



Invited review article

Scientific and clinical developments in Merkel cell carcinoma: A polyomavirus-driven, often-lethal skin cancer

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ABSTRACT

Merkel cell carcinoma (MCC) is a primary neuroendocrine skin cancer that recurs in ~40% of cases. Merkel cell polyomavirus (MCPyV) and ultraviolet (UV)-induced mutations are two major causative factors of MCC. Virus-positive MCCs express polyomavirus oncoproteins that are highly immunogenic yet are required for ongoing tumor growth. Virus-negative MCCs have a high burden of UV-DNA mutations that encode tumor-specific UV-neoantigens. Thus, both UV- and virus-induced MCCs are highly immunogenic, enabling diverse T-cell targeted therapies. Optimal MCC management is challenging given its rarity, aggressive nature, rapidly evolving care guidelines, and fundamental differences in management compared to other skin cancers. MCC is often managed aggressively with extensive surgery, radiotherapy or systemic therapy, frequently leading to toxicities that might have been avoidable while still achieving optimal disease control. Thus, multi-disciplinary care is crucial for providing patients with the best possible outcomes. The outlook for many patients with advanced MCC has progressed remarkably over the past decade due to PD-1 pathway blocking agents that provide durable benefit for a substantial subset of MCC patients. The management of early-stage MCC has also improved due to better approaches to integrate surgery and radiotherapy. Prognostic accuracy and ongoing surveillance have advanced due to stage-specific recurrence data and sophisticated “liquid biopsies” that allow early detection of disease recurrence. Here we summarize both recent striking progress and pressing challenges such as PD-(L)1-refractory MCC, and management of MCC patients with immune dysfunction. We also highlight diverse resources to allow providers to take advantage of recent progress in this fast-moving field.

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1. Background/introduction

Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine cancer in which about 40% of patients experience recurrent disease, often in distant sites [1]. Although rare, its incidence is increasing rapidly. During 2000–2013, the number of MCC cases increased by 95%, strikingly faster than all solid tumors (15%) or melanoma (56%) [2]. Advanced age is one of the risk factors for developing

melanoma and MCC. However, unlike melanoma, the rate of MCC continues to rise among older individuals (≥70 years of age) [2].

Risk factors for MCC include advanced age, fair skin, and chronic T cell immunosuppression such as HIV, chronic lymphocytic leukemia, and solid organ transplant [2,3]. The most frequent site of the primary MCC tumor was reported as the head and neck (43%), upper limbs and shoulder (24%), lower limbs and hip (15%), trunk (11%), and others (9%) [4].

Abbreviations: MCC, Merkel cell carcinoma; UV, ultraviolet; MCPyV, Merkel cell polyomavirus; SCC, squamous cell carcinoma; FDG PET/CT, fluorodeoxyglucose positron emission tomography/computerized tomography; MRI, magnetic resonance imaging; SLNB, sentinel lymph node biopsy; RT, radiation therapy; SFRT, single fraction radiotherapy; NCCN, the National Comprehensive Cancer Network; PFS, progression-free survival; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; FDA, Food and Drug Administration; MHC, Major Histocompatibility Complex; CTLA-4, cytotoxic T lymphocyte antigen-4; VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; SSTR, somatostatin receptor; T-VEC, Talimogene laherparepvec; ctDNA, circulating tumor DNA

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MCC usually appears as a firm, non-tender, red, or skin-colored nodule (Fig. 1). Clinical features of MCC are summarized in an acronym: AEIOU (Asymptomatic, Expanding rapidly, Immune suppression, Older than 50 years, and Ultraviolet (UV)-exposed site on a person with fair skin) [5]. In a 2008 systematic analysis of 195 MCC patients, 89% of patients present with at least 3 of the AEIOU characteristics. However, these features are nonspecific, and the majority of MCC lesions were presumed to be benign in nature with cyst, lipoma, or folliculitis being the most common presumed diagnoses at the time of biopsy [5]. A lesion that is asymptomatic but rapidly growing and red/purple to skin-colored should be evaluated pathologically with a biopsy. Therefore, the management of MCC is typically initiated following an unexpected pathology result.

Given this rare but aggressive and high-risk nature, MCC management is challenging as its treatment and surveillance are very different from other skin cancers, as summarized below. MCC is often managed overly aggressively with inappropriately extensive surgery, radiotherapy or systemic therapy leading to long-term toxicities. It is fortunate that new therapies and outcomes data indicate that MCC patient care can now be both less toxic and more effective.

This review highlights resources and guidelines to help physicians ensure optimal initial care and participate in MCC patients' longitudinal management.

2. Two etiologies for MCC: virus and UV

In most parts of the world, the majority of MCCs are associated with Merkel cell polyomavirus (MCPyV), including the United States (~80% are MCPyV-associated), Europe (~70–85%) and Japan (~90%) [6,7]. In Australia, however, the proportion of virus-positive MCC tumors is only 20–30%, with the balance being caused by extensive UV-induced mutations [7].

