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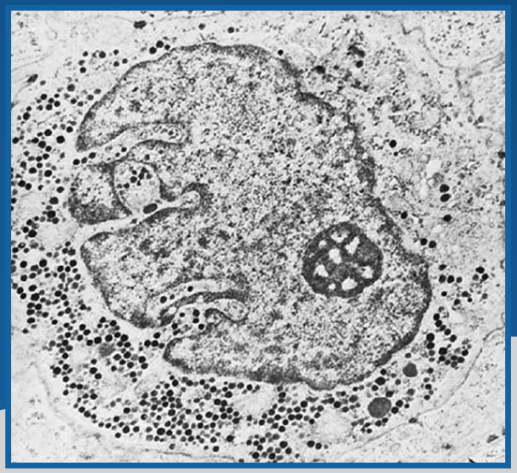
MERKEL CELL CARCINOMA



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NEW FRONTIERS IN THE MULTIDISCIPLINARY MANAGEMENT OF MERKEL CELL CARCINOMA

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In October of 2017, the University of Rochester Medical Center was presented with an educational grant from Pfizer/Merck KGaA Darmstadt, Germany to design and hold a multidisciplinary symposium on new developments in the comprehensive management of Merkel cell carcinoma. This was one of the first of its kind because o f the uniquely multidisciplinary approach dedicated solely to the topic of this aggressive form of skin cancer. Invited speakers and attendees spanned the specialties of dermatology, surgical oncology, otolaryngology, radiation oncology, medical oncology, radiology, and plastic surgery. The result was an extremely informative and engaging exchange of information that had great impact on those who attended. In an effort to disseminate this knowledge to a wider audience, this synopsis of the presented data has been compiled with assistance from the University of Rochester Medical Center Institute for Innovative Education for your reference.

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Disclosure statement for audience; This project was supported by a medical education grant provided by Pfizer/Merck KGaA Darmstadt, Germany – Call of Grant Applications (CGA) Merkel Cell Carcinoma (MCC) The authors had full responsibility and latitude in producing this publication.

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MERKEL CELL CARCINOMA: AN OVERVIEW

By Sherrif F. Ibrahim, MD, PhD

Merkel cell carcinoma (MCC) is an aggressive skin cancer of neuroendocrine origin with a mortality rate 3 times that of malignant melanoma. MCC is among the most dangerous forms of skin cancer, with approximately one third of patients presenting with regional or metastatic disease.

Sherrif F. Ibrahim, MD, PhD
Associate Professor, Dermatology
Wilmot Cancer Center
University of
Rochester Medical Center
Rochester, New York

Reported cases of MCC are increasing at a rapid rate. Over the past 20 years the reported incidence has more than tripled; with an 8% increase per year in cases of MCC from 1986 – 2001. In 2008, there were approximately 1500 cases of MCC reported, increasing to over 2000 by 2017. Currently, new cases of MCC surpass that of cutaneous T cell lymphoma. The increasing incidence of MCC is thought to be linked to an expanding population of elderly patients at risk. MCC tends to occur most in fair skinned individuals over the age of 50.

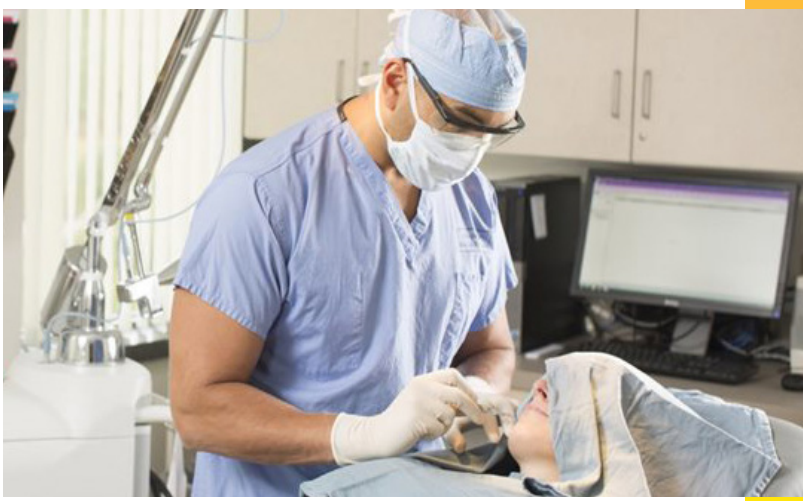
CLINICAL PRESENTATION:

Clinical diagnosis of MCC can be challenging to the practitioner. Tumors typically occur in a sun-exposed distribution, presenting on the face or extremities as a painless rapidly enlarging red to violacious growth. As with other forms of UV-related skin cancer, there is a strong risk associated with immunosuppression. Solid organ transplant patients have an approximate 10-fold risk, while patients with chronic lymphocytic leukemia have as high as a 50 fold increased risk for the development of MCC. However, it is important to note that 90% of MCC cases occur in non-immunosuppressed patients.

A common mnemonic exists to aid in the characteristics of MCC tumors and patients[1].

A: Asymptomatic/ non tender
E: Expanding rapidly
I: Immune suppressed
O: Older than 50
U: UV exposed skin

Deep lesions of unknown primary origin are not an uncommon presentation, and these are particularly difficult to diagnosis, resulting in a delay in treatment. These may mimic a benign cyst or lipoma and most commonly occur on the flanks, buttocks or lower extremities. While cysts typically contain an epidermal connection, or central punctum, a deep MCC tumor will lack these findings and be much firmer than a fluctuant lipoma.



