ORIGINAL RESEARCH

Utility of Preoperative Staging for Clinically Localized Merkel Cell Carcinoma

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ABSTRACT

Introduction: For Merkel Cell Carcinoma (MCC), a rare cutaneous neuroendocrine cancer, treatment varies based on disease stage at presentation. For patients with localized disease, primary treatment is surgical resection. There is wide practice variation in the performance of preoperative imaging studies, which may upstage patients and/or change plans for surgical resection. The purpose of this study was to evaluate how preoperative staging with cross-sectional imaging influenced management of patients with clinically localized Merkel Cell Carcinoma.
Methods: We identified patients who were evaluated at our facility between January 1, 2012 and December 31, 2020 for clinically localized MCC (confined to the skin, without evidence of nodal spread or signs/symptoms of distant disease) prior to surgical resection. The primary outcome was the proportion of patients whose management changed based on preoperative imaging.
Results: There were 97 patients, of whom 84 (87%) had preoperative staging studies. Patients had a median age of 75 years, 13% were immunosuppressed, and 81% had tumors <2cm. There were no differences in the clinical characteristics of patients based on whether staging was performed. PET/CT was performed in 52(67%) patients, 51(62%) CT, 31(41%) brain MRI. There were 5 patients with indeterminate findings (all on PET/CT), but there were no patients for whom preoperative staging changed the plan for surgical resection.
Conclusion: There were no changes in surgical management based on results of preoperative imaging. More selective use of preoperative imaging staging may be warranted, potentially considering risk factors for clinically occult micro-metastatic disease.

INTRODUCTION

Merkel Cell Carcinoma (MCC) is a rare neuroendocrine tumor that arises from Merkel cells, neural crest derivatives which reside at the basal layer of the epidermis and serve as mechanoreceptors. MCC affects approximately three out of every one million people, is more common in immunosuppressed patients, and has a poor prognosis.[1] Though rare, the incidence of MCC has risen 5.4 fold over the last 18 years and 3 fold over the past 10 years.[2]

Half of patients with MCC present with clinically localized disease, while the remainder have nodal or distant metastases. Treatment for localized disease typically consists of surgical resection with nodal staging with or without adjuvant radiation. Advanced disease is usually managed with systemic therapy.[4] Given its aggressive biology, patients presenting with clinically localized disease may undergo preoperative staging studies to identify occult metastatic disease. The impact of these studies on management is unknown, with significant variation in preoperative staging in clinical practice.

Although the National Comprehensive Cancer Network (NCCN) states that preoperative imaging is encouraged in most cases, current guidelines addressing preoperative staging imaging of MCC are broad, leaving this decision to the discretion of individual providers. The purpose of this study was to evaluate the utility of cross-sectional imaging including brain magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) for preoperative staging of patients with clinically localized disease. Utility was determined based on whether imaging findings resulted in a change in surgical management of the patient.

METHODS

In a retrospective study performed at the University of Alabama at Birmingham from 1/1/12 to 12/31/20, we identified adult patients with Merkel Cell Carcinoma based on billing codes (Supplemental Table) using UAB's Enterprise Data Warehouse and registry data from our institutional cancer registry. Patients were included if they had clinically localized disease based on history and physical exam, meaning the tumor was confined to the skin without clinical evidence of nodal spread or signs/symptoms of distant disease, and were evaluated at our institution prior to surgery. The study was approved by UAB's Human Research Protection Program and Institutional Review Board.

Data were collected through electronic medical record review including referring provider documentation and pathology results from outside biopsies. Patient information included demographics, immunosuppression status, and current and prior history of cancer. Immunosuppression was defined as patients on immunosuppressive medications, with hematologic malignancies, and with autoimmune diseases. Tumor features included anatomic location, clinical size, and pathologic characteristics. Treatment details and long-term outcomes were also obtained.

