher number of FDG avid lesions and higher SUV, which suggests higher disease burden; this has often been reported in other malignancies as well (*28*). None of the prior studies in the literature have demonstrated the prognostic role of surveillance

FDG-PET/CT scans in MCC patients. In the study by TROG (Trans Tasman Radiation Oncology Group), post radiation-treatment FDG-PET/CT scans were acquired at 9 weeks after end of radiation therapy in patients with ongoing systemic treatment. The study showed positive findings in 5/41 patients (12%) and no impact on patient survival at 3 years (*16*). The non-significant results were attributed to small number of patients with positive PET findings and early intervention with salvage treatment (*16*).

In our study, FDG-PET/CT showed false positive findings in 8 patients, mainly in cutaneous sites and reactive lymph nodes with relatively low-grade uptake. This can be explained by overexpression of glucose transporters in infectious/inflammatory etiology (*29*). Histopathologic correlation is therefore needed to confirm diseases in sites that appear equivocal on FDG-PET/CT. Compared to CT/MRI, FDG-PET/CT scan detected disease in sites that were outside the conventional imaging field-of-view and in nodes that were not suspicious by size criteria on CT/MRI. The in-transit metastases were falsely negative on both conventional and metabolic imaging, perhaps related to the small size.

Our study is limited by retrospective design, variable timing of initiation of, and continuation of surveillance imaging, as well as the lack of pathologic correlation for all lesions. We did not study the cost benefit analysis of performing FDG-PET/CT scans for surveillance as it was beyond the scope of the current study, however the risk-benefit ratio will need evaluation in future studies to understand the economic impact.

In conclusion, surveillance whole-body FDG-PET/CT is a sensitive imaging modality in post-treatment follow-up of asymptomatic stage III MCC patients. Our data indicates that initiating surveillance FDG-PET/CT within 6 months after completion of definitive treatment in

stage III MCC may be useful in early detection of recurrence. Further scans spaced at intervals of 6-9 months for at least 2 years may be beneficial. Larger prospective studies may help further validate these findings.

KEY POINTS

Question: What is the diagnostic and prognostic value of 18F-FDG PET/CT in surveillance imaging of stage III MCC patients?

Pertinent Findings: In this retrospective study, 61 post-treatment stage III MCC patients were included who were clinically asymptomatic, and 18F-FDG PET/CT detected unsuspected recurrent disease in 33% patients, with high sensitivity and specificity of 92% and 93%, respectively. Risk of death was increased with higher number of FDG avid lesions ($p<0.001$) and higher lesion SUV ($p=0.006$) on 18F-FDG PET/CT scan. Patients detected with recurrent disease on 18F-FDG PET/CT scan, within one year of definitive treatment, had relatively worse overall survival ($p<0.0001$).

Implications for patient care: Early implementation of surveillance 18F-FDG PET/CT in patients with stage III MCC, allows detection of unsuspected recurrences leading to appropriate treatment planning and has a potential prognostic role.

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Table 1. Patient, tumor, and FDG-PET/CT scan characteristics.

Number of patients	61
Sex, Male:Female, n (%)	44 (72%):17 (28%)
Age at the time of diagnosis, y, mean±SD (range)	69±13.0 (25-93)
Site of primary disease, n (%)	
Cheek/Chin	5 (8.1%)
Ear/Eyelid/Nose	4 (6.6%)
Forehead/Scalp	5 (8.1%)
Neck node	2 (3.3%)
Axilla	4 (6.6%)
Back/Chest	2 (3.3%)
Groin	11 (18.0%)
Buttocks	10 (16.3%)
Finger/Hand	2 (3.3%)
Forearm/Elbow/Arm	8 (13.2%)
Knee/Leg/Thigh	8 (13.2%)
Stage of primary disease at diagnosis, n (%)	
Stage IIIA (Known Primary)	23 (37%)
Stage IIIA (Unknown Primary)	20 (33%)
Stage IIIB	18 (30%)
Prior treatment received, n (%)	
Surgery	20 (33%)
Surgery+Chemotherapy/Radiation/Chemoradiation	38 (62%)
Chemoradiation	3 (5%)

Number of FDG-PET/CT scans	221
Scans performed per patient, n	
1 - 4	43
5 - 10	18

Table 2. Univariate and Multivariate prognostic models for Overall Survival.