The diagnosis of MCC has been facilitated by the use of immunohistochemical markers. Staining with CK20 in the characteristic peri-nuclear dot pattern is diagnostic for the disease in the absence of TTF1 staining, which differentiates MCC from neuroendocrine markers of lung origin. In 2008, a virus known as the Merkel cell polyoma virus was discovered and felt to be linked to the etiology of MCC in as many as 80% of cases in the United States[2]. Complex interplay between the skin, UV radiation, MCC polyoma virus and the host immune system are all felt to contribute to the initiation, progression and response to treatment of the disease.

Staging is a key determinant for counseling and treatment planning. Prior to 2010, there were 5 published staging systems for MCC, mostly derived from single institutions and relatively few numbers of patients. Early staging systems grouped MCC with other non-melanoma skin cancers such as basal cell carcinoma and squamous cell carcinoma. Updated AJCC and NCCN guidelines have been developed to allow for more accurate staging of MCC patients. The most recent guidelines include separate pathologic staging systems to reflect the importance of nodal staging in the workup for MCC patients. As a high number of patients who present with MCC already have nodal involvement, assessing the regional lymph node basin is of utmost importance in essentially all patients. Unlike in cases of thing melanomas where small, thin tumors have a 95% survival rate, the same cannot be stated for MCC. Each new case must be taken seriously with a full and thorough workup in multidisciplinary fashion. It is clear that those patients who are pathologically proven to be lymph node negative fair better overall.

For those patients with metastatic disease, traditional cytotoxic chemotherapy has an initial effect that is not durable. More recent advances in the use of immune checkpoint inhibitors have great promise in the treatment of MCC. Two sections contained herein are dedicated to the use of these agents in the management of MCC.

Successful management of the MCC patient requires input from the dermatologist, surgical oncologist, radiologist, and medical oncologist at a minimum. Other specialists depending on organ involvement as well as supportive care from primary care physicians, social workers, and nurses are integral to optimizing outcomes. The sections in this publication are intended to serve as a guide to help the practitioner understand the need for the multidisciplinary nature to the management of MCC. With continued research efforts and a more uniform approach to diagnosis, treatment and surveillance, we hope to better optimize outcome for our patients.

THE SURGICAL MANAGEMENT OF MERKEL CELL CARCINOMA

By Ryan C. Fields, MD

Ryan C. Fields, MD
Chief of Surgical Oncology
Professor of Surgery
The Alvin J. Siteman Comprehensive Cancer Center
Washington University School of Medicine
St. Louis, Missouri

Merkel cell carcinoma (MCC) has a propensity for lymphatic spread

- 30% of patients present with clinically evident nodal disease.
- Survival is decreased in patients with nodal disease.
- The natural history of MCC is not well characterized due to the rare nature of the disease and reliance on large database studies (SEER, NCDB) that have limited treatment and follow-up information.

Detailed analysis of larger studies with more complete treatment and follow-up information inform us that:

- Overall survival is a poor measure of the impact of disease on life expectancy in the population affected by Merkel cell carcinoma.
- With complete follow-up, near equal numbers of patients die of Merkel cell carcinoma compared to other causes.
- Patients with clinically localized MCC have similar disease-specific survival, irrespective of primary tumor size and microscopic nodal status (stage 1, 2, and 3a).
- Patients with clinically involved LN (stage 3b) or metastatic disease (stage 4) have significantly decreased disease-specific survival compared to those with clinically localized disease.
- Lymphovascular invasion (LVI) of the primary tumor is highly correlated with death from MCC.

The status of the sentinel lymph node (SLN) is an important determinant of outcome in patients with early stage MCC.

- 20-30% of patients with clinically localized MCC will have a +SLN.

- If SLNB negative, no care other than close long -term follow up is needed."
- Primary tumor size (and by definition clinical stage) and presence of LVI in the primary tumor are significantly associated with a positive SLNB. This includes a 25% positive SLN rate in small (≤1cm) tumors. This argues for SLN staging of all patients with early stage MCC.
- Recurrence and death from MCC are <10% in patients with clinically localized MCC.
- We did not observe nodal recurrences in patients with a positive SLNB treated with nodal RT (adjuvant after CLND or therapeutic RT alone).
- Only 6% of patients with a positive SLNB treated without adjuvant systemic chemotherapy developed distant recurrence.
- SLN status was not associated with recurrence or death from MCC. However, patients with a positive SLN were more likely to receive subsequent CLND, nodal RT, and/or chemotherapy.
- LVI is strongly associated with recurrence and death from MCC. Lymphovascular invasion of the primary tumor is strongly associated with a positive SLNB, recurrence, and survival in patients with clinically localized Merkel cell carcinoma.
- SLN status is not associated with recurrence or survival. Effective treatment of a positive SLN may interrupt the metastatic cascade.

An understanding of the rates and patterns of recurrence after treatment for non-metastatic Merkel cell carcinoma is critical for defining follow-up and adjuvant treatment strategies.

- Low recurrence in clinically node-negative MCC can be achieved with adequate surgery, including SLNB, and the selective use of adjuvant RT for high-risk tumors.
- Clinically node-positive MCC has significantly higher rates of recurrence.
- Low response rates and significant toxicity argue against the routine use of adjuvant chemotherapy.
- The role of adjuvant immunotherapy is currently being defined in several trials.
- Recurrence is rare in the absence of primary tumor LVI.

The surgical management of early stage Merkel cell carcinoma is successful in achieving long-term cure.

- Primary treatment: surgery and SLNB
  - If SLNB negative, no further care is needed
  - If SLNB positive (stage 3a), treat nodal basin with completion LND (axilla) or nodal RT (groin), but not both.
  - No role for adjuvant chemotherapy.
  - (Hopefully!) a role for adjuvant immunotherapy.
  - No need for local RT if surgical margins are adequate and negative.
- Clinically node-positive Merkel cell carcinoma (stage 3b) has a worse prognosis.
  - Primary treatment: "Neoadjuvant" immunotherapy versus surgery and lymph node dissection (RT for patients unfit for surgery).
  - Lymph node dissection and nodal RT is very morbid.
  - Given high likelihood of distant recurrence, reserve RT for isolated nodal recurrence that is not conducive to surgery.
  - Adjuvant chemotherapy is reasonable, but unproven.
  - No role for local RT.
  - Encourage clinical trial participation.