The primary outcome was change in management based on results of any staging imaging studies that were obtained prior to surgery. We evaluated the most commonly performed pre-operative imaging studies: CT, PET/CT, and brain MRI. The decision to perform preoperative staging studies and selection of study types were made by the surgical team who evaluated the patient. There was no standard preoperative staging protocol in place at this time. Informative findings including indeterminate results were abstracted, and their impact on management (i.e. decision not to resect, additional testing prior to surgery, change in planned extent of resection, or provision of neoadjuvant treatment) was determined based on review of clinic notes and the documented clinical course.

Descriptive statistics included patient demographics, risk factors, and tumor specific features. Characteristics of patients who did and did not undergo preoperative

imaging were compared using chi-squared and student's T-tests. We evaluated the proportion of patients who underwent preoperative imaging evaluation and had informative findings, as well as the proportion with a change in surgical management.

RESULTS

Of the 236 patients initially evaluated through chart review, 97 patients met the inclusion criteria and were subsequently included **(Figure 1)**. Forty-four patients were excluded due to not having a diagnosis of MCC, 33 patients had distant, regional, or indeterminate disease at presentation, 37 patients had recurrent disease at time of presentation, and 25 patients did not have a documented evaluation at our institution prior to surgery. Of the 33 patients excluded due to having non-localized disease at time of presentation, 23 were diagnosed at our hospital based on symptoms and/or physical exam findings. The remaining 10 patients presented to our institution after receiving imaging at an outside facility for what appeared to be localized disease, 6 of whom were found to have distant metastases and 4 of whom had nodal metastases. Overall, 97 patients met all of the inclusion criteria, of which 84 (87%) received pre-operative imaging.

Characteristics of the study population are shown in **Table 1**. When comparing patients who did and did not have preoperative staging **(Table 2)**, none of the population characteristics affected the likelihood of receiving pre-operative imaging. Of the 84 people who received pre-operative imaging, 31 received a brain MRI, 52 patients received a PET scan, and 51 received a CT scan.

No imaging studies revealed definitive evidence of metastatic disease, though five patients had indeterminate findings on PET scan **(Table 3)**. One patient had indeterminate lung and bony lesions seen on both PET and CT scan which were stable on post-surgical surveillance. Another patient had an FDG-avid lung lesion on PET scan which was not amenable to biopsy and remained stable on surveillance. One patient had indeterminate lung and mediastinal findings, found to be negative for malignancy on biopsy. Another patient had indeterminate lung and renal parenchymal findings, also found to be negative on biopsy. The fifth patient had MCC of the right eyebrow, with preoperative PET/CT showing an indeterminate focus in the right parotid that was thought to represent a reactive lymph node. He underwent primary tumor right eyebrow lesion excision and right parotid sentinel lymph node biopsy, which was negative for nodal metastasis. Four months after excision, a palpable mass was found in the right parotid, and fine needle aspiration of the mass confirmed recurrent MCC. He underwent right superficial parotidectomy and right neck dissection, which revealed 2/2 parotid nodes and 1/26 right neck lymph nodes positive for MCC.

Overall, 79 of the 84 patients who received pre-operative imaging showed no distant disease, and the surgical plan for the 5 patients with indeterminate findings remained unchanged. None of the patients who received imaging had a change in management based on pre-operative imaging **(Table 3)**.

In terms of post-surgical treatment of MCC, 50 (52%) patients received radiation. Forty-seven (48%) received radiation to the primary site and 29 (30%) received radiation to the lymph nodes only. Five (5%) patients received adjuvant chemotherapy while 6 (6%) patients received immunotherapy. In a median follow-up of 7 months (25^{th}-75^{th}

Table 1. Characteristics of study population.