MCPyV is nearly ubiquitous, often can be detected on normal skin, and does not generally cause any symptoms [8]. However, in very rare circumstances, in approximately 1 in 3000 persons over their lifetime, it can lead to MCC. This extremely rare occurrence requires two major events to happen within the same cell: the viral genome must integrate into a host chromosome and the large T antigen must be mutated, causing it to be truncated and to form a functional oncoprotein that is markedly smaller than the normal viral version of the protein [8]. These events occur early in oncogenesis and every MCC tumor cell within a given patient is identical in its clonal integration of MCPyV [3,6]. Of note, between patients, there are no preferred integration sites for MCPyV within the genome and no preferential integration adjacent to specific tumor suppressors or oncogenes [3]. Importantly, growth of an MCPyV-positive MCC tumor requires ongoing expression of viral oncoproteins which are highly visible to both T- and B-lymphocytes [8]. In contrast, virus-negative MCCs have a very high burden of UV-induced DNA mutations, which translates to the expression of tumor-specific UV-neoantigens [8]. Thus, both virus-positive and virus-negative MCCs are immunogenic.

In terms of their neuroendocrine features, both virus-positive and virus-negative MCC tumors have many of the "PARCB" factors that are known to drive neuroendocrine differentiation: alterations in p53, Akt1, RB1, c-Myc and Bcl2 [3]. Specifically, in MCC, tumor suppressor genes such as retinoblastoma-associated protein (RB1) and p53 are inactivated while Myc signaling is upregulated [3]. In virus-positive tumors, the viral oncoproteins directly or indirectly modulate these cellular processes. In contrast, in virus-negative MCC tumors, UV-induced mutations directly lead to dysregulation of these pathways [3,8].

Normal Merkel cells are located in the basal layer of epidermis and are involved in the sensation of fine touch. Although normal epidermal Merkel cells and Merkel cell tumor cells share several immunohistochemical (neuroendocrine) features, the cell of origin of MCC is unlikely to be a normal Merkel cell [8]. In the case of virus-negative MCC, the cell of origin is very likely to be a keratinocyte/epidermal precursor cell that was heavily UV mutated [3]. Evidence for this etiology is based on numerous case reports of collision tumors in which squamous differentiation (squamous cell carcinoma, SCC) is immediately adjacent to neuroendocrine differentiation (MCC) [7], with heavily UV-damaged keratinocyte in the middle. In every one of these cases, the MCC tumor is virus-negative. However, in the case of virus-positive MCC, the cell of origin remains entirely unknown. Circumstantial evidence exists to support the possibility that the cell of origin for MCPyV-positive MCC is dermal fibroblasts, pro- or pre-B lymphocytes, or epidermal precursor cells [3,9,10].

3. Role of multi-disciplinary care

Patient-specific care that integrates multiple relevant specialties is extremely important for ensuring the best outcomes for MCC patients. For example, initial management of MCC should often ideally involve specialists from dermatology, surgical oncology, plastic surgery, radiation oncology and medical oncology. However, the delivery such multidisciplinary care by specialists who are expert in MCC management is only available at limited number of centers.

Additionally, due to its rarity, many physicians are not familiar with the importance of multidisciplinary MCC management. With this mind, a list of centers that focus on multidisciplinary MCC management has been made available (www.merkelcell.org/centers), with 68 sites currently included from around the world.

4. Initial workup

4.1. Baseline imaging

Imaging is encouraged in most MCC patients since occult metastatic disease that results in upstaging has been detected in 12–20% of patients presenting without suspicious history or physical findings [11]. This risk is far higher than that reported for melanoma (<1%) [11].

Baseline imaging with whole-body fluorodeoxyglucose positron emission tomography/computerized tomography (FDG PET/CT) should ideally be performed before surgical lymph node evaluation and definitive therapy to assess the actual extent of disease. This is because upstaging based on imaging occurs in approximately one in six cases and has a major impact on the short-term management, prognosis, and surveillance of MCC patients [11]. PET/CT is more sensitive for detecting baseline occult MCC than diagnostic CT. In the largest study published to date, 16.8% of 352 patients were upstage by PET/CT as compared to only 6.9% of 231 patients for CT alone ($p=0.0006$). Brain magnetic resonance imaging (MRI) is not routinely recommended since the frequency of brain metastases is extremely low compared to other sites including lymph nodes, skin/body wall, liver or bone [12].