	Univariate				Multivariate		
Variable	**HR**	**95% CI**	**p-value**		**HR**	**95% CI**	**p-value**
FDG-PET/CT scan positive	15.7	4.34, 56.5	<0.001		-	-	-
SUVmax (for 1 unit)	1.27	1.17, 1.39	<0.001		1.17	1.05, 1.31	0.006
Number of positive lesions (for 1 lesion)	1.45	1.27, 1.64	<0.001		1.60	1.25, 2.04	<0.001
Stage			0.16				0.05
IIIA (KP)	Ref.				Ref.		
IIIA (UP)	0.27	0.06, 1.27			0.09	0.01, 0.99	
IIIB	0.86	0.28, 2.64			0.38	0.08, 1.94	

*CI – Confidence Interval, KP – Known Primary, UP – Unknown Primary

Figure 1. Asymptomatic 70-year-old woman with left arm MCC (s/p excision, left axillary lymphadenectomy, radiation to axilla), underwent surveillance FDG-PET/CT scan, 3.3 months post-treatment. FDG-PET/CT (A; MIP, *arrow*) scan revealed solitary focal FDG uptake in left pelvis (B; fused PET/CT, SUV 9, *arrow*) in a nodular soft tissue density lesion in left adnexa (C; axial CT, *arrow*). USG pelvis showed solid mass in left ovary measuring 1.81.4x1.6cm corresponding to the site of abnormality on FDG-PET/CT. Patient underwent salpingo-oophorectomy and pathology was positive for MCC.

