Treatment of Merkel cell carcinoma in organ transplant recipients—A systematic review

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Background: There are no clear treatment guidelines for solid organ transplantation (SOT) patients with Merkel cell carcinoma (MCC) despite increased incidence rates.

Objective: To review treatment outcomes of MCC patients with prior SOT.

Methods: A systematic review (Prospective Register of Systematic Reviews CRD42024569200) of studies that reported treatment modalities and outcomes for MCC patients with SOT were selected. Databases screened included PubMed, Web of Science, Scopus, and Embase.

Results: Thirty articles comprising 21 case reports, 8 cohort studies, and 1 clinical trial were included. Treatment modalities reported in case reports and clinical trials included surgery (77.7%), radiotherapy (62.9%), and chemotherapy (25.9%), with 3 patients receiving immune checkpoint inhibitors and 1 patient receiving an oncolytic virus. Cohort studies reported varying usage of surgery, radiotherapy, chemotherapy, and immunosuppression regime modifications.

Limitations: Heterogeneity in methodologies and data reporting of studies included impeded meaningful comparisons. Lack of stratification of immunosuppressed populations in the excluded studies reduced the available patient data for comparison.

Conclusion: Oncolytic virotherapy has the potential to mediate a localized, targeted response with minimal side effects in SOT patients. Inclusion of SOT patients with MCC into future clinical trials involving immunotherapy and immunosuppression combination therapies is needed to establish future treatment guidelines. (JAAD Int 2025;19:75-82.)

Key words: Merkel cell carcinoma; organ transplant; outcomes; systematic review; treatment; treatment guidelines.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine skin cancer that has a high recurrence rate and poor prognosis.[1] An incidence rate of 0.7 cases per 100,000 person-years, or 2488 cases per year was reported in the United States.[2] Risk factors include exposure to UV light, age, and immunosuppression.[3] MCC can be broadly categorized into 2 distinct etiological subtypes: Merkel cell polyomavirus-induced or UV-induced, with the latter associated with a higher mutational burden.[4,5]

Diagnosis of MCC remains challenging clinically due to the nonspecific appearance of lesions, typically requiring immunohistochemical testing of excised lesions.[5] MCC progresses aggressively with

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a 5-year recurrence rate of 40%, resulting in poor prognosis with metastatic disease.[6] Given its aggressiveness, curative surgery remains the first-line treatment modality for local disease.[7] Radiotherapy has been shown to improve survival as an adjuvant.[8] Chemotherapy, however, is associated with poor response rates, and increasingly, immunotherapies and targeted therapies are instead recommended for use in advanced and metastatic cases.[7,9]

MCC is highly immunogenic, and spontaneous regression has been observed with tumor-infiltrating lymphocytic activity.[10,11] Consequently, the incidence of MCC in immunosuppressed populations, including solid organ transplantation (SOT) patients, is higher, with a standardized incidence ratio of 23.8 and an overall incidence rate of 12.8 per 100,000 person-years.[10] SOT recipients are also younger at diagnosis and experience significantly higher rates of progression and mortality as compared to their immunocompetent counterparts.[12,13] Treatment in this subpopulation of patients remains challenging as any reduction in immunosuppressants prescribed, while beneficial in tumor regression, increases the risk of transplant rejection. Hence, we aimed to review the treatment modalities that have been reported in post-transplant MCC patients and assess their treatment outcomes.

CAPSULE SUMMARY

- Solid organ transplantation patients with Merkel cell carcinoma experience elevated incidence and poorer prognosis than immunocompetent patients.
- Inclusion of solid organ transplantation patients with late-stage Merkel cell carcinoma into future clinical trials involving immune checkpoint inhibitors and oncolytic viruses is needed to establish Merkel cell carcinoma treatment guidelines for this subgroup of patients.

METHODS

Inclusion and exclusion criteria

Included articles consisted of case reports, case series, completed clinical trials, cross-sectional studies, and cohort studies. Studies selected had (1) at least 1 patient diagnosed with MCC, with patients having received a (2) solid organ transplant prior to diagnosis of MCC and (3) at least 1 mode of MCC treatment rendered with (4) treatment outcomes reported. Excluded studies consisted of articles that did not stratify solid organ transplant patients from the larger cohort of immunosuppressed patients, articles that did not report treatment outcomes, and non-English articles.

Treatment outcomes were classified into 4 categories, complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Patient outcomes extracted from the articles included the current state of the patient at the latest follow-up (alive or dead), overall survival (OS), disease-free survival, and other relevant metrics provided by the studies.