4.2. Sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB) is a sensitive test to detect MCC spread to the regional lymph nodes. Even among patients

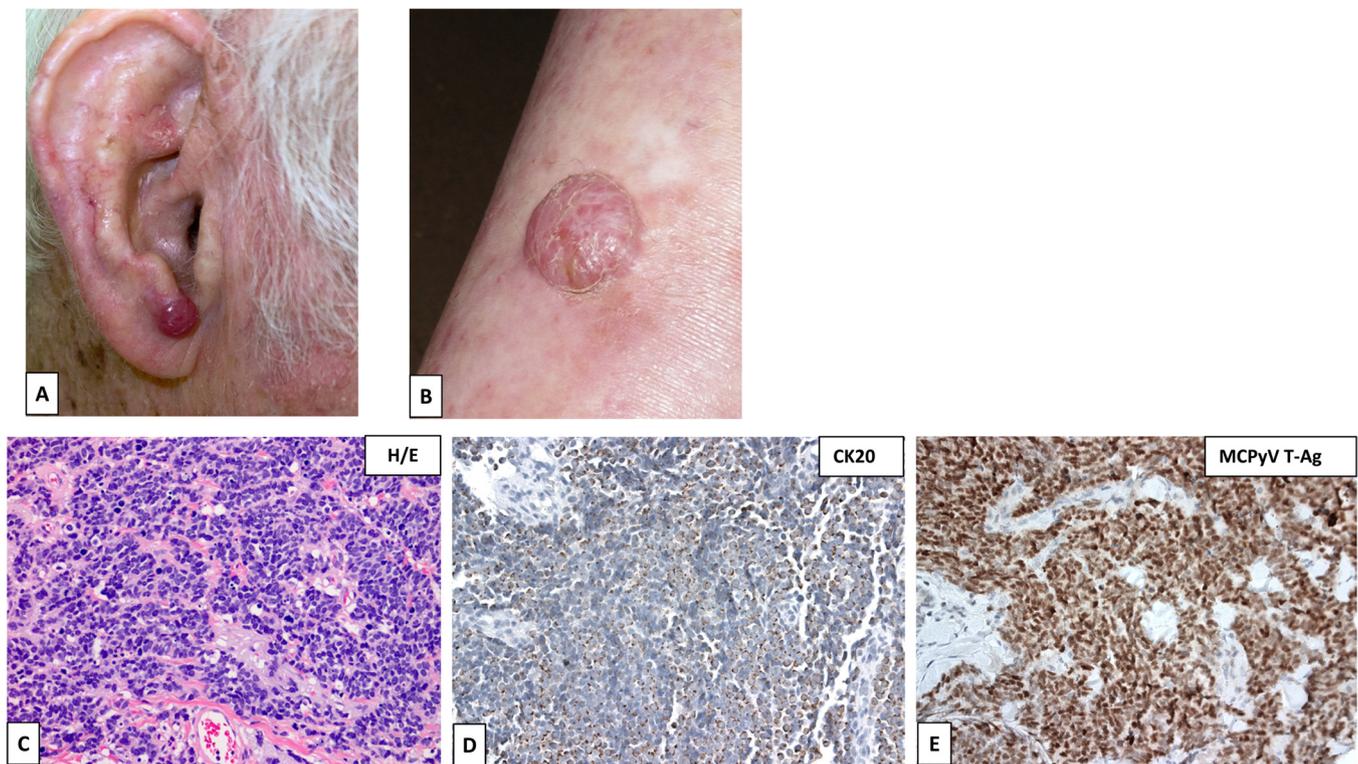


Fig. 1. Clinical features of Merkel cell carcinoma. **Panel A** A 92-year-old man who presented with a rapidly growing red nodule on the right earlobe. **Panel B** A 77-year-old woman who presented with a 2.0 × 1.6 cm raised lesion on the anterior lower extremity. **Panel C-E** Histopathology of typical Merkel cell carcinoma. **Panel C** There are numerous round basophilic cells with an increased nuclear/cytoplasmic ratio and nuclear molding that are crowding out the dermal stroma (Hematoxylin and eosin stain). **Panel D** Immunohistochemistry staining shows the classic dot-like perinuclear expression pattern of CK20. **Panel E** Anti-Merkel cell polyomavirus T antigen antibody (CM2B4 clone) shows nuclear expression of Merkel cell polyomavirus oncoprotein in a virus-positive Merkel cell carcinoma.

without evidence of clinical nodal disease (e.g., physical examination, imaging study), SLNB identifies micrometastasis in one-third of early-stage MCC patients [13,14]. Since patients who have a positive SLNB are approximately three-fold more likely to develop recurrent MCC than SLNB-negative patients (60% risk vs. 20% at three years after diagnosis) performing pathologic nodal evaluation is important in determining their surveillance plans [14].