Characteristic		N=97
Sex, N (%)		
	Male, N (%)	64 (66)
	Female, N (%)	33 (34)
Age, years, median (25^{th}-75^{th} percentile)		75 (69-80)
Race, N (%)		
	White	93 (96)
	Other	3 (3)
	Missing	1 (1)
Ethnicity, N (%)		
	Hispanic	1 (1)
	Non-Hispanic	95 (98)
	Missing	1 (1)
Distance Traveled, miles, median (25^{th}-75^{th} percentile)		73 (50-103)
Immunosuppressed, N (%)		
	Yes	13 (13)
	No	84 (87)
History of Non-Cutaneous Cancer Prior to MCC Diagnosis, N (%)		
	Yes	55 (57)
	No	42 (43)
Concurrent Non-Cutaneous Cancer, N (%)		
	Yes	25 (26)
	No	72 (74)
Tumor Size, median, mm (25^{th}-75^{th} percentile)		9.6 (3-20)
Concurrent Skin Cancer, N (%)		
	Melanoma	7 (7.2)
	Non-melanoma	41 (42)

percentile 1-22 months), 17 (18%) patients had disease recurrence, and 10 (10%) died.

DISCUSSION

Current guidelines pertaining to preoperative staging imaging of MCC are broad, leaving substantial opportunity for practice variation. Imaging accounts for approximately 10% of total healthcare costs annually, and an estimated 30% of imaging may be unnecessary.[10] Research pertaining to the utility of imaging for staging of cancer patients can better inform current guidelines. In this study, we evaluated the utility of imaging in patients with clinically localized MCC at our institution over a 9-year period. Though most patients had some form of cross-sectional imaging, we found that surgical treatment plan did not change in any circumstance.

Although MCC is becoming more commonly diagnosed, clear guidelines as to the efficacy of imaging remain unclear. A significant body

Table 2. Characteristics of Patients who received and did not receive preoperative staging.

Characteristic	Received Pre-Operative Imaging N=84	Did not receive Pre-Operative Imaging N=13	P-value
Sex, N (%) Female Male	 28 (33) 56 (67)	 5 (38) 8 (62)	.72
Age, median (25th-75th percentile)	76 (69-80)	69 (60-80)	.19
Race, N (%) Other White	 4 (5) 80 (95)	 0 (0) 13 (100)	.72
Hispanic Ethnicity, N (%) No Yes	 83 (99) 1 (1)	 12 (100) 0 (0)	.70
Distance Traveled to UAB, Miles (25th - 75th percentile)	70 (50-104)	98 (52-103)	.62
Immunosuppression, N(%) No Yes	 72 (86) 12 (14)	 12 (92) 1 (8)	.52
History of Non-Cutaneous Cancer Prior to MCC Diagnosis, N (%) No Yes	 37 (44) 37(56)	 5 (38) 8 (62)	.71
Concurrent cancers, N (%) No Yes	 62 (74) 22 (26)	 10 (77) 3 (23)	.81
Clinical Stage prior to imaging, N (%) I II III	 68 (81) 15 (18) 1 (1)	 11 (85) 2 (15) 0 (0)	.90

of work has evaluated the utility of imaging for detection of nodal disease; findings show that the sensitivity ranged from 47-80% for CT and 83-95% for PET. This was not limited to micrometastases which would not be expected to be visible on cross-sectional imaging. In one study, CT failed to detect larger lymph node metastases in 6 of 69

Table 3. Results of findings found on imaging.

	Number of Patients N=97, N (%)
No Findings on Imaging	92 (95)
Indeterminate Findings on Imaging	5 (5)
Change in management post Imaging	0 (0)

