Cancer Association of South Africa (CANSA)

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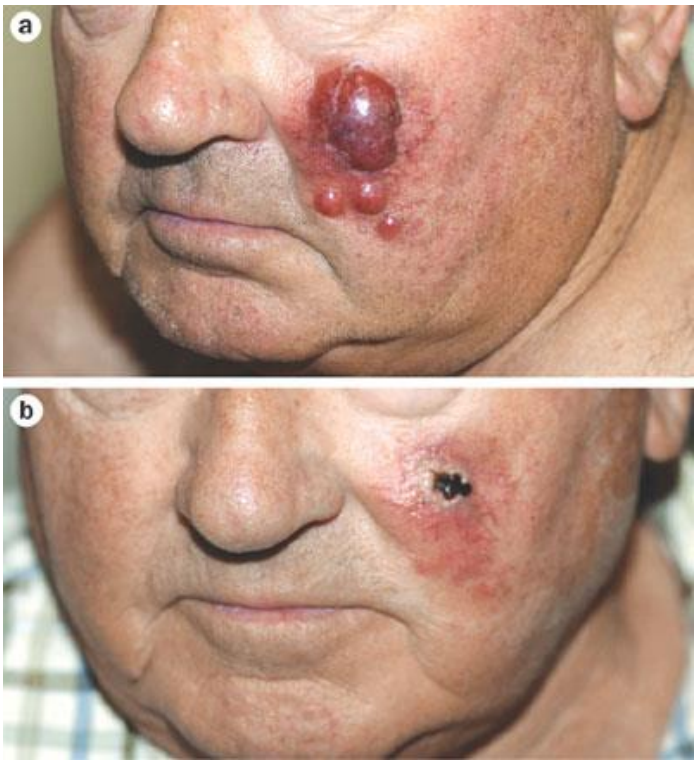
Fact Sheet
on
Merkel Cell Carcinoma

Introduction

Merkel Cell Carcinoma (MCC), sometimes referred to as a neuroendocrine carcinoma of the skin, arises from the uncontrolled growth of Merkel cells in the skin. It is a rare skin cancer with roughly 1 500 cases diagnosed per year in the United States of America. It is about 40 times less common than melanoma. MCC has the potential to be lethal, and thus prompt aggressive treatment is warranted.



[Picture Credit: MCC]

MCC does not have a distinctive appearance. It usually develops on sun-exposed skin (e.g. head, neck, arms) as a painless, firm, flesh-coloured to red or blue bump (refer to photograph). Frequently, patients seek advice from their doctor because the bump grows rapidly or the overlying skin breaks down. Most MCCs are diagnosed when a skin biopsy is performed to rule out another sun-induced skin cancer or a cyst. In the vast majority of cases, both the doctor and the patient are surprised by the diagnosis of MCC.

Merkel Cell Carcinoma

Merkel Cell Carcinoma is a rare but highly aggressive skin cancer, which, in most cases, is caused by the Merkel cell polyomavirus (MCV) discovered by scientists at the University of Pittsburgh in 2008. It is also known as cutaneous APUDoma, primary neuroendocrine carcinoma of the skin, primary small cell carcinoma of the skin, and trabecular carcinoma of the skin.

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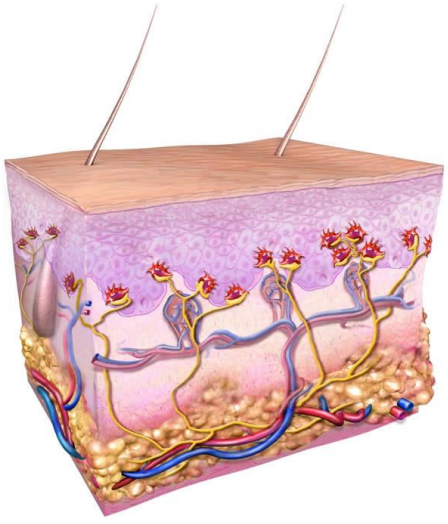
Normal Merkel cells in the skin: In this illustration of a cross-section of skin, normal Merkel cells are shown in red and connect to nerves shown in yellow. The structures drawn include the epidermis (upper third), dermis (middle), and deeper adipose layer containing the fatty tissue. Arteries are depicted as red and veins are blue.



