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Outcome of Multidisciplinary Treatment of Merkel Cell Carcinoma of the Hand and Wrist

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Abstract. *Background/Aim: Skin cancers are the most common malignancy of the hand and wrist. Merkel cell carcinoma (MCC) is a rare, aggressive non-melanoma skin cancer arising from cutaneous neuroendocrine cells and is known for local and distant recurrence. The purpose of the current study was to examine the treatment outcome of patients with MCC of the hand and wrist. Patients and Methods: We reviewed 25 patients (18 males:7 females) with MCC that occurred in the hand and wrist. The mean age at the time of biopsy of 71±11 years. Results: Tumors were located on the hand (n=13), finger/thumb (n=9), and wrist (n=3). Local control included wide local excision (n=22). This included 21 non-amputation resections and one 5th digit ray amputation. Sentinel lymph node biopsy was performed in 21 patients with positive nodal disease in seven cases. Adjuvant radiotherapy was delivered to the primary site in 17 patients and additionally to the regional lymph node basin in six patients. Recurrence within five years was noted in 40% of patients (mean time to recurrence 18.4±20.6 months). Recurrence-free and disease-specific survival rates at 5-years were 54.8% and 67.6%. Conclusion: MCC is a rare cutaneous neuroendocrine carcinoma with a high propensity for regional nodal spread. Despite aggressive local treatment, adjuvant radiotherapy to the primary site and regional nodes, MCC of the hand and wrist has a high rate of recurrence and mortality within five years of diagnosis.*

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Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous malignancy of neuroendocrine origin (1). Diagnosis is made with biopsy that demonstrates positive staining for the neuroendocrine marker cytokeratin-20 (CK20) (2). Clinically, MCC presents as a red or purple, painless nodule or indurated plaque (3). It typically develops on the extremities (38% of cases) and head and neck (29% of cases) (4), which suggests that sun exposure and associated ultraviolet radiation may predispose to development of the malignancy. Patients with hematological malignancies, immunosuppression, Merkel cell polyomavirus infection, advanced age, and male sex are also more susceptible to the development of MCC (5, 6).

In comparison to other cutaneous malignancies, MCC is exceptionally rare. There are approximately 500 new cases of MCC in comparison to more than 31,000 new cases of melanoma per year in the United States of America (2), however, since 1986, the incidence of MCC has tripled from 0.15 to 0.45 per 100,000 cases (5, 7, 8). More than one-third of patients diagnosed with MCC initially present with loco-regional, lymph node, or distant metastases (1, 9-12). MCC is also associated with high recurrence rates between 25% and 85%, often locally or in regional lymph nodes (2, 10, 11, 13). Presentation with metastatic disease and high recurrence rates result in a dismal prognosis, with more than one-third of patients ultimately succumbing to the disease (1).

Contemporary treatment strategies include wide local excision and radiotherapy for localized lesions and systemic chemotherapeutics for metastatic disease or lesions not amenable to surgery and radiotherapy (2, 14). Treatment and outcome of patients treated for MCC in the upper extremity are further complicated by a paucity of literature concerning treatment strategies and long-term outcomes of patients afflicted with hand and wrist lesions. Most literature concerning MCC of the upper extremity is comprised of case reports and series (15-19). The lack of evidence regarding therapeutic regimens and outcomes of MCC treatment present a challenge for hand and upper

extremity surgeons who must balance maintenance of upper extremity functionality and maximal tumor resection. Therefore, the present study aimed to examine the evaluation and treatment outcome of patients with MCC of the hand and wrist.

Patients and Methods

The diagnostic index database from our institution was queried for all patients with a diagnosis of MCC who were treated between 1994 and 2021. Patients with a primary cutaneous lesion of the hand or wrist were considered for inclusion in this study. All biopsy slides were reviewed by dermatopathologists and soft-tissue pathologists at our institution. Patients with a diagnosis of MCC but without documentation of in-person physical examination or records of workup and treatment for MCC were excluded from this study. This study was approved by the Institutional Review Board.

The medical record of each patient was reviewed and patient demographics, comorbidities, tumor characteristics, diagnostic studies, staging, and treatment plans were recorded. Disease response and recurrence were assessed using subsequent imaging and clinical documentation.