Search strategy

Databases screened included PubMed, Web of Science, Scopus, and Embase. Searches were conducted within the month of June 2024, with the latest search being performed on July 12, 2024. Search terms consisted of a combination of "MCC," "Merkel cell carcinoma," "transplant," "treatment," and "therapy." No restrictions on study design, date of publication, or language were initially applied during the search.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[14,15] guided this systematic review. This study was registered with PROSPERO (CRD42024569200).

Data collection and quality assessment

Both authors (D.C. and O.C.C.) independently screened the titles, abstracts, and full texts to assess for eligibility for inclusion into this study. Data collected from eligible articles included patient demographics, transplanted organs and subsequent immunosuppressive treatment administered, diagnostic details about the MCC tumor of interest, treatment modalities rendered, and treatment outcomes.

The Joanna Briggs Institute checklist[16,17] was used to assess for bias (Supplementary Tables IIIa-d, available via Mendeley at https://data.mendeley.com/datasets/gv57thwcjv/1). Studies with limited information on treatment outcomes and follow-up post-treatment were reviewed carefully to ensure accurate interpretation of study results and were excluded if data were lacking or deemed ambiguous.

RESULTS

Searches from all 4 databases returned a total of 560 results (Fig 1). After duplicates were removed (n = 231), title and abstract screening was performed for 329 articles. Forty-nine articles were subsequently shortlisted for full-text screening. Thirty articles were included in our systematic review, consisting of case reports (n = 21, 25 patients), cohort studies (n = 8, 148 patients), and a clinical

Abbreviations used:

CR:	complete response
ICI:	immune checkpoint inhibitor
MCC:	Merkel cell carcinoma
OS:	overall survival
PD:	progressive disease
PR:	partial response
RT:	radiotherapy
SD:	stable disease
SOT:	solid organ transplantation
TVEC:	talimogene laherparepvec

trial (n = 1, 2 patients).[1,12,18-45] Nineteen articles were excluded for the following reasons: conference abstracts without an associated full-text publication (n = 12), inadequate treatment outcomes reported (n = 4), lack of information on the patient cohort (n = 2), and inability to access the full text of an article (n = 1).

Across the 30 studies included, 175 patients were identified. The locations of 137 cutaneous MCC tumors from 128 patients (73.1%) were reported in Table I. Head and neck were the most common site (n = 75, 54.7%), followed by the chest and upper body (n = 28, 20.4%), trunk (n = 23, 16.8%), and lower limbs (n = 11. 8.0%). The locations of cutaneous MCC tumors were not reported in 47 patients (26.9%).

Twenty-seven patients were identified from 21 case reports and 1 clinical trial included (Table II) (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/gv57thwcjv/1). The mean age of patients at MCC diagnosis was 59.9 years (age range: 25-78 years), of which 19 were males (76.0%) and 6 were females (24.0%). All included studies provided treatment outcomes (PD, SD, PR, CR) and patient outcomes (dead/alive at the latest follow-up). Duration of OS was made known for the majority of patients (n = 22, 81.5%). Staging of MCC disease was not provided by most case reports. Treatment outcomes of patients included 16 PD (59.3%), 9 CR (33.0%), 1 PR (3.7%), and 1 SD (3.7%). Recurrence was observed in 16 patients (59.3%).

Surgery was the most common treatment modality given (n = 21, 77.7%), followed by radiotherapy (n = 17, 62.9%). Among the 17 patients that had received radiotherapy, 6 attained CR (35.3%), of which 1 patient received radiotherapy without surgical intervention.[22] One patient attained PR (5.9%). Among patients who received chemotherapy (n = 7, 25.9%), local recurrence or metastasis were the precipitating factors for chemotherapy use. One patient that had received an immune checkpoint inhibitor (ICI), nivolumab, for liver and spinal MCC metastatic recurrence and achieved SD with improved quality of life without signs of renal allograft rejection.[20]

Six cycles of an oncolytic virus, talimogene laherparepvec (TVEC), at a dosage of 1-3 ml of 10^8 plaque-forming units/ml was administered to a patient that did not receive prior surgery due to in-transit metastasis in a study by Hirotsu et al,[39] resulting in CR. No recurrence was noted at 5 months follow-up and no rejection of the cardiac allograft was observed, with fatigue being the only adverse effect.