[Picture Credit: Merkel Cell Carcinoma]

This cancer is considered to be a form of neuroendocrine tumour. While patients with a small tumour (less than 2 cm) that has not yet metastasised to regional lymph nodes have an expected 5-year survival rate of more than 80 percent, once a lesion has metastasised regionally, the rate drops to about 50 percent. Up to half of patients that have been seemingly treated successfully (i.e. that initially appear cancer-free) subsequently suffer a recurrence of their disease. Recent reviews cite an overall 5-year survival rate of about 60% for all MCC combined.

Merkel cell carcinoma (MCC) occurs most often on the sun-exposed face, head, and neck.

Walsh, N.M. & Cerronia, L. 2021.
"Merkel cell carcinoma has been a focus of active scientific investigation in recent years and new information on the topic has emerged. Although uncommon, this primary cutaneous neuroendocrine carcinoma, usually involving the head/neck of elderly individuals, has a poor prognosis. Within the past two decades, an increase in the incidence of the tumor and the discovery of its link to the Merkel cell polyomavirus have focused medical attention on the lesion. The resulting studies have improved our understanding of the biology of the neoplasm and contributed to clinical care. Specifically, two pathogenic subsets of the tumor have come to light, the majority due to Merkel cell polyomavirus and the minority caused by ultraviolet radiation-induced genetic damage. This dichotomy carries prognostic implications favoring the former subset. In addition, having capitalized on the known susceptibility of the tumor to immune influences, investigators have recently discovered its responsiveness to immune checkpoint inhibition. This revelation has constituted a therapeutic milestone at the clinical level. Herein we provide an overview of the topic, outline updates in the field and place an emphasis on dermatopathologic aspects of Merkel cell carcinoma."

Incidence of Merkel Cell Carcinoma (MCC) in South Africa
The National Cancer Registry (2017) does not make any mention of Merkel Cell Carcinoma.

Cause of Merkel Cell Carcinoma (MCC)

A virus was discovered in 2008 to be frequently involved in MCC. This new virus is called Merkel Cell Polyomavirus (MCPvV).The virus was found in 8 of 10 tumours tested, and it was associating with the DNA of the tumour cells in such a way to suggest that it is involved in the development of MCC. Several additional studies have validated this study, finding MCPvV in 43 of 53 patients.

Recently it was suggested that MCC also occurs more often in persons with HIV infection. In a search of the Aids and cancer registers of the USA (1978–1996), ten MCC cases were identified as occurring in both registers. In four of these cases, the MCC was diagnosed before the patient developed Aids. In the remaining six cases, the MCC was diagnosed in persons with Aids, corresponding to a relative risk of 13.4 compared with the general population.

Stages of Merkel Cell Carcinoma (MCC)

As of 2009 a new MCC staging system has been established. This new system is based on an analysis of over 5,000 patients using the National Cancer Database as well as extensive review of the literature. Stages I & II MCC are defined as disease that is localized to the skin at the primary site. Stage I is for primary lesions less than or equal to 2 centimetres, and stage II is for primary lesions greater than 2 cm. Stage III is defined as disease that involves nearby lymph nodes (regional lymph nodes). Stage IV disease is found beyond regional lymph nodes.

Stage	Primary Tumour	Lymph Node	Metastasis
0	In situ primary tumour	No regional lymph node metastasis	No distant metastasis
IA	Less than or equal to 2 cm maximum tumour dimension	Nodes negative by pathologic exam	No distant metastasis
IB	Less than or equal to 2 cm maximum tumour dimension	Nodes negative by clinical exam* (no pathologic node exam performed)	No distant metastasis
IIA	Greater than 2 cm tumour dimension	Nodes negative by pathologic exam	No distant metastasis
IIB	Greater than 2 cm tumour dimension	Nodes negative by clinical exam* (no pathologic node exam performed)	No distant metastasis
IIC	Primary tumour invades bone, muscle, fascia, or cartilage	No regional lymph node metastasis	No distant metastasis
IIIA	Any size tumour (includes invading tumours)	Micrometastasis**	No distant metastasis
IIIB	Any size tumour (includes invading tumours)	Macrometastasis*** -OR- In transit metastasis****	No distant metastasis
IV	Any size tumour (includes invading tumours)	Any lymph node metastasis	Metastasis beyond regional lymph nodes

*Clinical detection of nodal disease may be via inspection, palpation, and/or imaging

**Micrometastases are diagnosed after sentinel or elective lymphadenectomy

***Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy

****In transit metastasis: a tumour distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion

(Merkel Cell Carcinoma.Org).