All chronological endpoints, including length of follow-up, time to recurrence, and time to death, were measured from the date of diagnostic biopsy. Local recurrence was defined as disease recurrence at the primary site, whereas regional recurrence was considered to be recurrence of disease within the upper extremity or draining lymph node basin. Distant recurrence was defined as development of new metastasis or recurrence outside of the upper extremity. All patients were staged in accordance with the AJCC system (Eighth Edition) (20). Functional outcomes following tumor resection were characterized by the Musculoskeletal Tumor Society scoring system for the upper extremity (MSTS-UE) (21). Categorical variables were described as frequency and percentages while continuous variables are presented as mean±standard deviation (SD). Cox hazard analysis was used to describe the impact of clinical or treatment characteristics on disease recurrence and survival. A p-value <0.05 was defined as statistically significant. Disease-free survival and overall survival estimates were calculated using the Kaplan–Meier method. Statistical analysis was performed *via* the BlueSky Statistics software package (BlueSky Statistics LLC, Chicago, IL, USA; Version 7.40).

Results

Clinical presentation. A total of 415 consecutive patients with a diagnosis of Merkel cell carcinoma were evaluated at our institution. Of these, 25 (6.0%) had a primary cutaneous lesion of the hand or wrist, which was defined as a tumor located at or distal to the ulnar styloid and radiocarpal joint. Tumors were located on the hand (n=13), finger or thumb (n=9), and wrist (n=3) (Table I). Mean age at diagnostic biopsy was 71 years (range=40-91 years) and 28% (n=7) of patients were female. Two patients were of Hispanic ethnicity and the remainder were Caucasian. Seven patients were immunosuppressed from either immunosuppressive medications (n=4), chemotherapy (n=2), or hematologic malignancy (n=1).

Table I. *Clinical characteristics of patients with Merkel cell carcinoma of the hand/wrist.*

Description (Total n=25)	Value
Age, mean (range), years	71 (40-91)
Females, n (%)	7 (28%)
Caucasian ethnicity, n (%)	23 (92%)
Immunosuppressed patients, n (%)	8 (32%)
Presenting tumor location, n	
Finger	9
Hand	13
Wrist	3
Histologic staining, n positive/total n tested	
CK20	25/25
Synaptophysin	18/18
Chromogranin	13/14
Pankeratin	9/9
CK7	1/10
LCA	0/5
Tumor maximum dimension, mean (range), cm	1.6 (1.6-10)
Tumor volume, mean (range), cm^3	5.2 (0.1-19.3)
Positive sentinel lymph node biopsy, n (%)	7 (33%)
Distant metastases on presentation, n	0

CK20: Cytokeratin 20; CK7: cytokeratin 7; LCA: leukocyte common antigen.

Table II. *Clinical outcomes of patients with Merkel cell carcinoma of the hand/wrist.*

Description (Total n=25)	Value
Recurrence-Free Survival	
1-year	71.8%
3-year	61.7%
5-year	54.8%
Time to recurrence, mean (SD), months	18.4 (20.6)
Local recurrence, n	0
Regional recurrence, n (%)	6 (24%)
Distant recurrence, n (%)	6 (24%)
Disease-specific survival	
1-year	88.0%
3-year	67.6%
5-year	67.6%
Time to disease-specific death, mean (SD) months	23.5 (18.0)
Status at final follow-up*	
Alive, no evidence of disease	14 (69.7)
Died of disease	8 (15.9)
Died of other cause	3 (48.2)

*Values shown are number of cases with median follow-up in months in parentheses. RLND: Regional lymph node dissection; XRT: radiation therapy; SD: standard deviation.

No patients had evidence of distant metastases during initial workup. Three patients had palpable axillary lymphadenopathy on initial examination. Pre-operative positron emission tomography – computed tomography (PET-CT) imaging was negative for lymph node involvement in 13 of 15 patients. Four

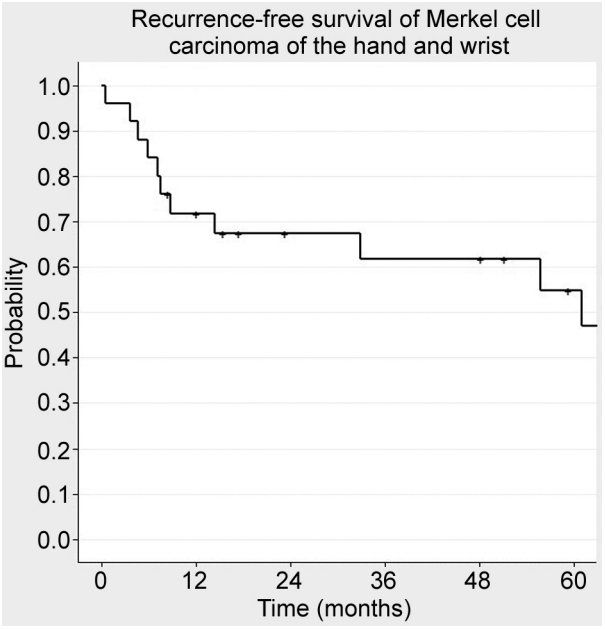

Figure 1. *Recurrence-free survival for Merkel cell carcinoma of the hand and wrist.*