The clinical trial included contributed an additional 2 patients. Schenk et al assessed the treatment outcomes of a combination of ICIs and low-dose immunosuppressants.[38] Both patients had their immunosuppressant regime modified to low-dose tacrolimus and prednisolone before nivolumab (480 mg, IV, every 4 weeks) was initiated. PD was observed in both patients, following which 4 cycles of nivolumab (3 mg/kg, IV, every 3 weeks) and ipilimumab (1 mg/kg, IV, every 3 weeks) was administered, also resulting in PD. One patient subsequently developed allograft loss and survived for 7 months postadministration of nivolumab. The remaining MCC patient subsequently received carboplatin and etoposide 10 months after nivolumab initiation. CR was observed, and the patient survived for an additional 27 months before succumbing to a hypertensive emergency.

From the 8 cohort studies selected, 148 patients were identified (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/gv57thwcjv/1). Patient outcomes were reported either as a cohort survival statistic (n = 4, 50.0%) or individual patient outcomes (n = 3, 37.5%), although 1 study did not provide any of such metrics. Treatment outcomes were provided for a majority of the studies included (n = 7, 87.5%). Among the 7 studies that reported treatment outcomes, 3 studies with cohort sizes ranging from 1 to 3 patients[41-43] observed PD in all 5 patients, while the remaining 4 studies observed PD for most patients in each cohort (range: 68% to 89%).

Surgical intervention was the primary treatment modality among the cohort studies. Surgery was given to all patients for the 3 studies with cohort sizes ranging from 1 to 3 (n = 5, 100%).[41-43] Penn et al[45] did not report surgery adoption rates. The remaining 4 studies reported adoption rates ranging from 79% to 100%. Radiotherapy was the second most common treatment modality administered, with the 3 most recent cohort studies reporting adoption rates of 41%, 78.9%, and 100%.[1,12,40] Other interventions given included chemotherapy and reduction of

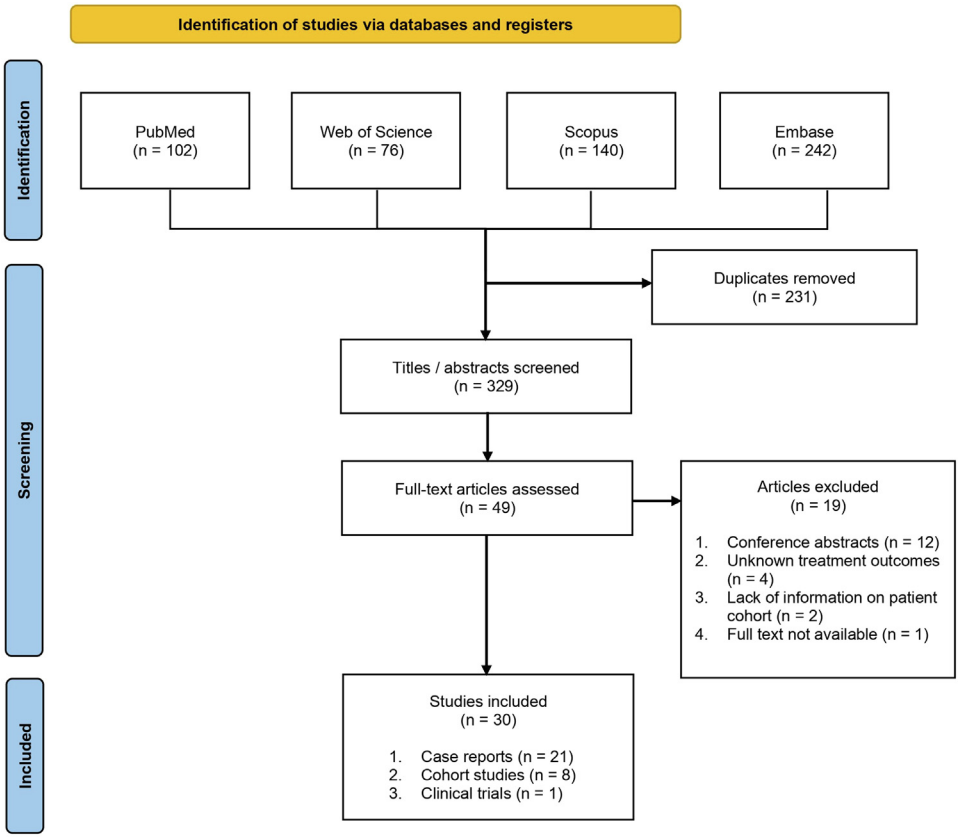

Fig 1. Flowchart depicting the screening process for articles to be included in this study, adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

immunosuppressants. Additionally, acitretin was given to 4 patients in the study by Ferrándiz-Pulido et al.[12]