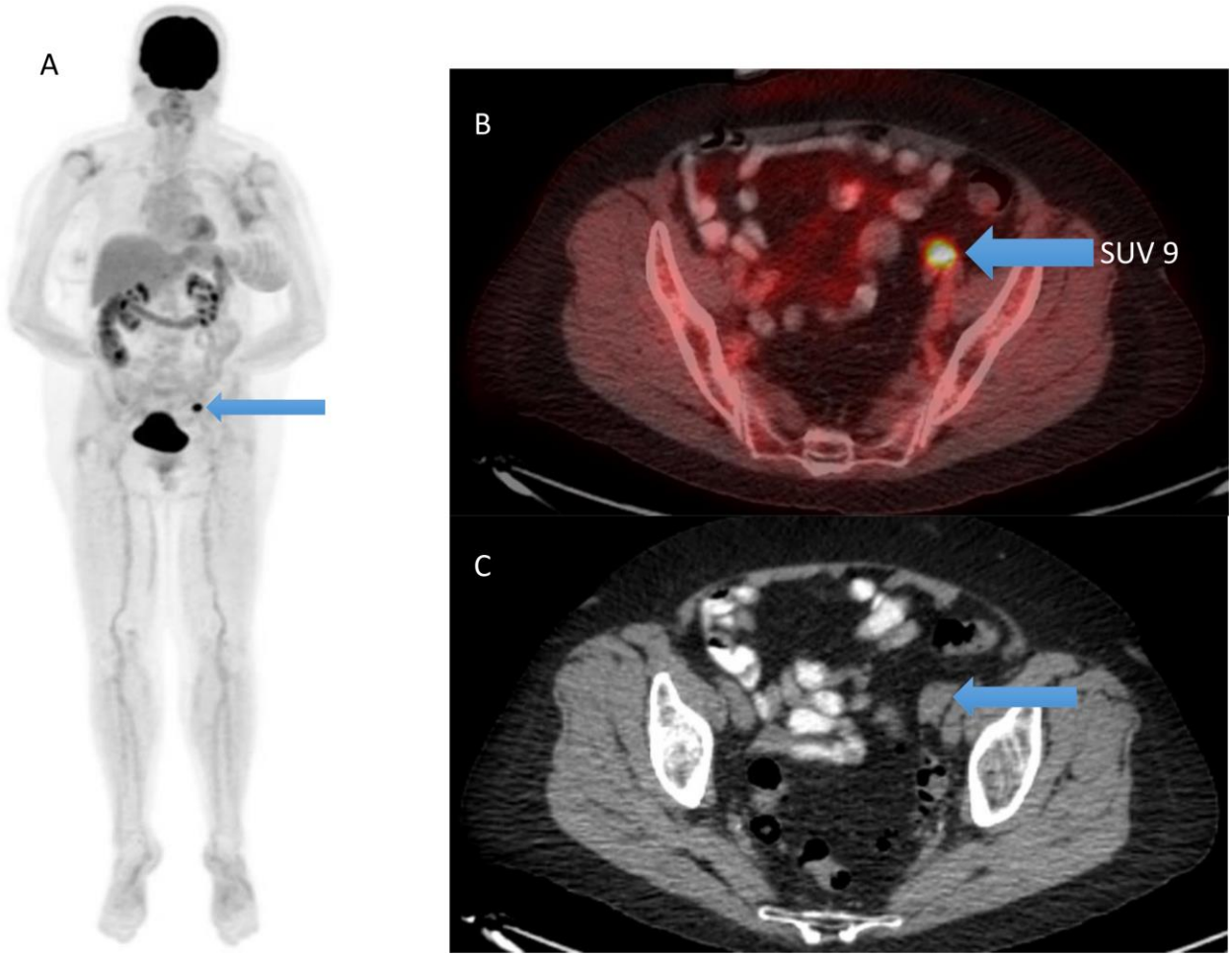
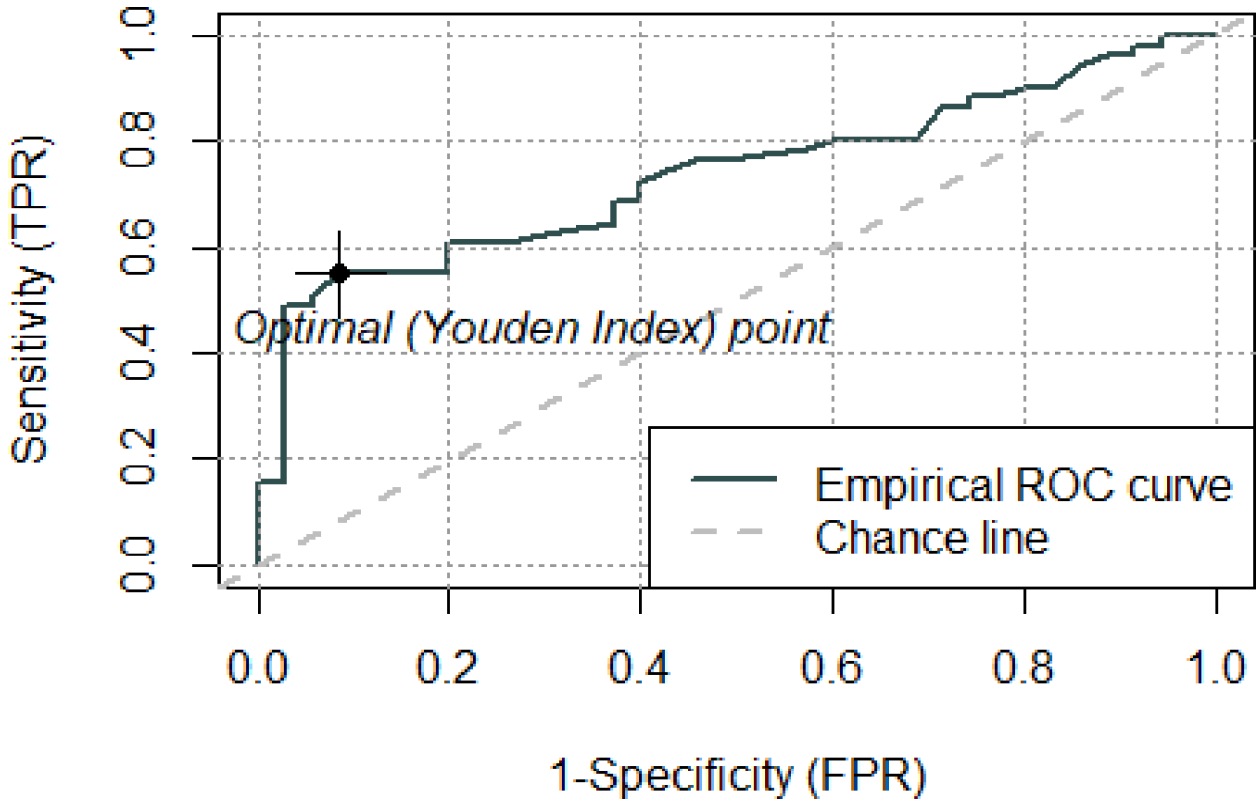