4.3. Locoregional treatment

Local treatment of MCC often includes wide excision of the primary site [15]. However, it is important that surgery does not lead to significantly delayed wound and/or graft healing. Because MCC often spreads discontinuously, recurrence beyond pathologically negative margins is frequent and local radiation is often given in higher risk cases to prevent local recurrence [16]. Six factors that are associated with greater risk of recurrence include 1) chronic T-cell immune suppression, 2) larger tumor size (diameter > 1 cm), 3) presence of lymphovascular invasion within the tumor, 4) positive SLNB, 5) pathologically positive surgical margins, and 6) primary tumor on the head and/or neck [4,16]. When patients have ≥ 1 of these risk factors, adjuvant radiation therapy (RT) should be considered although the decision needs to be tailored based on each patient's preference and clinical circumstances. If no adjuvant RT is given to the local site, wider margins are important because surgical margins >1 cm are associated with better local control in the absence of RT [16]. In contrast, if patients are treated with adjuvant RT, wide excision is

not necessary because even when margins are pathologically positive, local control is excellent if adjuvant RT is given [16]. In conclusion, “wide” margins are not always needed, and surgical margins should be decided “wisely” with or without integrating radiation therapy based on the tumor risk factors.

4.4. Single-fraction adjuvant radiation therapy

Single fraction radiotherapy (SFRT) has been used for palliative treatment especially for those who have bone metastases associated with a variety of types of cancers [17]. Given the known safety of SFRT (typically given as an 8 Gray dose), this approach has been used to palliate distant MCC metastases with few side effects and greater than 94% response rate [18]. More recently, in patients who chose not to undergo conventional RT (typically 50 Gray divided across in 25 doses), adjuvant RT was given with a single 8 Gray fraction for local control. Early results show no recurrences in the radiated field and minimal side effects [19]. This study concluded that SFRT could offer a potential alternative to conventionally fractionated, post-operative adjuvant RT for particularly elderly or frail MCC patients, with promising in-field local control and minimal toxicity.

4.5. Surveillance

Approximately 40% of MCC cases recur [1], which is a higher rate compared to other skin cancers including melanoma. The vast majority of recurrences arise within the first two years [1]. The intensity

of surveillance can be significantly decreased during the five-year period after diagnosis. Detecting a recurrence early is advantageous because it provides more time during which the patient is well enough to undergo a subsequent treatment in case the first or second therapeutic approach is not successful. On the other hand, unnecessary surveillance leads to excess costs, physician visits, and potential side effects of scans. Therefore, gauging recurrence risk accurately is very important for proper surveillance.

Stage-specific recurrence-free survival data is very useful in assessing the residual recurrence risk for a given patient at various times following diagnosis. A web-based recurrence-risk calculator is now available (www.merkelcell.org/recur), which takes into account stage, time since diagnosis, sex, body site of the primary MCC tumor, and immune status. This tool can be used for MCC patients once they complete initial management to appropriately adjust the intensity of surveillance during the months and years following diagnosis.

4.6. Merkel cell polyomavirus oncoprotein antibody test

There are several potential benefits for an MCC patient to have a baseline assessment of whether or not they produce circulating antibodies to the MCPyV oncoprotein at the time of initial diagnosis. Patients who have undetectable antibody levels at MCC diagnosis (seronegative) are ~42% more likely to recur compared to seropositive patients who produce antibodies to the MCPyV oncoprotein [20]. Thus, sero-status is a useful prognostic indicator, and seronegative patients need to be followed with frequent imaging studies because this blood test will not reveal recurrent disease in virus-negative patients. In seropositive patients, the MCPyV antibody level decreases if they do not experience a recurrence and increases rapidly if MCC recurs [20]. Seropositive patients can thus be monitored by this blood test to detect recurrence early, significantly reducing the need for surveillance imaging. The National Comprehensive Cancer Network (NCCN) guidelines include this blood test as an established surveillance method [15]. An emerging tool that appears to be particularly useful for virus-negative MCC patients is circulating tumor DNA, described below in the future direction section.

4.7. Systemic therapy

For advanced MCC such as metastatic or unresectable disease, systemic treatment is indicated. Prior to 2016, cytotoxic chemotherapy was the only available systemic option. Although MCC is sensitive to chemotherapy (approximately two thirds of patients will have a clinically significant response), MCC typically becomes refractory very quickly, with disease progression in most patients by only 90 days after starting chemotherapy [21–23].

In recent years, several clinical trials of programmed cell death-1 (PD-1) pathway inhibitors have demonstrated improved progression-free survival (PFS) and overall survival (OS) compared to historical data for conventional cytotoxic chemotherapy in advanced MCC patients [24–31]. Across all trials, the response rate was similarly high (55–62% for first-line immunotherapy) regardless of programmed cell death ligand-1 (PD-L1) expression within the tumor or MCPyV status of the tumor [27–29]. In contrast, the immunotherapy response rate is lower (about 30%) for second- or higher-lines of therapy, likely due to immunosuppressive effects of initial chemotherapy [25,26]. Unlike for chemotherapy, the majority of

immunotherapy responses were durable for multiple years [27]. Favorable outcomes from these trials have led the US Food and Drug Administration (FDA) to approve avelumab (anti-PD-L1) in March 2017 and pembrolizumab (anti-PD-1) in December 2018 for advanced MCC. These data are summarized in Fig. 2. Avelumab has been approved for advanced MCC in other regions such as Europe, Japan, Australia, Brazil, and Canada.