RADIATION THERAPY IN THE TREATMENT OF MERKEL CELL CARCINOMA

By Christopher Barker, MD

Christopher Barker, MD
Director of Clinical Investigation, Department of Radiation Oncology
Memorial Sloan Kettering Westchester
West Harrison, New York

Radiation therapy (RT) may be valuable to patients with Merkel cell carcinoma (MCC) in several situations. Categorically, RT can be considered for MCC in three distinct clinical scenarios: the patient with no clinical evidence of nodal metastasis, the patient with clinical evidence of nodal metastasis, and the patient with unresectable and metastatic MCC.

The first randomized controlled trial in MCC evaluated RT for the patient without clinical evidence of nodal metastasis. In this study, patients with clinical stage I MCC all underwent wide local excision of MCC (without sentinel lymph node biopsy), followed by tumor bed irradiation. Patients were randomized to receive elective lymph node basin RT or to have the lymph node basin observed.

With the advent of sentinel lymph node biopsy, the study was terminated before accrual was complete. Eighty-three patients representing a typical cohort of MCC patients were accrued to the study between 1993 and 2004. The authors demonstrated a low rate of adverse events associated with RT. The most common site of first recurrence was in the regional lymph node basin; however, none of the patients randomized to elective lymph node basin RT experienced regional lymph node basin recurrence, while the risk of regional lymph node basin recurrence was approximately 20% by 4 years in patients randomized to observation. RT was not associated with a significant increase in progression free survival (approximately 80% at 4 years) or overall survival (approximately 90% at 4 years)[1].

The trial above demonstrated that the risk of regional lymph node basin recurrence without treatment closely approximates the risk of a positive sentinel lymph node biopsy[2]. In practice, the sentinel lymph node biopsy may be a useful test to help select patients for lymph node basin RT. This strategy may allow for the avoidance of RT in patients that do not require treatment and the simultaneous identification of patients who will benefit from a highly effective treatment. In the trial, all patients underwent wide excision and tumor bed irradiation and therefore it provides no guidance on the necessity of tumor bed irradiation[1]. Large single institution studies have reported that the risk of primary tumor site recurrence is low after an appropriate wide excision of the primary tumor and calls into question the need for primary tumor site irradiation after wide excision[3]. However, there are some circumstances where a wide excision of the primary tumor is not possible because of anatomy or underlying medical comorbidity. In these situations, definitive RT monotherapy for the primary tumor can be effective. A summary of reported cases suggested that the crude risk of local recurrence after definitive RT monotherapy is 7.6%, thus representing a viable strategy when appropriate[4].

Among patients with clinically evident lymph node metastasis, most studies suggest that the highest rate of regional disease control is associated with therapeutic lymphadenectomy and adjuvant RT[3]. However, this strategy is likely to be associated with the highest risk of adverse events. For this reason, monotherapy with either surgery or RT has been employed, with relatively similar outcomes observed[4].

Patients with unresectable and metastatic MCC are often treated with systemic therapy. However, RT may be a valuable treatment for this population. Studies have shown that relatively low doses of RT (8 Gy in a single fraction) yields a response in a large proportion of patients [7]. However, other data suggest that tumor recurrence after 8 Gy in a single fraction is not uncommon, and that more durable control may be possible with higher doses (24 Gy in 3 fractions of 8 Gy). Remarkably, approximately 25% of patients treated with comprehensive RT for a limited number of metastases can experience durable control [8].

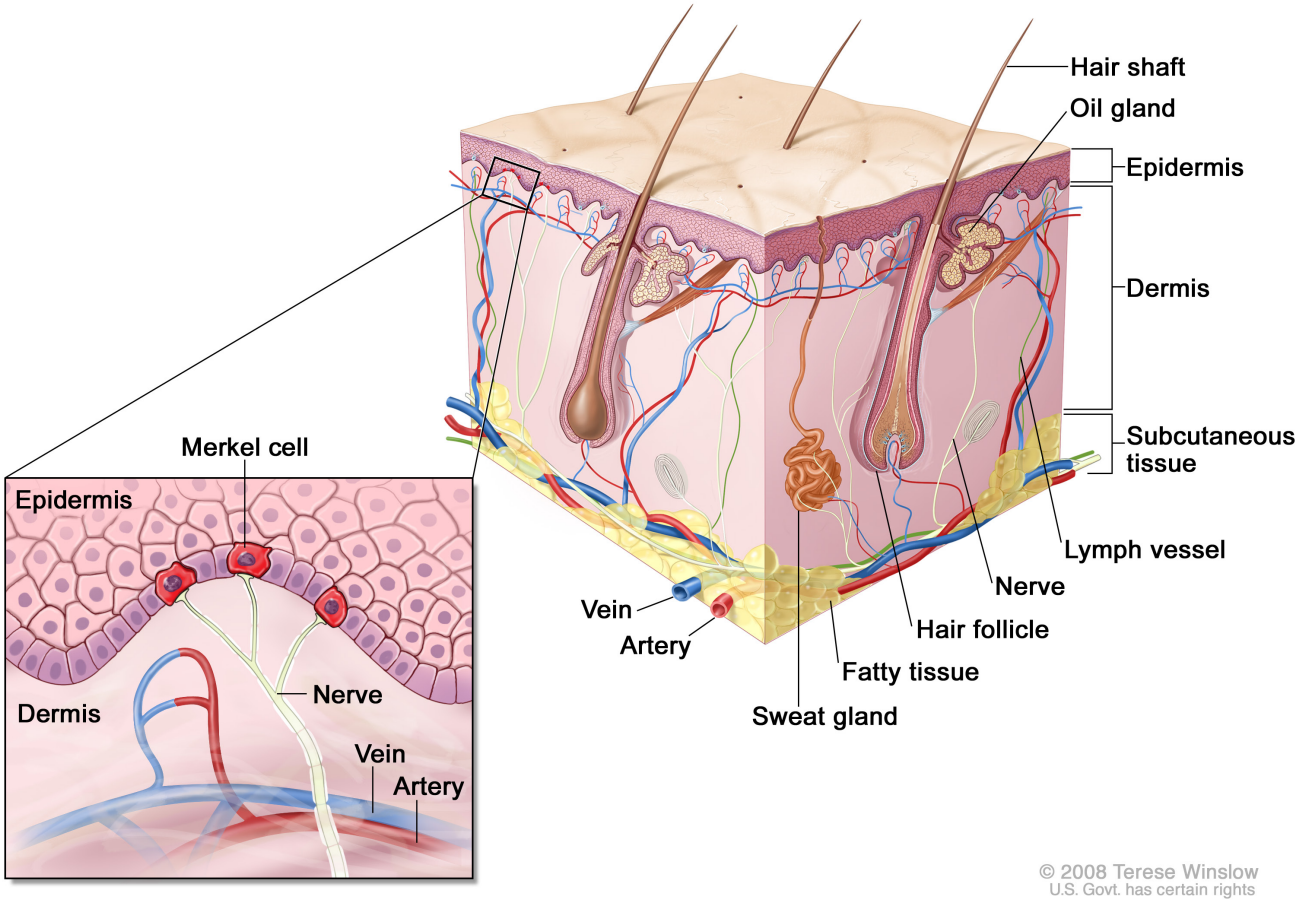
WHAT IS MERKEL CELL CARCINOMA?