DISCUSSION

Despite the elevated MCC burden on SOT patients, with an increased standardized incidence ratio of 23.8[10] and overall mortality rate (hazard ratio: 3.26) as compared to immunocompetent populations,[12] there are still no clear guidelines dictating treatment strategies in transplant patients.[7,12] Current MCC guidelines for immunocompetent populations recommend surgical excision with 1-2 cm margins as a first-line treatment to manage local disease.[7,46] Following this, sentinel lymph node biopsy may be employed to assess for nodal metastasis. Radiotherapy is frequently offered, either as an adjuvant to surgery or as a standalone therapy, to patients with advanced MCC disease at a recommended dose of 50-55 Gy.[7,46] In MCC patients with nodal metastasis, radiation monotherapy can provide comparable outcomes in regional control of MCC disease and OS as compared to completion lymphadenectomy.[47]

Various immunotherapeutic agents such as nivolumab, an anti-PD-1 monoclonal antibody, have been indicated as a neoadjuvant in advanced, resectable MCC disease.[7] Nivolumab has shown promise in MCC treatment, with the CheckMate 358 trial reporting a combined pathological CR and major pathological response rate of 61.5%.[48] Unfortunately, ICIs have been associated with T-cell-mediated rejections in SOT recipients, especially after a reduction in maintenance immunosuppression for treatment.[49] Despite this risk, ICI is still considered in some SOT patients, although more clinical trials are required to establish protocols dictating its use.

Current guidelines recommend adjuvant radiotherapy in patients with narrow surgical margins or nodal metastasis.[7] While most patients who received radiotherapy experienced PD, among the 9 patients who had experienced CR, 6 had received radiotherapy as part of their treatment. Garrett et al had reported a patient who experienced CR to 66 Gy radiation monotherapy for 4 months, but prior detection of nodal metastasis and rapid growth of tumor still posed a risk for recurrence.[22] The current National Comprehensive Cancer Network guidelines

Table I. Distribution of cutaneous MCC lesions reported

Cutaneous MCC tumor location	Occurrences
Head and neck (total: 75)	
Head	5
Neck	4
Face	3
Ear	3
Forehead	1
Inner canthus	1
Scalp	1
Unspecified	57
Chest and upper body (total: 28)	
Arm	5
Finger	2
Shoulder	1
Unspecified	20
Trunk (total: 23)	
Torso	7
Buttock	4
Unspecified	12
Lower limb (total: 11)	
Thigh	2
Lower leg	2
Unspecified	7
Unknown	47

MCC, Merkel cell carcinoma.

for radiotherapy dosage in clinically evident lymphadenopathy are 60-66 Gy,[7] and tumor regression observed in this patient suggests that the current MCC guidelines for radiotherapy can be translated to SOT recipients. In addition, Xin et al report a successful case of a patient with stage 2A MCC who underwent surgery and adjuvant radiotherapy, experiencing CR over a follow-up duration of 24 months.[19]

Adoption of ICIs remains challenging in organ transplant patients due to allograft rejection risk, which could prove fatal in transplants involving the heart or other essential organs. Nevertheless, adoption rates in kidney and liver transplant patients have been increasing, with attention being directed toward addressing risk factors and rejection rates.[50] Singh et al report a case of SD of metastatic MCC disease after initiation of nivolumab at a reduced monthly dose (instead of twice monthly) over the span of a year.[20] Schenk et al report 2 patients who were initially given nivolumab, low-dose prednisolone, and tacrolimus, followed by the addition of ipilimumab for 4 cycles.[38] Both patients experienced PD, of which 1 had allograft rejection. The other patient experienced CR attributed to chemotherapy administration after cessation of the clinical trial. While a stronger immunosuppressive regime could reduce the incidences of allograft rejection, it inevitably opposes the immunomodulating effects of ICIs, which would lead to subpar efficacies. An alternative approach would require pivoting away from systemic immunosuppression to unlock ICI's full potential in SOT patients. Nanoparticle-based delivery of immunosuppressants is currently a growing field of research and could address this gap, and a murine model using hydrophobically modified glycol chitosan nanomicelles for selective delivery of tacrolimus to the kidneys has demonstrated enhanced effects and reduced systemic toxicity as compared to systemic administration of tacrolimus.[51,52] Perhaps, in future, ICIs could be safely administered in these MCC patients with renal allografts when paired with localized nanoparticle-based immunosuppression and attain comparable response rates to immunocompetent MCC patients.