Figure 2. ROC curve for benign versus malignant lesion prediction based on SUVmax value.



F**igure 3.** Swimmer plot illustrating information about local and distant recurrences, confirmed on pathology, during follow up on surveillance FDG-PET/CT scans since the end of primary treatment for all included Stage IIIA Known Primary (KP), IIIA Unknown Primary (UP) and IIIB Merkel cell carcinoma patients (n=61).

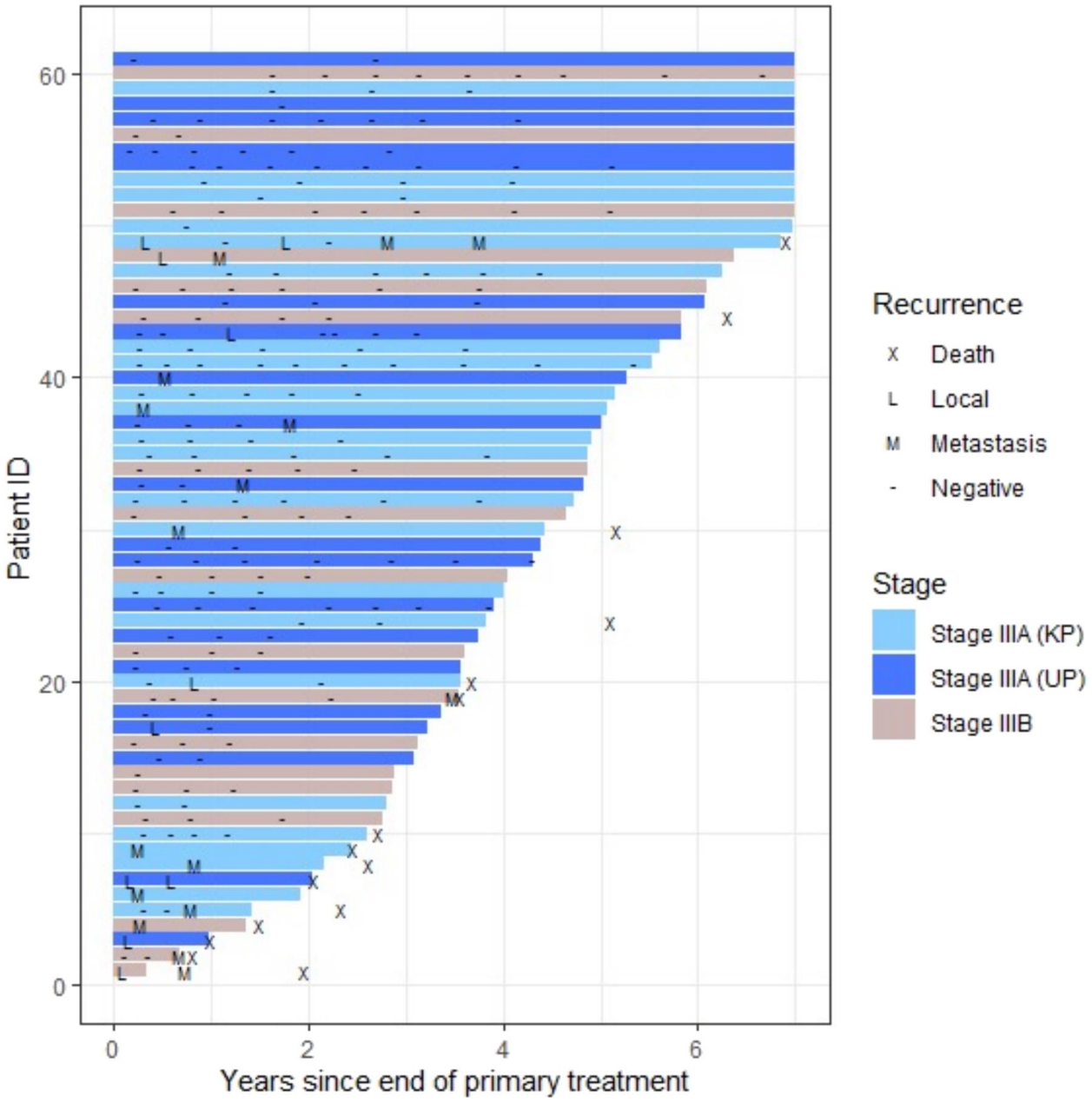
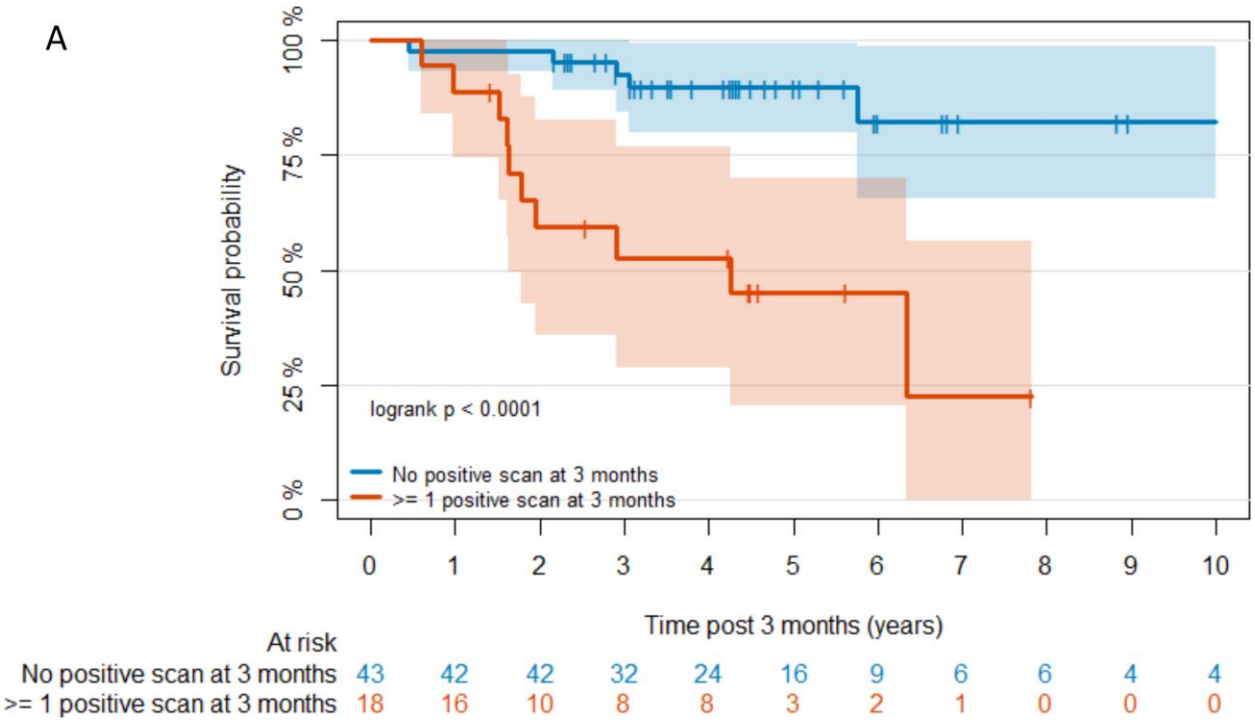


Figure 4. Overall survival of patients based on the findings and timing of the FDG-PET/CT scan (A, at 3-months; B, at 6- and, C, at 12-months post-definitive treatment, respectively).