The NCCN guidelines now include anti-PD-(L)1 agents as preferred first-line systemic therapies for the treatment of advanced MCC [15]. These cancer guidelines are updated annually. A comprehensive summary of MCC management is available through the NCCN website (<http://www.nccn.org>). General MCC management is summarized in Fig. 3.

Up-front or neoadjuvant immunotherapy will rapidly shrink locally advanced MCC in approximately 50% of cases and can be considered on a case-by-case basis [32].

Adjuvant immunotherapy for higher-risk patients who have no current evidence of disease is currently being investigated in multiple clinical trials (e.g., US: NCT03271372, NCT03712605, Europe: CA184-205; EudraCT2013-000043-78).

4.8. The big challenge: MCC refractory to immunotherapy

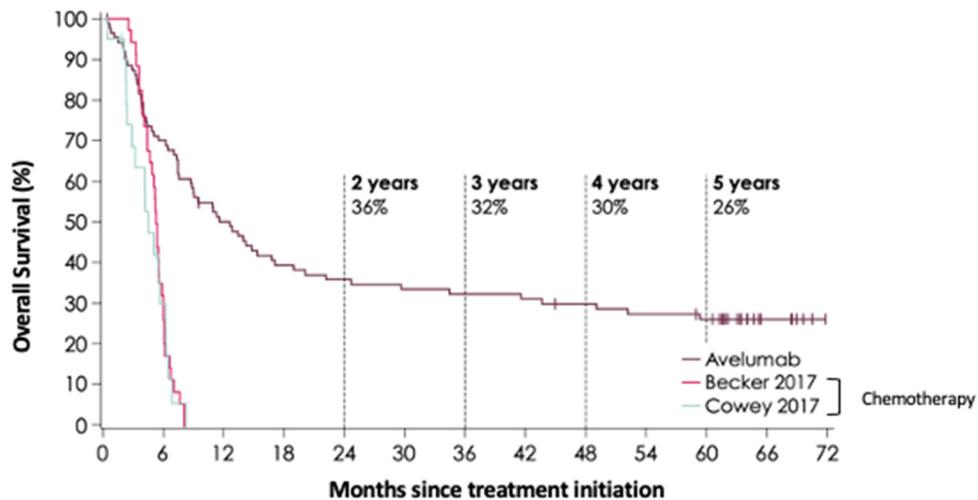
Despite the documented benefits of immunotherapy for many patients with MCC, about half of advanced MCC patients do not persistently benefit from anti-PD-(L)1 agents due to primary or acquired resistance [27]. Therefore, there remains a great unmet need to assist patients with advanced MCC who are either ineligible for or refractory to PD-(L)1 pathway blockade.

Furthermore, there are still no clinical biomarkers or patient characteristics that can provide a clinically useful prediction of whether or not a patient will respond to an anti-PD-(L)1 agent. Fortunately, there are many encouraging approaches to address these important clinical challenges as summarized below.

Many studies have demonstrated the potential of radiation therapy to induce inflammation and the release of tumor-associated antigens that should increase the sensitivity of tumors to subsequent immunotherapy [8]. Specifically, radiation therapy can reverse the downregulation of major histocompatibility complex (MHC) class I expression, a common immune evasion mechanism in many immunogenic cancers including approximately 80% of MCC tumors [33]. Indeed, adding a short course of radiation therapy while continuing anti-PD(L)1 is a preferred approach in PD(L)1-refractory patients who have a small number of non-responsive lesions that can be readily targeted by radiation [34,35].

Combination of a cytotoxic T lymphocyte antigen-4 (CTLA-4) targeted antibody such as ipilimumab and an anti-PD(L)1 agent, with or without radiation therapy can augment anti-tumor immunity in MCC that is resistant (primary or acquired) to anti-PD(L)1. Among 13 patients who subsequently received anti-CTLA-4 (typically while anti-PD(L)1 was continued), 4 patients had objective responses of MCC that had previously been unresponsive to anti-PD(L)1 monotherapy [36]. In another small retrospective study, 3 out of 5 PD-(L)1-refractory MCC patients had objective responses when anti-CTLA-4 was added to their regimen [37]. There is an ongoing phase 2, randomized, multi-institutional study of nivolumab and ipilimumab versus nivolumab, ipilimumab and stereotactic body radiation therapy for mMCC (NCT03071406).