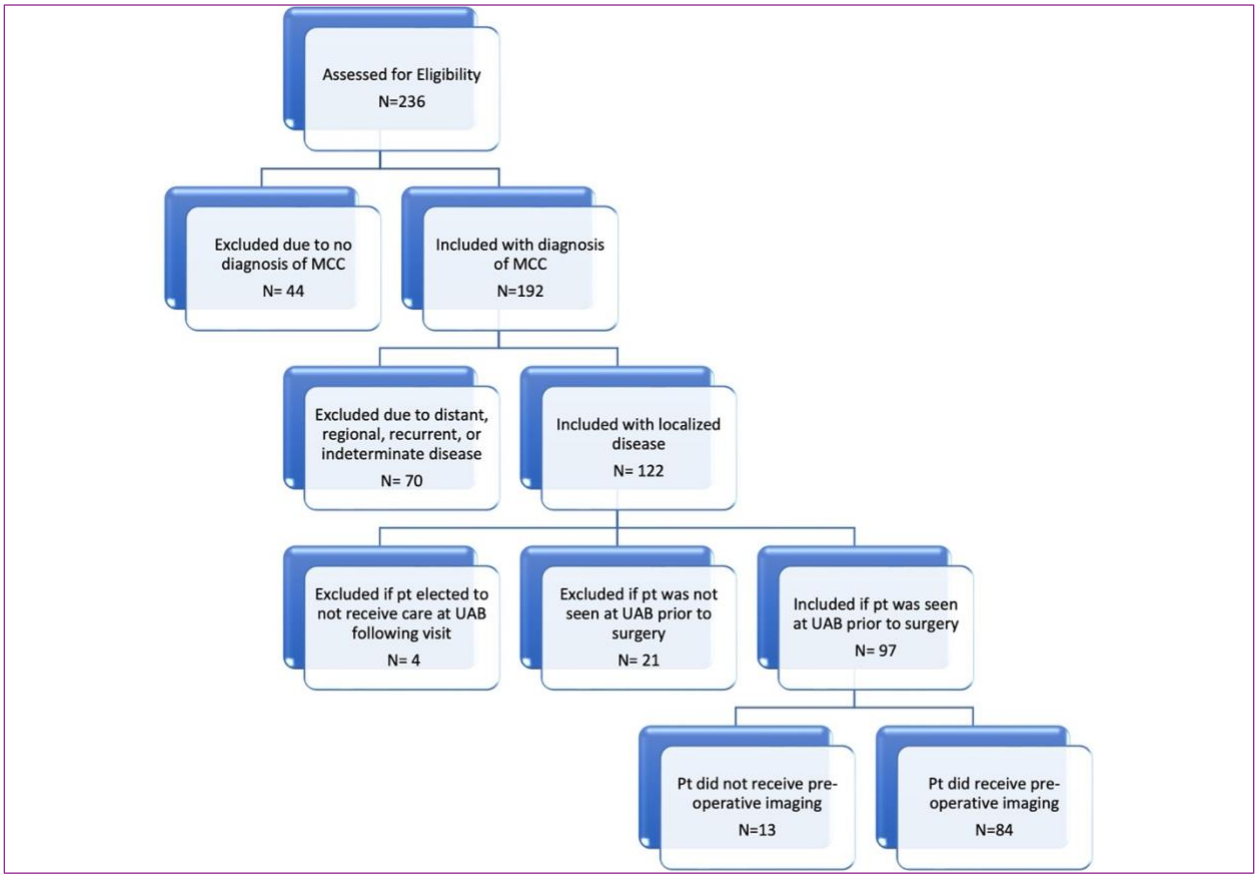

Figure 1. Consort diagram of study population.

patients (8.7%).[5] This supports routine performance of sentinel lymph node biopsy in all patients with clinically localized MCC, regardless of preoperative imaging findings.

While our study did not identify any patients whose management changed following preoperative imaging, many studies have noted significant upstaging following imaging for patients with clinically localized MCC. In an analysis of 584 patients, 492 patients were found to have localized disease, and 13.2% of patients were upstaged following imaging.[11] Furthermore, patients receiving PET scans were more likely to be upstaged than those receiving CT scans.[11] Another retrospective analysis of 23 patients who received staging PET/CT showed that 39% of patients were upstaged and management changed for 33% of patients following baseline imaging.[12] These studies suggest a role for staging imaging, specifically PET

scans, prior to operation. The discrepancy between our study results and these previous findings is interesting and may be due to limitations in study design or management variations among different institutions. Our results suggest that MCC preoperative workup could be streamlined by the establishment of routine sentinel node biopsy without necessary prior imaging.