Merkel cell carcinoma (MCC) was originally described by Toker in 1972 as trabecular carcinoma of the skin. Other names include Toker tumor, primary small cell carcinoma of the skin, primary cutaneous neuroendocrine tumor, and malignant trichodiscoma.

MCC is an aggressive neuroendocrine carcinoma arising in the dermoepidermal junction, and it is the second most common cause of skin cancer death after melanoma. Although the exact origin and function of the Merkel cell remains under investigation, it is thought to have features of both epithelial and neuroendocrine origin and arise in cells with touch-sensitivity function (mechanoreceptors).

Therapeutic options have been historically limited for patients with advanced disease; however, new immunotherapeutic approaches are associated with durable responses.

A special type of cell found right below the epidermis (top layer of skin). These cells are very close to the nerve endings that receive the sensation of touch and may be involved in touch. The cells also contain substances that may act as hormones.



ADVANCES IN SURVEILLANCE AND TREATMENT OF MERKEL CELL CARCINOMA

By Paul Nghiem, MD, PhD & Coley Doolittle-Amieva, PA-C

Paul Nghiem, MD, PhD
Head of UW Dermatology
Seattle Cancer Care Alliance
Seattle, Washington

Coley Doolittle-Amieva, PA-C
Physician Assistant
Seattle Cancer Care Alliance
Seattle, Washington

Improvements in Surveillance:

Surveillance strategies for Merkel cell carcinoma continue to evolve and play a critical role in catching early disease recurrences which is important given the overall high risk of recurrence. (MCC recurs in about 40% of patients.) Additionally, catching recurrences early has become relevant as we now have meaningful treatment options with immunotherapy. NCCN surveillance guidelines are vague, stating "imaging and other studies as clinically indicated and consider routine imaging for high-risk patients." Fortunately, two tools have recently become available to guide clinicians in making informed decisions regarding frequency and type of surveillance in MCC patients. These include a blood test that quantifies Merkel polyomavirus oncoprotein antibody titer and the use of stage-specific MCC recurrence curves.

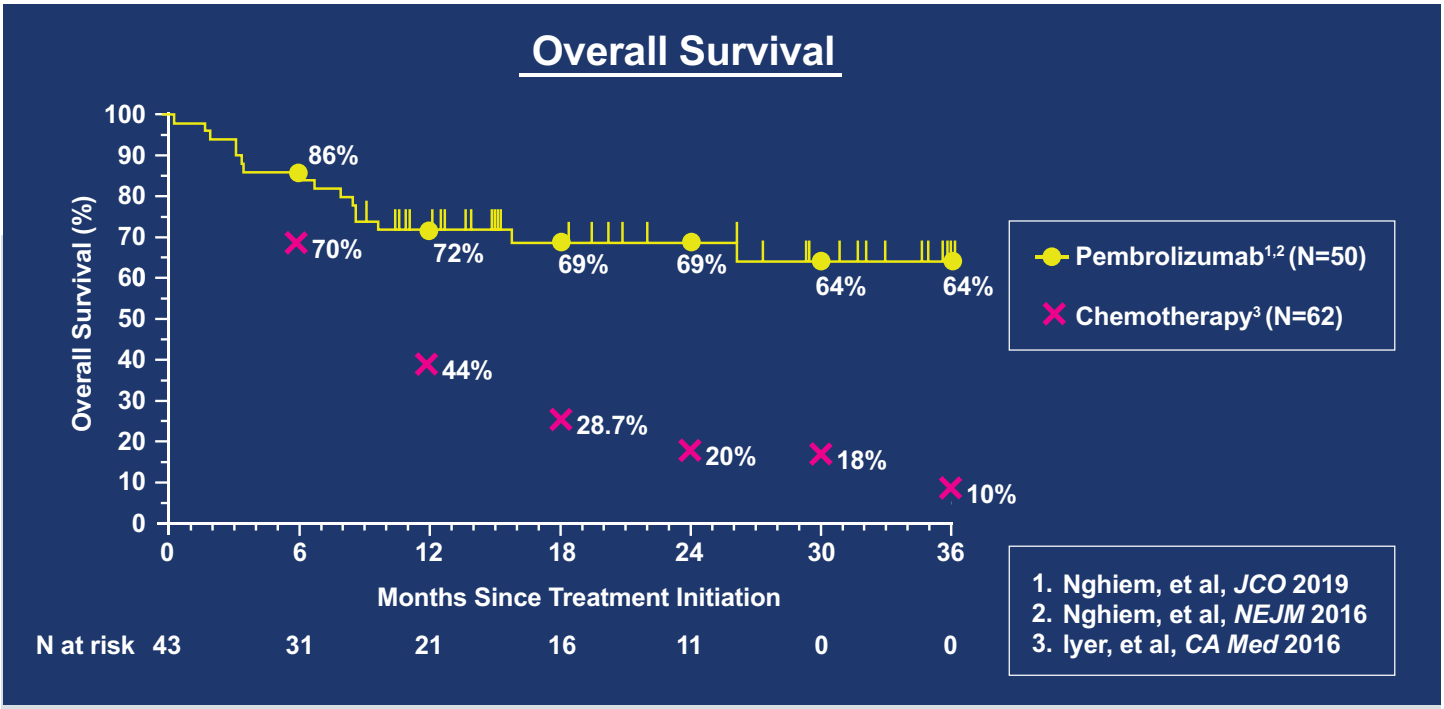
Merkel Oncoprotein Antibody Testing:

The majority of Merkel cell carcinoma cases are associated with the Merkel polyomavirus, and several recent studies have indicated that determining the titer of oncoprotein antibodies is useful for surveillance (details at www.merkelcell.org/sero and https://www.ncbi.nlm.nih.gov/pubmed/27925665). This blood test is now indicated in the NCCN Guidelines and is useful for MCC patients whether or not they are found to produce these antibodies. Patients who have undetectable antibody levels at time of MCC diagnosis (seronegative patients) are 42% more likely to have a recurrence than seropositive patients. It is thus highly appropriate to follow seronegative patients with imaging because this test is not useful for detecting MCC recurrences in these patients and seronegative patients are at higher risk of disease recurrence. In contrast, following the titer of Merkel virus antibodies is useful in an ongoing way in seropositive patients because these antibodies fall in patients without disease and rapidly rise if disease recurs. Indeed, it is now clear that this test is a sensitive, reliable indicator of disease recurrence in seropositive patients. This test can markedly decrease the number of surveillance scans that are required for seropositive patients.

The Merkel antibody test has shown excellent performance in a recently updated analysis of data gathered over a 10-year-period, from over 2,000 blood draws. This most recent analysis included 254 patients who had at least two blood tests over time and was presented at the Society for Investigative Dermatology meeting in Chicago in May 2019. The test had a positive predictive value for disease recurrence of 99% among patients who had an increasing Merkel virus antibody titer. The majority of recurrences were clinically detectable within 45 days of the observed rise in antibody titer, however there were outliers whose clinical recurrence was not observed until a median of 292 days after the antibody titer increase was initially noted. These findings indicate the test is sensitive and capable of detecting disease recurrence well before it is clinically evident by imaging study or physical exam. The test also had a 99% negative predictive value (indicating no current evidence of disease) among seropositive patients whose titers had significantly decreased and remain low. Information to assist clinicians in the use of this test is available at www.merkelcell.org/sero.

Recurrence Curves:

National cancer databases typically collect and report data on whether patients are alive ('overall survival'). Data regarding whether a patient's cancer has recurred or not ('recurrence-free survival') are more challenging and laborious to collect and are thus much less available. Using our Seattle-based cohort, we have generated data on recurrence free survival that we have found to be very useful clinically. This allows a clinician to take



Comparison of Overall Survival in patients with advanced MCC who received anti-PD1 (pembrolizumab) as compared to historical control subjects who received cytotoxic chemotherapy.

into account the stage at diagnosis as well as the time since diagnosis to determine a patient's 'residual risk of recurrence' as well as their chance of having an MCC recurrence in the next 6-12 months. Using this information allows us to determine if a patient has, for example, 3% or 30% remaining risk of recurrence and thus whether follow-up studies should happen every 3 months, 6 months, or less often. Clinically, these data are so useful that we review recurrence curves with patients at every visit. Please visit https://merkelcell.org/prognosis/disease-recurrence/ to view recurrence curves, which are being prepared for publication.

Advances in Therapy: From Chemotherapy to Immunotherapy:

Treatment for advanced Merkel cell carcinoma has drastically changed in the last few years with a primary focus now on immunotherapy. In the past two years, two PD1 pathway-targeted checkpoint inhibitors, avelumab and pembrolizumab, have been FDA-approved for treatment of metastatic Merkel cell carcinoma. Chemotherapy was the standard of care for MCC until 2016 and leads to frequent initial responses. Unfortunately, chemotherapy responses have not proven durable, and by one year after starting chemotherapy, only about 5% of patients still have their cancer under control.

In contrast, immunotherapy benefits about 60% of patients initially and the vast majority of those responses last one year or longer. As shown in Figure 1, pembrolizumab had greater overall survival at every time point up to 36 months when compared to traditional chemotherapy. Although not a randomized study, at 3 years, patients receiving pembrolizumab had 64% survival, compared to only 10% of 64 historical control subjects who had received chemotherapy as their first systemic treatment for advanced MCC.