Panel A



No. at risk		0	6	12	18	24	30	36	42	48	54	60	66	72
Avelumab	88	60	42	33	30	28	27	26	24	22	20	6	0	0
Becker 2017	34	9	0	0	0	0	0	0	0	0	0	0	0	0
Cowey 2017	20	5	0	0	0	0	0	0	0	0	0	0	0	0

Panel B

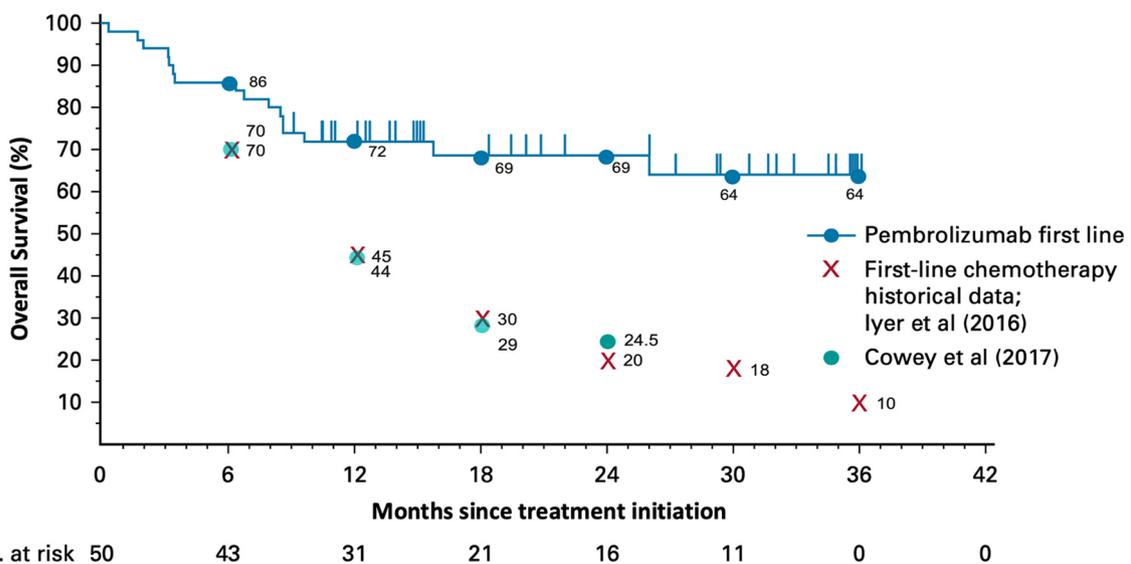


Fig. 2. Kaplan-Meier curves of patients with advanced Merkel cell carcinoma who were treated with immunotherapy as compared to historical cohorts of patients who were treated with chemotherapy. Panel A Overall survival (OS) of patients with chemotherapy-refractory MCC who were treated either with avelumab (anti-PDL1; brown-upper line) or with additional chemotherapy (red & blue lines; from two historical cohorts from the literature; Becker 2017 [23], Cowey 2017 [22]). Panel B Overall survival of patients who were treated with first-line pembrolizumab (anti-PD1) as compared to historical cohorts of patients who received first-line chemotherapy. Numbers that align with 6-month time periods indicate survival percentage for each cohort.

(a) Adapted, with permission, from Nghiem et al., ASCO 2021 [26]. (b) Adapted, with permission, from Nghiem et al., JCO 2019 [29].

5. Alternative therapies

5.1. Pazopanib

Pazopanib, a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI), demonstrated clinical benefit in a case series [38]. In a single-arm multicenter phase 2 clinical trial of pazopanib in metastatic MCC in the UK (clinicaltrialsregister.eu;

Eudra CT# 2011–003226–27), the data demonstrated that 9 of 16 response-evaluable patients had disease control (PR: n = 3, SD: n = 6, for >12 weeks) [39].

5.2. Somatostatin analogs

Advanced MCC tumors showed an unexpectedly high rate of somatostatin receptor (SSTR) expression (85% of cases) as assessed