It is notable that some patients who were referred with nodal and/or distant disease did have imaging prior to referral. Failure to include these patients could result in selection bias. If the ten patients were included who were found to have asymptomatic non-localized disease on imaging performed prior to being seen at our institution, then the proportion of patients for whom management changed based on imaging would be 10/94 (11%). This represents a maximal estimate of the proportion of patients with change in management based on preoperative imaging if only those patients who were found to have metastatic disease had undergone imaging. This fails to include in the denominator the patients who underwent imaging prior to presentation and were not found to have metastases. So, we conclude that the proportion of patients with a management change is between 0 and 11%.

We are able to make some comments regarding specific imaging modalities. The use of brain MRI for detecting MCC metastases is widely debated among NCCN panel members. While brain MRI is not indicated for initial workup of patients with MCC, some recommend the inclusion of brain MRI when screening for distant disease in patients with known nodal disease. Others recommend that brain MRI should be reserved only for patients with evidence of brain metastases. Data on the MRI's sensitivity, specificity, and the impact on staging on management remains limited. In this study there were no patients with informative findings based on brain MRI.[9] Likewise, all indeterminate findings were identified on PET or PET/CT while there were no management-changing or indeterminate findings on CT alone. One cost effective solution would be to use CT rather than PET for preoperative staging given that performance of PET resulted in additional indeterminate findings and additional biopsies without changing initial surgical management in any case. We recommend the establishment of a unified imaging strategy for MCC management to optimize disease detection, while limiting redundancy and modalities that are low yield in terms of their ability to change management. If certain preoperative imaging techniques are indeed limited in their prognostic value for this type of malignancy, further studies are indicated to identify ideal predictors of disease course.

While our work addresses the utility of preoperative imaging for staging and our main outcome pertains to whether or not surgical management was altered following imaging, we recognize that preoperative imaging may serve other purposes. An additional purpose of preoperative imaging is to allow the comparison of scans before and after surgery in order to assess disease recurrence. This is particularly helpful in patients receiving systemic immunotherapy or chemotherapy in order to evaluate whether lesions are stable, progressing, or regressing. For these reasons, preoperative imaging may be used for purposes other than staging.

This work suggests that pre-operative imaging studies may be over-utilized for clinically localized MCC. However, with our small sample size we were limited in our ability to evaluate specific risk factors for distant disease such as tumor size,

immunosuppression, and prior history of skin cancer, among other high-risk features. While we did not identify any specific disease factors that were associated with detecting occult metastases on imaging, future work in larger patient populations may be used to identify those patients at greatest risk of occult micro-metastatic disease for whom selective preoperative staging studies may have greatest utility.

LIMITATIONS

Limitations of this study include the generalizability of the study to all patients with MCC, as our study was limited to a patient population treated at an academic medical center in the Southeastern United States. Another limitation of our study includes our sample size of 67 as compared to other studies, such as the Singh et al study which evaluated 492 patients with clinically localized MCC and found that 13.2% of patients were upstaged due to imaging.[11] Additionally, the sampling bias of most, 79%, of our patients having Stage 1 disease could have led to a lower rate of upstaging by imaging as compared to other studies. Further, the retrospective study design limits our ability to determine specific reasons for selecting patients for staging imaging. For example, imaging performed due to patient symptoms may not be accurately reflected in electronic medical record documentation. This and other potential selection biases such as selective performance of imaging in patients who are perceived to be at higher risk of clinically occult metastases spread would be expected to increase the likelihood of finding metastatic disease on imaging, which was not found in any patient in this cohort. An additional limitation of our study is the median follow up time of seven months, which may reflect the nature of referrals from rural communities to our tertiary referral center with most patients receiving postoperative follow up care in their local communities.

CONCLUSION

Our study evaluated the utility of imaging on patients with clinically staged localized MCC and determined that imaging did not impact the surgical plan for any of the 84 patients who received imaging. Based on these findings, more selective use of preoperative imaging staging may be warranted. Future work should seek to characterize risk factors for clinically occult metastases which could be used to refine current guidelines for preoperative staging.

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