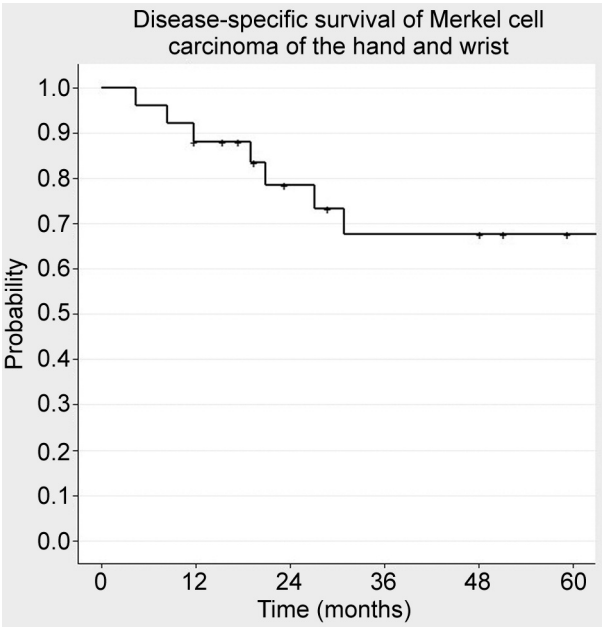

Figure 2. *Disease-specific survival for Merkel cell carcinoma of the hand and wrist.*

patients had Merkel cell polyoma virus antibody titers in the blood drawn pre-operatively, two of which were negative (<74) and two of which were positive (128 and 686).

Histopathology. Biopsies were performed between 2004 and 2021 and were excisional (n=11), shave (n=6), unspecified non-excisional biopsy (n=5) or punch (n=3). Mean maximum tumor diameter was 1.7 cm (range=0.2-5 cm) and mean elliptical tumor volume was 3.9 cm^3 (range=0.1-19.3 cm^3) based on resected specimen pathology report.

Initial treatment. Twenty-two patients were treated with wide local excision (WLE), including one patient who received a 5^{th} digit ray amputation and 21 non-amputative resections. Circumferential margins of excision were either 0.5 cm (n=1), 1 cm (n=1), 1.5 cm (n=1), 2 cm (n=9), 2.5 cm (n=2), 3 cm (n=3), or 3.5 cm (n=1). Paratenon was taken as the deep margin in all but three patients, in which cases either extensor retinaculum, subcutaneous fat, or fascia were used as the deep margin. There were no positive margins after WLE (mean closest margin 7 mm, range=2-25 mm). Three patients received Mohs micrographic surgery. Sentinel lymph node biopsy was performed in 21 patients, seven of whom had histopathological evidence of nodal disease. Two patients with positive sentinel biopsy had negative pre-operative PET-CT scans. Two patients with positive sentinel biopsy had palpable lymphadenopathy on examination, three had no palpable lymphadenopathy, and two patients did not have a documented lymph node exam.

Adjuvant radiotherapy was administered to the primary site in 17 patients. The dose of radiation was either 50 Gy in 25 fractions (n=7), 56 Gy in 28 fractions (n=3), or 60 Gy in 30 fractions (n=5). Radiation was also delivered to the regional lymph node basin in six patients, all of whom had evidence of nodal disease. Three patients received adjuvant chemotherapy in the form of etoposide combined with either carboplatin (n=2) or cisplatin (n=1).

Outcomes. All patients had at least one year of follow-up except for those who were deceased within twelve months. Mean MSTS-UE score at 6-months post-operation was 25.3 (range=17-30). Fourteen patients were alive with no evidence of disease at last known follow-up (median 69.7 months, range=12-220 months), and 11 were deceased (20.9 months, range=8-65 months) (Table II). Cause of death was MCC in eight cases (median 15.9 months) and unrelated to MCC in three cases (48.2 months). Eleven patients (44%) had disease recurrence at a mean time of 18 months (SD 20.6 months, range=0.5-61 months). There was one instance of local recurrence, and five instances of regional recurrence in the form of new nodal involvement (epitrochlear, n=2; axillary, n=2) and one metastasis in transit to the dorsal forearm. Six patients developed new metastases at a mean interval of 19 months from biopsy (range=4-56 months). Sites of distant metastasis included bone (n=2), liver (n=3), mesentery (n=2), chest or abdominal wall (n=3), and mediastinum (n=2).

Recurrence-free survival (RFS) was 71.8% at 1 year, 61.7% at 3 years, and 54.8% at 5 years (Figure 1). Disease-specific survival (DSS) was 88.0% at 1 year, 67.6% at 3 years, and 67.6% at 5 years (Figure 2). Cox hazard analysis did not identify any clinical, histopathologic, or treatment variables associated with RFS or DSS.