Risk Factors for Merkel Cell Carcinoma (MCC)
Factors that may increase your risk of Merkel cell carcinoma include:

- Excessive exposure to natural or artificial sunlight - Being exposed to ultraviolet light, such as the light that comes from the sun or from tanning beds, increases one's risk of Merkel cell carcinoma. The majority of Merkel cell carcinomas appear on skin surfaces frequently exposed to sun.
- A weakened immune system - People with weakened immune systems - including those with HIV infection or those taking drugs that suppress the immune response - are more likely to develop Merkel cell carcinoma.
- History of other skin cancers - Merkel cell carcinoma is associated with the development of other skin cancers, such as basal cell or squamous cell carcinoma.
- Older age – One's risk of Merkel cell carcinoma increases with age. This cancer is most common in people older than age 50, though it can occur at any age.
- Light skin colour - Merkel cell carcinoma usually arises in people who have light-coloured skin. Whites are much more likely to be affected by this skin cancer than are blacks.

Brady, M. & Spiker, A.M. 2020.
"Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine tumor of the skin with increasing incidence. It most frequently presents on the head and neck region of elderly, white males. Specific risk factors include ultraviolet (UV) exposure, advancing age, and immunosuppression, and its development is associated with Merkel cell polyomavirus (MCPyV) infection. Skin biopsy is diagnostic, and sentinel lymph node evaluation should be performed in all patients who are diagnosed with MCC, as the disease typically has a rapidly progressive course. Treatment consists of wide local excision with or without adjuvant radiotherapy for local disease. New therapies for metastatic MCC have shown promise and include immune-based therapies."

Diagnosis of Merkel Cell Carcinoma (MCC)
Most MCCs are diagnosed when a skin biopsy is performed to rule out another sun-induced skin cancer or a cyst.

Sachpekidis, C., Sidiropoulou, P., Hassel, J.C., Drakoulis, N. & Dimitrakopoulou-Strauss, A. 2020.
"Merkel cell carcinoma (MCC) is a rare neuroendocrine skin malignancy usually arising as a nonspecific nodule on sun-exposed areas of the head and neck. Given the poor prognosis of this aggressive tumor, assessment of disease burden in pre- and post-treatment care may ensure an optimal management with significant implications for patient surveillance and prognosis. Although imaging has established its role in locally advanced or distant metastatic MCC, a standard imaging algorithm is yet to be determined and respective recommendations are mainly based on melanoma. Positron emission tomography/computed tomography (PET/CT) is increasingly evolving as a valuable imaging tool in metastatic or unresectable MCC, mostly utilizing the glucose analogue ^{18}F-fluorodeoxyglucose (^{18}F-FDG) as a radiotracer. Despite being inferior in detecting the disease in its early stages compared to the "gold standard" of sentinel lymph node biopsy, recent evidence suggests an important role for ^{18}F-FDG PET/CT in the routine workup of localized MCC. Moreover, ^{68}Ga-labeled somatostatin analogues have been employed as PET tracers in the field of MCC with promising, yet comparable to ^{18}F-FDG, results. This article provides a structured literature

review of the most important studies investigating the role of PET or PET/CT in the clinical practice of MCC."

Treatment of Merkel Cell Carcinoma (MCC)

Merkel cell carcinoma is highly treatable with surgical and nonsurgical therapies, particularly if caught early. Treatments are often highly individualised, depending on a patient's general health, as well as the tumour's location, size, depth, and degree of spread.

Patients with Merkel cell carcinoma are usually first treated with surgery. Patients with more advanced disease may receive adjuvant (additional) treatments such as radiation therapy and chemotherapy following, or instead of, surgery.