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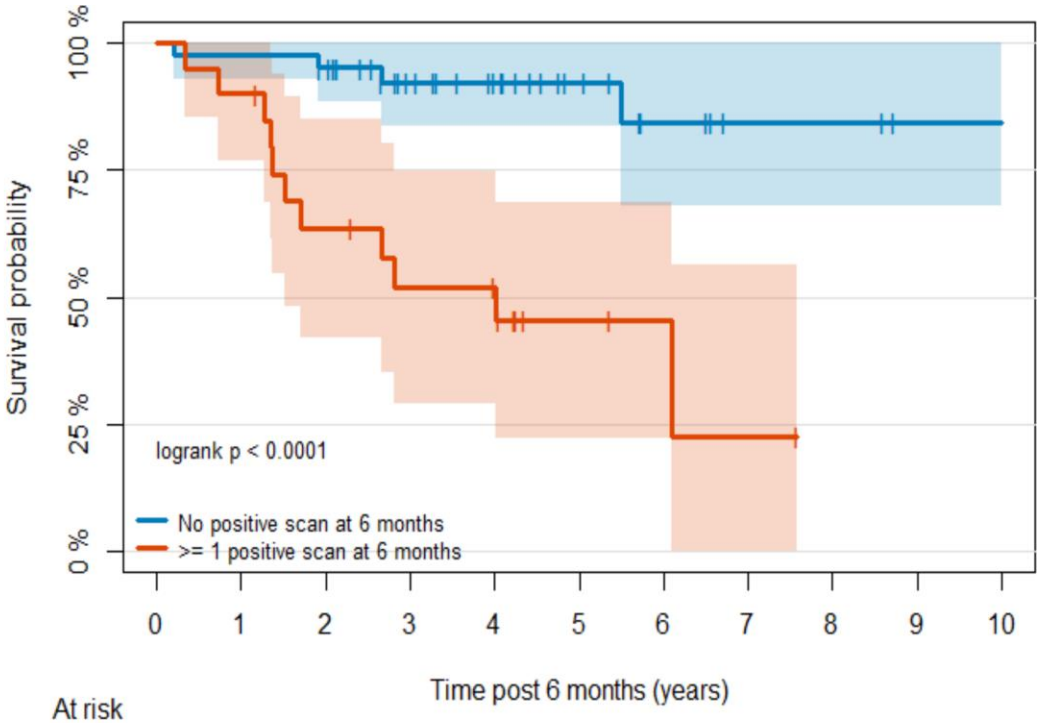
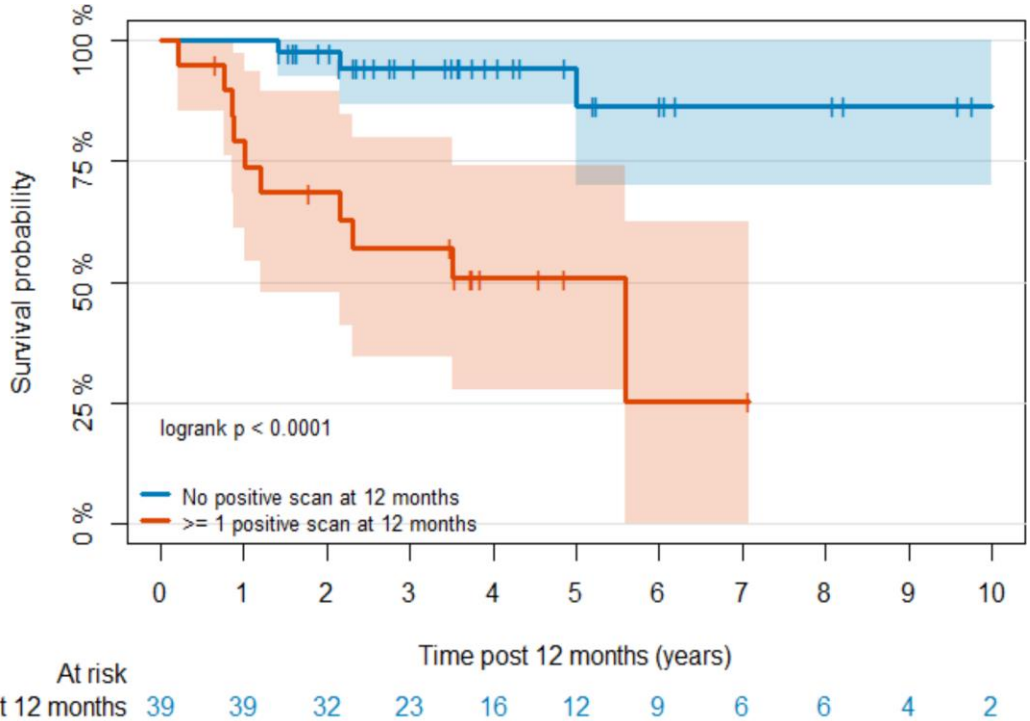