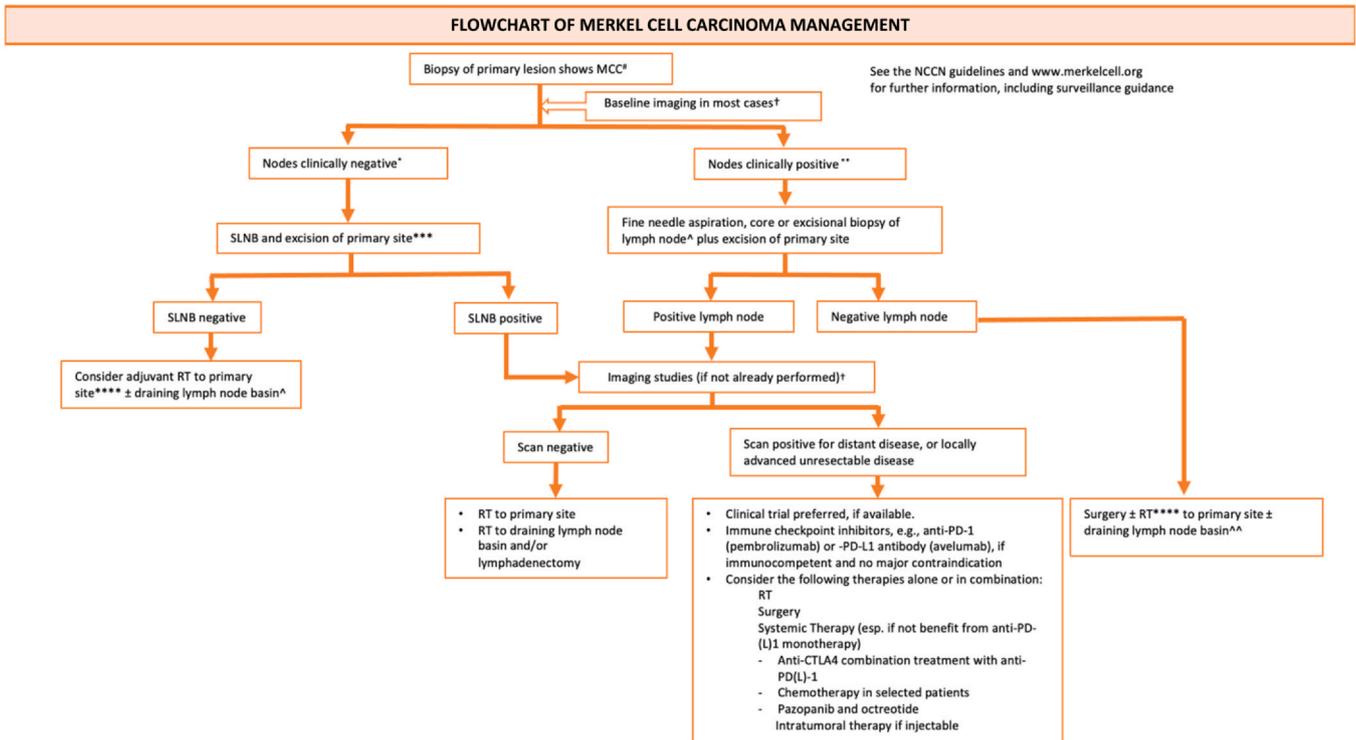


Fig. 3. Flow chart for Merkel cell carcinoma management # Consider baseline Merkel cell polyomavirus serology test for prognostic significance and to track disease † Whole body FDG-PET/CT (preferred) or CT of chest, abdomen, pelvis and/or neck with contrast; brain MRI if symptomatic. * No pathologically enlarged nodes on physical examination and by imaging study ** Pathologically enlarged nodes on physical examination or by imaging study *** SLNB may not be indicated if a patient would not benefit from the prognostic information, if it would not alter management of the regional nodes, or if a patient is not a good candidate for surgery/ anesthesia. **** Adjuvant RT is often indicated unless the following low-risk features are present: primary lesion ≤1 cm, primary site not on head/neck, no lymphovascular invasion, widely negative pathologic margins, negative SLNB, and patient not immunosuppressed ^ Consider excisional biopsy primarily or after negative needle/core biopsy to exclude false-negative biopsy result ^^ Consider radiation therapy to the nodal basin in high-risk patients Adapted, with permission, from Park et al., Future Oncol 2021 [50].

by a clinical imaging study (Octreoscan) that measures radiolabeled peptide binding to SSTRs. In comparison, other high-grade neuroendocrine tumors rarely express SSTRs (~15%). This is important because SSTR-positive tumors are amenable to therapy using peptide-based approaches to impede cancer growth (e.g., Sandostatin, a somatostatin peptide analogue given intramuscularly every month) [40]. Additionally, there are a few case reports that show encouraging objective responses in advanced MCC patients treated with a radiolabeled peptide (SSTR-analogue targeted peptide receptor radionuclide cytotoxic therapy with ¹⁷⁷Lu-DOTATATE) [41]. This treatment is being explored in combination with immunotherapy for possible synergistic efficacy.

5.3. Intratumoral therapy

If patients have superficial injectable, but unresectable MCC tumor(s), intratumoral treatment can be considered. An advantage of this approach is that toxicities are typically focused at the site of injection.