Surgery - Surgery to remove the tumour is the most common treatment for Merkel cell carcinoma. A surgeon will also typically remove a safety margin of up to 2,5cm of normal skin around the tumour, and often underlying fatty and fibrous tissue as well, to ensure that all cancer cells have been removed. This is usually done in conjunction with a sentinel lymph node biopsy to determine if the cancer has spread to regional lymph nodes. Surgery may be the only treatment needed if the tumour is small and a wide margin of skin and soft tissue can be removed. Patients whose tumours have no lymph-node involvement have a greater than 60 percent chance of long-term survival or cure.

Surgical removal of nearby lymph nodes, usually followed by radiation and chemotherapy, may also be required in patients whose tumours have spread regionally. Spread to lymph nodes is found in more than half of patients.

Radiation Therapy and Chemotherapy - Localized radiation therapy is commonly used to destroy any remaining cancer cells following surgery to remove Merkel cell tumours. Radiation is also occasionally used to treat the area surrounding lymph nodes that have been surgically removed. Radiation therapy delivers penetrating beams of energy waves or streams of particles to the cancer cells and a small margin around the tumour. Radiation therapy can also be used to treat patients who are not candidates for surgery because of ill health or the location of their tumour, or to treat tumours that have returned after an initial round of treatment.

Chemotherapy is another treatment option following surgery. The same platinum-based chemotherapy that is used for small cell lung cancer can be used against Merkel cell carcinoma that has spread to the lymph nodes. Patients whose tumours have spread to distant areas of the body or returned following initial treatment may also be treated with chemotherapy.

Neoadjuvant chemotherapy (chemotherapy that is given before surgery) may be recommended for some patients with large Merkel cell tumours (greater than 2 centimetres) or lymph node involvement. Before this step is taken, however, consideration is needed to ensure that a patient treated with chemotherapy will still be healthy enough to subsequently undergo the surgery or radiation.

Although the rarity of Merkel cell carcinoma has made it difficult to study, researchers continue to evaluate the best ways to use radiation therapy and chemotherapy in caring for patients with the disease.

Reconstruction After Surgery for Skin Cancer - Any form of surgery can leave a scar, some more noticeable than others. When removal of a Merkel cell carcinoma leaves a wound that is too large to close with simple sutures, surgeons can use skin grafts, flaps, and other reconstructive procedures to help heal the skin and restore its appearance.

Follow-Up Care - Even after successful treatment, Merkel cell carcinomas can often come back. Also, people who have one skin cancer are at higher-than-average risk for developing new skin cancers of all types.

Individuals who have been treated for Merkel cell carcinoma should see their doctor immediately if they find a growth, bump, spot, or any changes in their skin that could indicate a recurrence of disease. Protection from sun exposure is also critical.

Patel, P. & Hussain, K. 2020.
"Merkel cell carcinoma (MCC) of the skin is a rare, aggressive form of skin cancer that metastasizes to other parts of the body. This cutaneous neuroendocrine tumour mainly affects older people, with most cases generally occurring over the age of 50 years. Merkel cell polyomavirus has been shown to induce gene mutations resulting in this skin cancer, with immunosuppression and ultraviolet radiation being other key risk factors in its pathogenesis. MCC is clinically seen as a rapidly enlarging, isolated, irregular erythematous nodule typically found on sun-exposed sites. Diagnosis is through clinical examination followed by tissue biopsy, which demonstrates characteristic histopathological neuroendocrine features. Immunohistochemistry plays a crucial role in diagnosis with the characteristic perinuclear staining with cytokeratin-20 helping to differentiate it from other morphologically similar tumours. Sentinel lymph node biopsy and imaging is essential for staging and determining prognosis. Surgical excision is the mainstay of treatment for localized disease although adjuvant radiotherapy is often required. Metastatic disease involves a very poor prognosis, and immune checkpoint inhibitors have recently shown promise in the treatment of metastatic disease. Avelumab, a monoclonal antibody that binds to the programmed death-1 receptor, has been approved by the National Institute for Health and Care Excellence and shown encouraging survival outcomes. It provides an option for treating metastatic carcinoma in adults after they have failed ≥ 1 line of chemotherapy for metastatic disease."