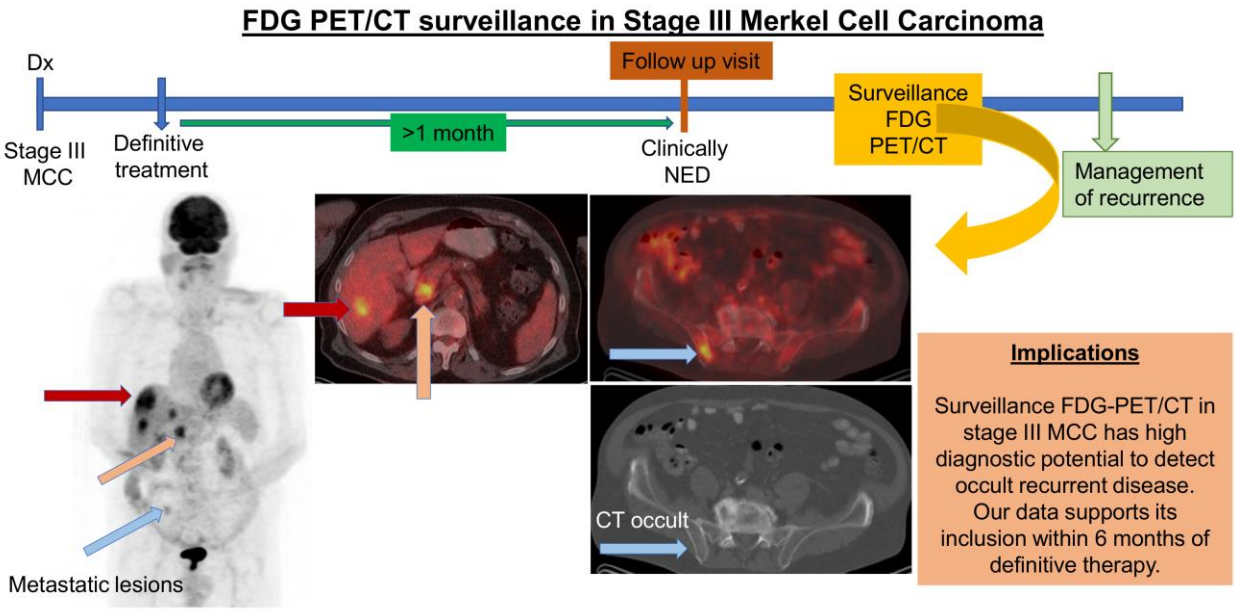
At risk											
No positive scan at 6 months	41	40	38	27	22	14	9	6	6	4	4
>= 1 positive scan at 6 months	20	18	12	9	8	3	2	1	0	0	0