Conclusion:

With important recent advances in therapies to treat metastatic Merkel cell carcinoma, surveillance for MCC recurrence plays an increasingly significant role. Although the NCCN guidelines are not currently as detailed as clinicians might like, we recommend using recurrence data to assess a patient's risk of recurrence in their next year of follow-up, and then carrying out risk-appropriate surveillance with traditional CT imaging and/or Merkel antibody blood tests. High-risk patients are thereby reassured their disease is not recurring, or when disease does recur, early detection allows more time for newly available immune therapy or other clinical trials to be explored.

SYSTEMIC TREATMENT OPTIONS FOR MERKEL CELL CARCINOMA

By Evan Rosenbaum, MD & Sandra P. D'Angelo, MD

Evan Rosenbaum, MD
Head of UW Dermatology
Seattle Cancer Care Alliance
Seattle, Washington

Sandra P. D'Angelo, MD
Medical OncologistSeattle Cancer
Memorial Sloan Kettering
Cancer Center

Advanced Stage MCC Associated with Poor Clinical Outcomes

Overall survival (OS) in MCC is largely a function of disease stage at diagnosis. While the overall 5-year rate survival of primary MCC is 62% according to one study, this number decreases to 25% in patients with distant metastases at diagnosis, compared to 75% for those with localized disease. An additional analysis of close to 10,000 MCC patients from the National Cancer Database found 5-year OS was 51%, 35%, and 14% for local, nodal, and distant disease, respectively. Sixty-five percent of these cases presented with localized disease, while 26% had nodal metastases and 8% presented with distant metastases.[2] As MCC is commonly a disease of the elderly, disease-specific survival (DSS) may be a more sensitive endpoint for MCC-related mortality in MCC studies. A large single-institution study found that DSS, like OS, is highly dependent on stage, decreasing from 81% in stage I patients to 11% in stage IV patients.[3]

Cytotoxic Chemotherapy: A Temporizing Measure at Best

Prior to the advent of immune checkpoint blockade (ICB), cytotoxic chemotherapy was the standard of care in the metastatic setting. Platinum-based treatment with or without etoposide, or the combination of vincristine, doxorubicin, and cyclophosphamide, were the two most commonly used regimens. The overall response rate to first line cytotoxic therapy in metastatic MCC ranges between 50 and 60%, compared to 20 to 25% in the second line setting (Figure 2). Unfortunately, these responses are transient and patients rapidly progress in a matter of months (median PFS of 3.1 months in the first and 2 months in the second-line setting). The median OS after cytotoxic chemotherapy is less than one year, highlighting the need for novel treatment approaches in the metastatic setting.[4,5]

Immune Checkpoint Blockade: The Promise of Durable Responses

Eighty percent of MCCs are caused by genomic integration of the Merkel cell polyomavirus (MCPyV).[6,7] While virus-driven MCC have a very low somatic mutation burden, MCPyV-negative MCC are characterized by a high tumor mutation burden (TMB; approximately 10 mutations per Mb) and a UV-signature pattern dominated by C > T transitions.[8] Although genomically different, both virus-positive and negative MCC are predicted to be immunogenic, either due to highly immunogenic foreign antigens introduced by the MCPyV or to the high TMB leading to high numbers of tumor neoantigens in virus-negative MCC.[9] Prior to the advent of ICB, MCC cases with high numbers of intratumoral CD8+ lymphocytes were identified, and these cases had improved clinical outcomes compared to tumors with decreased immune infiltrations. These findings suggested that a portion of MCCs are highly immunogenic and these tumors likely respond more favorably to treatment.[10]

The immunogenicity of this disease led to multiple clinical trials of immune checkpoint inhibitors. A phase II open-label trial (JAVELIN Merkel 200 part A) of avelumab (anti-PD-L1 antibody) in 88 patients with metastatic chemotherapy-refractory MCC demonstrated a 33% objective response rate (ORR), including 8 complete responses (CRs) and 20 partial responses (PRs). In contrast to cytotoxic therapy, most responses to avelumab (72%) were durable.11,12 These results led the FDA to grant accelerated approval to avelumab in patients with metastatic MCC. An interim analysis of a follow-up study in treatment-naïve patients with metastatic MCC (JAVELIN Merkel 200 part B), with a similar study design, found an objective response rate (ORR) of 62%, with 78% of patients demonstrating an ongoing durable response.[13]

In parallel to the development of avelumab, a phase II trial of pembrolizumab (anti-PD-1 antibody) enrolled 26 patients with treatment-naïve metastatic MCC. The ORR was 56% among evaluable patients with 67% of patients progression-free at 6 months. More patients with MCPyV-positive tumors (65%) responded, compared to MCPyV-negative tumors (44%).[14] An expanded study of pembrolizumab (CITN-09/Keynote-017) in this patient population (total n = 50) was recently reported. The ORR remained 56%, with 59% of MCPyV-positive tumors responding compared to 53% of MCPyV-negative tumors. The median PFS was 16.8 months and the median DoR and OS were not reached.15 Based on these studies, the FDA granted accelerated approval to pembrolizumab for use in patients with recurrent or metastatic MCC.

Future Therapeutic Opportunities

Adjuvant Therapy

Although cytotoxic chemotherapy did not improve survival in a large retrospective study of patients with successfully resected stage III MCC16, multiple ongoing trials are investigating the role of ICB blockade (either alone [NCT03271372] or in combination with radiation [NCT03798639] or an additional checkpoint inhibitor [NCT02196961]) in the adjuvant setting in the hopes of reducing recurrence rates.