5.4. Oncolytic viral therapy

Talimogene laherparepvec (T-VEC) is a modified oncolytic herpes simplex virus that replicates in tumor cells and expresses granulocyte-macrophage colony-stimulating factor that induces local and systemic antitumor responses [42]. For regionally advanced, in-

transit metastatic MCC, intralesional T-VEC therapy has shown a favorable response in case reports [42,43]. Intralesional T-VEC could synergize with systemic immune therapy [42]. There are ongoing phase II clinical trials of intralesional T-VEC that includes persons with advanced MCC, combined with hypofractionated radiotherapy (NCT02819843) or nivolumab (NCT0297862).

Intratumoral G100 (a toll-like receptor 4 agonist) triggers innate and adaptive immune responses against tumors [44]. Three patients with locoregional MCC had neoadjuvant intratumoral G100 treatment followed by surgery and radiotherapy. Two of them remain recurrence-free at 44+ and 41+ months, including one patient who experienced a pathological complete response after G100 alone. Among 7 metastatic MCC patients treated with G100 with/without radiotherapy, 2 patients experienced sustained partial responses, both lasting 33+ months [44].

5.5. Autologous transgenic T cell therapy

A lack of high affinity, functional T cells specific for tumor antigens is a likely underlying reason that PD-(L)1 blockade does not benefit some MCC patients. It is now possible to rapidly reprogram a patient's own T cells using recombinant high-affinity transgenic T cell receptors. There is a clinical trial using this transgenic T cell therapy for patients with PD-(L)1-refractory MCC in the US (NCT03747484).

6. Emerging approaches to improve MCC management

6.1. Therapeutic vaccine

There is no approved adjuvant therapy for MCC patients after initial treatment with surgery or radiation. However, recurrence is common and approximately 20–50% of patients who present with local or regional disease will develop a local or distant recurrence [1]. Because the T cell mediated immune response targeting MCC decreases after tumor (and hence antigen) removal [45], a therapeutic vaccine given after initial treatment could augment the systemic anti-tumor immune response, and thus control microscopic MCC tumors [46]. Virus-positive MCC tumors all share viral antigens (approximately 400 amino acids) encoded by MCPyV oncoproteins. Because an MCPyV therapeutic vaccine would not target self-proteins, the risk of causing autoimmune disease would be low. Indeed, there are promising data carried out in mice that show that a therapeutic vaccine increased the immune response against MCPyV and prevented MCC recurrence [47]. A clinical trial of a therapeutic vaccine for MCC is planned, with a goal of reducing the risk of disease recurrence without significant systemic toxicities.

6.2. Circulating tumor DNA test

Tumors shed DNA into the bloodstream and this process can now be detected via a clinical test which is showing promise across multiple cancer types. Because of the exquisite sensitivity of modern DNA detection techniques, even single molecules of tumor-derived DNA can be reliably detected. For this approach, tumor-specific DNA mutations are identified by comparing whole genome sequencing of blood and archival tumor DNA. Tumor-specific DNA tests are then used to detect DNA mutations that are specific to a given patient's tumor. This circulating tumor DNA (ctDNA) test has proven to be useful in monitoring disease recurrence and to assess the depth of treatment response in lung and colon carcinomas [48].

In MCC, while the oncoprotein antibody test is very useful for detecting disease recurrence in virus-positive MCC patients, this test does not work in persons with virus-negative MCC [20]. Recent data suggest that serial ctDNA assays can be useful as a surveillance method in MCC, regardless of MCPyV status [49]. There is an active multicenter study to assess the utility of ctDNA testing for MCC patients using a Clinical Laboratory Improvement Amendments (CLIA) certified platform (Signatera®, Natera, Inc., Austin, Texas, USA).

7. Conclusion

There has been remarkable progress in the management of MCC over the past decade. Major changes include improved insight into the integration of surgery and radiation as well as new ways to track tumor recurrence via sensitive and specific blood tests. Prior to the era of immunotherapy, chemotherapy was the only available systemic approach to treat patients with metastatic MCC.

Although almost two-thirds of patients respond to cytotoxic chemotherapy, these responses are disappointingly transient, lasting less than 3 months from the time of chemotherapy initiation. In contrast, the majority of immunotherapy responders have prolonged benefit, often lasting years. Despite this progress, over 50% of patients with advanced MCC do not persistently benefit from immunotherapy. Addressing the needs of these patients who have primary or acquired resistance to immunotherapy is the most pressing challenge in the field. Fortunately, there are many encouraging avenues being explored.

The next few years in MCC research promise to be exciting and bring further benefit to these patients.

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Conflict of Interest Disclosure

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Today, Dr. Nghiem leads a multi-disciplinary team focused on improving management of MCC. He has several grants from the NIH, including a Program Project Grant that brings together diverse scientists to study the immune response to MCC and the Merkel polyomavirus that typically causes this cancer. Given his long-term interest in cancer biology and immunology, Dr. Nghiem feels very fortunate to study a disease in which cancer immunology can improve the lives of patients.