C



At risk											
No positive scan at 12 months	39	39	32	23	16	12	9	6	6	4	2
>= 1 positive scan at 12 months	20	15	12	10	4	2	1	1	0	0	0

Graphical Abstract:



Supplemental Data:

Methodology:

A total of 296 patients who were treated for stage III MCC were initially identified from an institutional database at Memorial Sloan Kettering Cancer Center between the years 2001–2017; among them 115 patients had obtained FDG-PET/CT scans. Of 115, 61 patients received surveillance FDG-PET/CT scans and were included in the study cohort. The remaining 54 of 115 patients were excluded; with FDG-PET/CT scans obtained for other indications including staging, evaluating treatment response and further assessment of clinical or imaging-based recurrence.

Patients

Sixty-one patients were included in the final study cohort. Staging was performed at the time of diagnosis, according to American Joint Committee of Cancer guidelines, 8th edition (23). Stage III disease included patients with suspected lymph node involvement either (i) positive only on sentinel lymph node biopsy in patients with known primary (Stage IIIA KP), (ii) positive on clinical examination in patients with unknown primary (Stage IIIA UP), or (iii) positive on clinical examination and confirmed by pathology (Stage IIIB) (*23*). Electronic medical records were reviewed for clinico-pathologic data and mean follow-up duration was 4.8 years.

FDG-PET/CT Acquisition

Following six-hours of fasting and pre-injection serum blood glucose of <200 mg/dl, patients were intravenously injected with 370-555 MBq F-18 FDG. Whole-body scans were acquired 60-90 minutes post-injection from vertex to toes, with patients in supine position. Low-dose (120-

140 kV, 80 mA) CT scans with oral contrast were obtained and used for attenuation-correction of PET images. All images were reviewed on PACS workstation using VCAR imaging suite (AW Suite 2, GE Healthcare, Chicago, IL, USA). Maximum standardized uptake values (SUV), normalized to body weight, were determined.

Image Analysis

A total of 221 FDG-PET/CT scans were reviewed by two experienced nuclear medicine physicians (SM, NPT). Focal areas of uptake with intensity greater than background, excluding physiologic sites, were considered suspicious. Location, size, and SUV of 107 suspicious lesions were noted. Histopathologic correlation was available for 30 lesions as standard of reference, while clinical/imaging follow-up (≥ 6 months) was performed for remaining 77 lesions. Findings were classified as true-positive for recurrence/metastasis if confirmed by either positive histopathology from biopsies/resections or presence of detectable lesion at corresponding site on follow-up imaging showing increase in SUV or size. Comparison of findings was performed in 28 pairs of PET/CT scans and CT/MRI (limited regions/areas) acquired within one month.

Statistical Methods

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy with 95% confidence intervals (95% CI) were calculated, using pathology and clinical/imaging follow-up as reference standard. Time-to-recurrence was defined as time from end of primary treatment to first recurrence detected on FDG-PET/CT, confirmed pathologically or clinically; alive patients without recurrences were censored at their last date of follow-up, and deaths before recurrence were considered as competing risk. Cumulative rates of recurrence were calculated using Aalen-Johansen estimator. Overall survival was defined from first surveillance

PET/CT scan to date of death; alive patients were censored at their last date of follow-up. Kaplan-Meier curve was used to estimate survival rates. Landmark analyses were used to compare survival, based on scan positivity at 3, 6 and 12 months, i.e., events occurring prior to the landmark time were excluding, and the time was calculating from the landmark time. Survival curves were compared with a log rank test. Cox-proportional hazards model were used for univariable/multivariable analysis to assess prognostic value of PET parameters including scan positivity, lesion SUV, and number of lesions, as well as disease stage ($p<0.05$ considered statistically significant). Factors with p-value<0.20 in univariate analysis were entered in multivariate analysis, and a backward variable selection was done. Adjusted hazard ratio (HR) are presented along with 95%CI. Statistical analysis was performed using R version 3.5.0 (R Core Team, Vienna, Austria).