Biomarker Development

While the benefit of ICB in advanced MCC has been established, additional work is needed to determine which patients will respond best to this modality of treatment. In the JAVELIN Merkel 200 trial, responses occurred irrespective of MCPyV status or PD-L1 expression, suggesting that alternative mechanisms govern response to treatment.[11]

Similarly, KEYNOTE-017 found no statistically significant difference between PD-L1 expression and clinical outcome or MCPyV status, although the association between PD-L1-positive tumor cells and PFS and OS approached statistical significance ($p = 0.057$). It is possible that the relatively small size of these studies masks the truly significant effect of viral-status or PD-L1 expression, for example, on response to checkpoint blockade. Translational research efforts utilizing genomic and transcriptomic sequencing of primary and resistant tumor samples are underway to identify factors predictive of response or resistant to ICB.

Novel Treatment Approaches

Numerous driver alterations have been detected in virus-positive and negative MCC, including TP53 and RB1 loss, as well as alterations in the PI3K, Notch, and DNA damage response pathways.[9] Clinical trials with mTOR (NCT02514824) and MDM2 inhibitors (NCT03787602), for example, are testing targeted treatments that may prove efficacious in patients resistant to ICB. MCC cells also express the somatostatin receptor[3], which can potentially be targeted with radio-pharmaceuticals (NCT02936323). Alternatively, trials investigating novel combinations of immunotherapeutics seek to provide alternatives for patients with primary or secondary resistance to single-agent PD-(L)1 inhibition. The addition of CTLA-4 blockade to PD-1 inhibition (NCT03071406), adoptive cell transfer (NCT03853317, NCT03747484), utilizing the abscopal effect with radiation therapy (NCT03304639), oncolytic viral therapy (NCT02819843), and intratumoral injection of TLR agonists (NCT03684785), represent some of the strategies in development in order to stimulate adaptive immunity against advanced MCC.

HEAD AND NECK MERKEL CELL CARCINOMA– CHALLENGES

By Timothy D. Doerr, MD FACS

Timothy D. Doerr, MD FACS
Otolaryngologist '
Wilmot Cancer Center
University of
Rochester Medical Center
Rochester, New York

Merkel cell carcinoma presents challenges to the head and neck specialist dealing with this aggressive cutaneous malignancy. The incidence of MCC is increasing with improved diagnosis, chronic immunosuppression and an aging population. A large percentage of MCC involves the sun exposed areas of the head and neck with some literature suggesting that head and neck sites carry a worse prognosis.

Head and neck MCC is treated with a multidisciplinary approach. The hallmark of this treatment is surgery. Guidelines for surgical excision of head and neck MCC advocate at least a 1 cm margin for Stage I lesions and 2 cm or greater for Stage II tumors. These margins are not always practical for many sites where such margins would result in significant surgical and functional morbidity. There is some recent evidence that suggests no difference in outcomes with the margins increasing from 1 to 2 or 3 cm. Given the anatomic challenges of obtaining 2 cm margins in the head and neck region, several studies have reported equivalent outcomes using Mohs micrographic surgery to facilitate tumor removal.

There are also challenges in reconstructing the facial defects following removal of a Merkel cell lesion. Depending on the surgeon's confidence in a negative permanent margin resection, a complex definitive reconstruction may be delayed. There may also be a benefit in reconstructing with a full-thickness skin graft instead of a local or pedicle flap to facilitate cancer surveillance. The decision for an early or delayed definitive reconstruction should be based on anatomic site, confidence in margins and ability for surveillance.

In treating head and neck MCC virtually all lesions should be managed with a sentinel lymph node biopsy (SLNB). Even small lesions <0.5 cm have demonstrated positive SLNB in more than 10% of cases. Some authors feel that SLNB alone is insufficient and advocate for an elective neck dissection. My practice is to perform a sentinel lymph node biopsy on all head and neck Merkel cell carcinoma patients both to provide prognostic and therapeutic value. Pathology findings from the excision specimen and the excised lymph node including lymphovascular invasion can be useful in directing subsequent treatment.

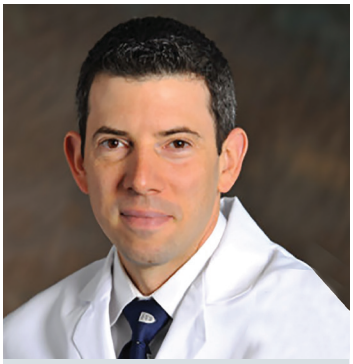
In the setting of a positive sentinel lymph node the head and neck specialist will usually proceed with a selective lymphadenectomy of the cervical lymph nodes as additional positive lymph nodes can be found in as many as 25% of cases. Depending on the anatomic location this may also include a parotidectomy or submandibular gland removal. Depending on the final pathology from the surgical specimen adjuvant radiation may also be employed.

There remains controversy as to whether outcomes from Head and Neck MCC are different than those of non-head and neck sites. Generally head and neck sites are identified sooner. However as previously noted anatomic constraints can limit resection and head and neck lymph node drainage can be more varied. Both of these allow for potential under treatment. The literature on outcomes for head and neck MCC is limited and conflicted with some studies showing poorer prognosis for head and neck sites while others do not.

In summary, MCC of the head and neck presents unique challenges to the treating surgeon. The structurally rich anatomy limits margin size with Mohs surgery offering a tissue sparing alternative. As a rule, disease surveillance concern should rarely deter appropriate reconstruction. Head and Neck MCC has a high rate of lymph node metastasis and presentation and assessment of the regional lymph nodes is critical. Sentinel node biopsy is appropriate for this assessment. The setting of a positive SLNB neck dissection improves locoregional control a prognostic datum to help direct additional treatment and surveillance.

CHALLENGES ASSOCIATED WITH ADMINISTRATION OF IMMUNE CHECKPOINT INHIBITORS

By Evan J. Lipson, MD



By Evan J. Lipson, MD
Johns Hopkins University School of Medicine
Sidney Kimmel Comprehensive Cancer Center
Bloomberg~Kimmel Institute for Cancer Immunotherapy

1. Immune-mediated adverse reactions (IMARs), also known as immune-related adverse events (irAEs), can affect any organ system so their manifestations can be wide-ranging. Thus, it can be challenging to recognize that a patient's complaint stems from an immune-mediated toxicity.
   - IMARs are often diagnoses of exclusion, so evaluating for other causes of a particular symptom (e.g., infection, tumor involvement, adverse reaction to another drug) is critical.