Discussion

Merkel cell carcinoma (MCC) of the hand and wrist is quite rare and literature on this entity is nearly absent. The present study identified 415 patients diagnosed with MCC at a single institution, of which 25 patients were afflicted with lesions of the hand and/or wrist. The results of the current study highlight the aggressive nature of these tumors.

Definitive diagnosis of MCC is made with biopsy (22), and in our series we were unable to detect any survival advantages to excisional *versus* non-excisional (shave or punch) biopsy. Evaluation of the patient with extremity MCC involves regional lymph node examination for lymphadenopathy (22). In our study, sentinel lymph node biopsy was performed in 21 patients; clinical lymph node examinations were documented in 19 of these patients, pre-operative PET-CT scans were performed in 14 cases, and seven biopsies were positive. Palpable lymphadenopathy on physical exam detected nodal involvement in half of the patients who had positive sentinel lymph node biopsy, and there were no falsely positive physical examinations. In patients who had both pre-operative PET-CT imaging and sentinel lymph node biopsy, PET-CT detected nodal involvement in one of three patients with positive node biopsy and did not have any false positives. Therefore, while positive PET-CT imaging and palpable lymphadenopathy on physical examination may assist with prognostication and treatment planning, these modalities should be viewed cautiously in light of the observed high false negative rate.

MCC is noted to have a high rate of recurrence despite aggressive treatment (2, 23-25). Here, we determined that rates of disease recurrence and disease-specific mortality within five years were 45% and 33%, respectively, for lesions of the hand. The mean time to recurrence was 18 months from diagnosis and 13.7 months from surgery, with seven of ten recurrences within 12 months and the latest recurrence occurring at 60 months from surgery. This highlights the importance of frequent surveillance within the first few years from resection and continued longitudinal monitoring afterward. Interestingly, there was only one instance of local recurrence within our cohort, which was comprised primarily of patients who received wide local excisions and a minority of patients who received Mohs micrographic surgery. This would suggest that non-amputative resection with adequate margins provides adequate local control. In the one patient with local recurrence, circumferential margin of excision was 2.5 cm with paratenon as the deep margin, and pathologic analysis revealed deep and lateral tumor-free margins were 4 mm and 12 mm, respectively. This patient did have a positive Merkel cell oncoprotein antibody titer of 686 pre-operatively. Interestingly, the only other patient with a positive antibody titer later developed metastases to the epitrochlear lymph nodes, and the two patients with negative antibody titers did not develop recurrence or metastasis. Since multiple studies have demonstrated oncoprotein seronegativity to be a risk factor for recurrence in MCC (26), we attribute the unexpected results of the Merkel cell antibody titers to sampling error.

Among the 21 patients undergoing wide local excision, radiation was delivered to the primary site in two-thirds of cases for additional local control. We did not detect any significant differences in survival or recurrence between those who did or did not receive radiation. Current National Comprehensive Cancer Network guidelines recommend completion node dissection and/or radiotherapy to the lymph nodes for patients with positive sentinel node biopsy (27). In our series, there was a trend towards worse outcomes in patients who underwent radiation to the regional nodes, however this was not statistically significant and is surely confounded by more advanced disease stage in these patients. Only one patient in the entire series underwent radical lymph node dissection after a positive sentinel node biopsy. The present study and prior literature illustrate that more work is needed to establish treatment modalities to better treat MCC. As with most soft tissue malignancies, survival rates may be improved with earlier detection of micro-metastatic disease afforded by blanket screening with sentinel lymph node biopsy for patients diagnosed with MCC.

The present study has limitations. First, the cohort of patients in our study was small and retrospectively-generated. Second, we were unable to perform multivariable statistical analysis and control for potential demographic, staging, or treatment regimens that may confound the findings of this study. Finally, patients included in this study were treated at a tertiary, referral center, which means that the cohort used may not be generalizable to all patients diagnosed with MCC in the United States of America. Although the present study has these limitations, our determination that physical examination and PET-CT are unreliable measures for micro-metastatic disease are pertinent findings for patients with MCC. Generalized screening with sentinel lymph node biopsy may lead to earlier diagnosis of micro-metastatic disease, implementation of more aggressive treatment modalities, increased disease-free intervals, and prolonged survival rates in afflicted patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Broida: Drafting of initial and final manuscript, data collection, data analysis; Alder: Drafting of initial and final manuscript, data collection, data analysis; Chen: Drafting of initial and final manuscript, data collection, data analysis; Moran: Reviewing and editing of final manuscript, supervision; Houdek: Drafting of initial and final manuscript, data analysis, supervision.

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