Naturally, the other approach that could be taken in SOT patients would be to induce a localized intralesional immune response, which naturally reduces the risk of allograft rejection. Hence, increasing attention has been directed toward intralesional oncolytic viruses in recent years, following the approval of TVEC for the treatment of melanoma.[53] It is postulated that oncolytic viruses act via selective infection and lysis of tumor cells, while remodeling the tumor microenvironment via the release of tumor neo-antigens and viral particles to induce a localized immune response.[54] The release of these tumor neo-antigens could trigger an additional systemic and selective antitumoral response via the activation of antigen-specific dendritic cells and lymphocytes,[54] although ongoing systemic immunosuppression in SOT patients would attenuate this response. A successful case of TVEC usage in an MCC patient with SOT was reported by Hirotsu et al, resulting in CR without cardiac allograft rejection and minimal adverse effects. Similarly safe administrations of TVEC without organ rejection have been observed in other skin cancers.[55,56] Although TVEC has been shown to provide clinical benefit for immunocompetent MCC patients,[57,58] its immunomodulating actions may be impaired in SOT patients. Clinical trials are thus needed to establish both the safety and efficacy of oncolytic viruses in MCC patients with prior SOT.

The majority of the patients in the cohort studies that reported disease progression experienced PD despite surgery and radiotherapy. None of the cohort studies reported any immunotherapy use. Ferrándiz-Pulido et al reported a 5-year mortality rate of 84%, significantly higher ($P < .001$) than the 5-year mortality rate of 48% as observed in immunocompetent

Table II. Summary of case reports/case series/clinical trial findings

Characteristic*	Case reports/clinical trials (n = 27)
Mean age* (±standard deviation)	59.9 ± 11.1
Male (%)*	19 (76.0%)
Local disease only at diagnosis*	17 (68.0%)
Local disease only at diagnosis that subsequently progressed to nodal or metastatic disease*	11 (44.0%)
Nodal metastasis at diagnosis*	7 (28.0%)
Distant metastasis at diagnosis*	1 (4.0%)
Recurrence	16 (59.3%)
Surgery	21 (77.7%)
Radiotherapy	17 (62.9%)
Chemotherapy	7 (25.9%)
Immunotherapy	4 (14.8%)
Reduction or modification in immunosuppressants	7 (25.9%)
Surgery + radiotherapy	11 (40.7%)
Surgery + radiotherapy + chemotherapy	5 (18.5%)
Not reported/None	1 (3.7%)

*Not reported in clinical trial.

patients.[12] Additionally, a switch in immunosuppressants to mammalian target of rapamycin inhibitors did not reduce the disease progression in this cohort, and a similar finding was observed in sirolimus initiation in an MCC patient reported by Boratyńska et al.[43] A study assessing the outcomes of different immunosuppressed populations that had developed MCC disease by Cook et al also presented similarly low 2-year OS of 40% with conventional therapies.[40]

There are inherent limitations to this study, and due to the heterogeneity of studies included, a meta-analysis was not possible. Only 1 published clinical trial satisfied the inclusion criteria, and thus there was an increased reliance on case reports and cohort studies for analysis of outcomes, which would present with reporting bias and variances in reporting treatment modalities. Additionally, some cohort studies did not stratify immunosuppressed patient cohorts into SOT and non-SOT patients, while others only reported epidemiological data without treatment outcomes, resulting in an exclusion of a significant number of patients. For many of the studies included, staging data at the time of diagnosis was not provided, rendering it difficult to perform intrastage and interstage comparisons. Inconsistent reporting of data in some cohort studies similarly resulted in difficulties in performing cross-study comparisons.

Oncolytic viruses remain a promising option, although their safety profile in organ transplant recipients has not been fully established. An upcoming phase 1b/2 clinical trial (NCT04349436) seeks to assess the safety and efficacy of RP1, an oncolytic virus derived from HSV-1, for skin cancers in organ transplant recipients.[59] Given the successful treatment observed in the administration of TVEC to a metastatic MCC case with a cardiac allograft with no allograft rejection,[39] oncolytic viruses could potentially address concerns of rejection that currently pose a significant challenge to ICI use.

There are high rates of progression observed with the administration of conventional therapies such as surgery and radiotherapy. ICI's efficacy is very variable and needs to be balanced with an appropriate immunosuppressant regime to minimize rejection risk. More clinical trials including organ transplant recipients are needed to establish suitable dosage guidelines for combinations of immunotherapeutic drugs and the immunosuppressive medications that would maximize treatment outcomes and minimize rejection risk.

Conflicts of interest

None disclosed.

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