2. Although corticosteroids are often an effective first-line therapy for patients experiencing IMARs, treating patients with steroid-refractory toxicities can be challenging.
   - "Steroid-refractory" can mean that the IMAR does not improve within ~48-72 hours of high-dose corticosteroids (i.e., 1-2mg/kg/day prednisone or equivalent), or that the toxicity improves initially but relapses during a steroid taper of appropriate length (≥4-6 weeks).
   - Infliximab 5mg/kg IV is generally administered in steroid-refractory cases. One exception is immune-mediated hepatitis, for which mycophenolate mofetil is added to prednisone.
   - The National Comprehensive Cancer Network recently published guidelines for "Management of Immunotherapy-related Toxicities." This document is an excellent resource for a wide range of clinical scenarios.
3. Because IMARs can occur many months after cessation of immune checkpoint blocking therapy, recognizing delayed toxicities can be challenging.
   - Careful assessments (e.g., periodic H&Ps, labs) should continue after cessation of therapy.
   - In a patient who has received an immune checkpoint blocking agent, even if the agent has been discontinued, a complaint that cannot otherwise be explained may be a delayed IMAR.

4. Understanding when to restart immune checkpoint blocking therapy after occurrence of an IMAR can be challenging.

- Immune checkpoint blockers can often be restarted safely after resolution of a grade 1-2 toxicity. Permanent discontinuation of therapy is often required in the case of a grade 3-4 toxicity.
- However, the anti-tumor activity of immune checkpoint blockers may persist long after drug discontinuation, so in some cases an immune checkpoint inhibitor does not need to be restarted after a toxicity resolves. This is particularly true for patients who experience a severe toxicity, in whom the risk of harm in restarting immune checkpoint inhibition may be prohibitively high.

5. Determining the optimal duration of therapy can be challenging.

- In patients with a complete response, some clinicians hold therapy and monitor patients closely.
- In patients with a prolonged partial response, a PET scan or biopsy can be useful in determining whether active cancer still exists in a particular lesion.

6. Understanding whether the appearance of tumor growth seen on early on-treatment imaging represents true disease progression or an immune-related response (i.e., lesion growth followed by regression) can be challenging.

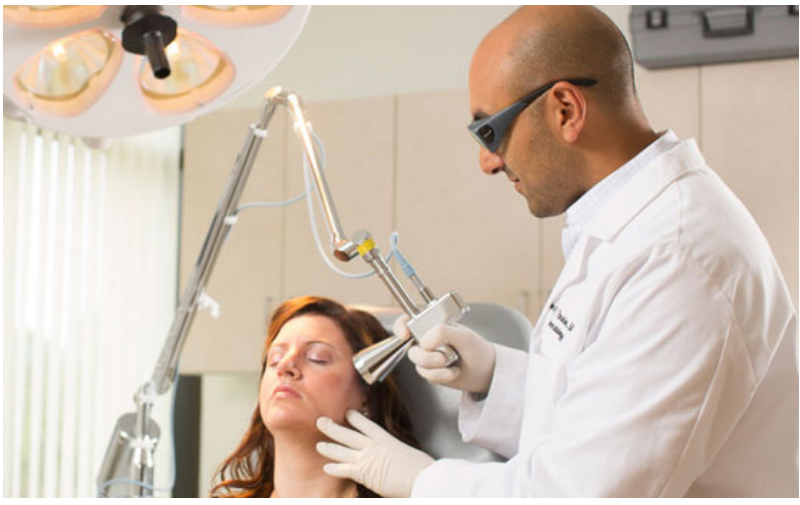
- In these cases, a patient's clinical status often informs the decision to continue current treatment or switch therapies. Improving symptoms (appetite, energy, pain, etc.)

7. It can be challenging to help patients understand that holding immunotherapy and treating an IMAR has not been shown to reverse the anti-tumor activity of immune checkpoint blocking agents.

- Patients are often reluctant to report symptoms out of concern that immunotherapy will be held. It can be helpful to reassure patients that retrospective studies evaluating the use of corticosteroids / infliximab used to alleviate IMAR symptoms combat the side effects of immunotherapy but do not reverse the activity against cancer.
- It is critical to impress upon patients that early recognition, evaluation and treatment of IMARs is vital for patient safety. Patients should be encouraged to report symptoms promptly.
- Every health care provider who has contact with the patient (e.g., triage nurses, infusion center staff, covering providers, etc.) should be educated about the importance of prompt IMAR recognition and evaluation.

8. Treating patient populations with underlying immune disorders can be challenging.

- In a patient with an underlying autoimmune disease (e.g., rheumatoid arthritis, psoriasis), administration of an immune checkpoint blocker can exacerbate symptoms of the disorder. Although this phenomenon does not occur in every patient, it is important to discuss the potential risks and benefits with each patient.
- In organ transplant recipients, administration of immune checkpoint blocking agents has triggered allograft rejection and loss. In cases of kidney transplantation, patients may choose to receive therapy and risk requiring dialysis. Referral for multidisciplinary evaluation may be helpful in these cases.



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Evan Rosenbaum, MD & Sandra P. D'Angelo, MD Article

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Wilmot Cancer Center
University of Rochester Medical Center
601 Elmwood Ave, Rochester, NY 14642

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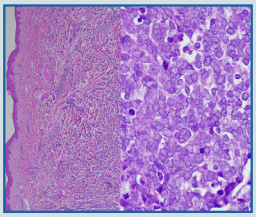

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