Topalian, S.L., Bhatia, S., Amin, A., Kudchadkar, R.R., Sharfman, W.H., Lebbé, C., Delord, J.P., Dunn, L.A., Shinohara, M.M., Kulikauskas, R., Chung, C.H., Martens, U.M., Ferris, R.L., Stein, J.E., Engle, E.L., Devriese, L.A., Lao, C.D., Gu, J., Li, B., Chen, T., Barrows, A., Horvath, A., Taube, J.M. & Nghiem, P. 2020.
Purpose: Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer commonly driven by the Merkel cell polyomavirus (MCPyV). The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immunosuppressive pathway is often upregulated in MCC, and advanced metastatic MCC frequently responds to PD-1 blockade. We report what we believe to be the first trial of anti-PD-1 in the neoadjuvant setting for resectable MCC.
Methods: In the phase I/II CheckMate 358 study of virus-associated cancer types, patients with resectable MCC received nivolumab 240 mg intravenously on days 1 and 15. Surgery was planned on day 29. Tumor regression was assessed radiographically and microscopically. Tumor MCPyV status, PD-L1 expression, and tumor mutational burden (TMB) were assessed in pretreatment tumor biopsies.
Results: Thirty-nine patients with American Joint Committee on Cancer stage IIA-IV resectable MCC received ≥ 1 nivolumab dose. Three patients (7.7%) did not undergo surgery because of tumor progression (n = 1) or adverse events (n = 2). Any-grade treatment-related adverse events occurred

in 18 patients (46.2%), and grade 3-4 events in 3 patients (7.7%), with no unexpected toxicities. Among 36 patients who underwent surgery, 17 (47.2%) achieved a pathologic complete response (pCR). Among 33 radiographically evaluable patients who underwent surgery, 18 (54.5%) had tumor reductions ≥ 30%. Responses were observed regardless of tumor MCPyV, PD-L1, or TMB status. At a median follow-up of 20.3 months, median recurrence-free survival (RFS) and overall survival were not reached. RFS significantly correlated with pCR and radiographic response at the time of surgery. No patient with a pCR had tumor relapse during observation.
Conclusion: Nivolumab administered approximately 4 weeks before surgery in MCC was generally tolerable and induced pCRs and radiographic tumor regressions in approximately one half of treated patients. These early markers of response significantly predicted improved RFS. Additional investigation of these promising findings is warranted.

Kwan, K., Ghazizadeh, S., Moon, A.S., Rünger, D., Sajed, D., Elashoff, D. & St John, M. 2020.
Objective: To evaluate the management and recurrence outcomes of head and neck Merkel cell carcinoma (HN-MCC) at a single institution.
Study design: A retrospective review of outcomes in patients with HN-MCC.
Setting: A tertiary center from May 1990 to December 2018.
Subjects and methods: Electronic medical records of patients with HN-MCC were reviewed.
Results: Sixty cases were included, with 67% (40 of 60) males and a mean age of 73.3 years. Imaging had a moderate sensitivity and specificity for detection of occult disease when compared with histopathologic analysis. Forty-two percent (25 of 60) of patients underwent neck dissection, and 12% (7 of 60) had a sentinel lymph node biopsy (SLNB). There was a high rate of negative SLNB findings. The majority of patients were treated with surgery alone (29 of 60), followed by a cohort (21 of 60) treated with surgery plus adjuvant treatment, and 10 of 60 patients were treated with radiation therapy with or without chemotherapy. Recurrence-free survival was 50%, 45%, and 42% at 1, 2, and 5 years.
Conclusions: We report higher recurrence rates and higher negative SLNB result rates than other studies. Our results affirm that imaging may not be a substitute for SLNB and that it had an intermediate ability to identify the occult disease. Traditional predictors, including SLNB and cervical node pathology, may not identify patients at risk for recurrence in HN-MCC. We report similar recurrence rates in patients who had treatment of the cervical nodes by radiation therapy or neck dissection as compared with those who did not receive neck treatment.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Merkel Cell Carcinoma
Figure Copyright by Paul Nghiem, MD, PhD & Quade Medical Group.
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