

Cancer Association of South Africa (CANSA)



Fact Sheet on Merkel Cell Carcinoma

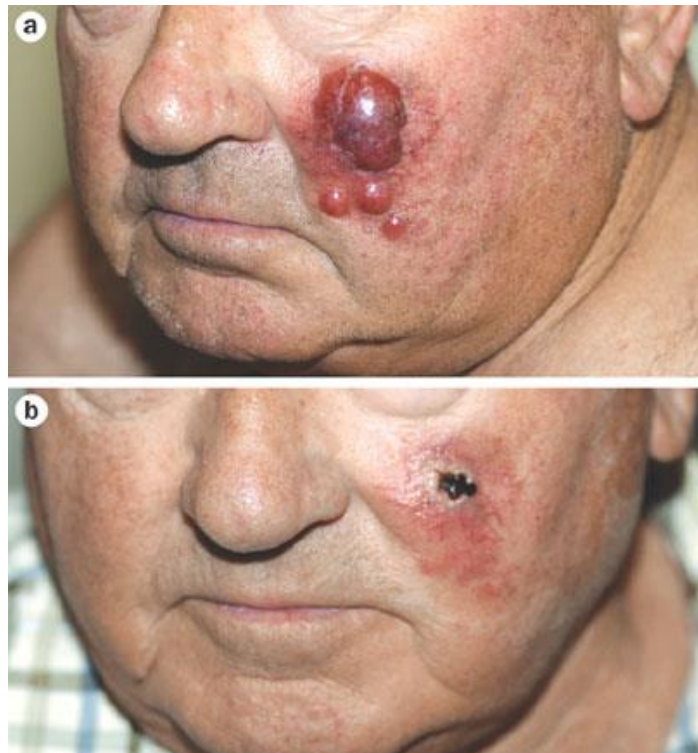
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Introduction

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.

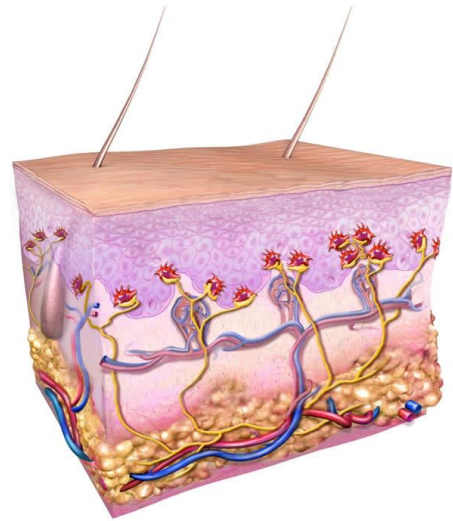
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Normal Merkel cells in the skin: In this illustration of a cross-section of skin, normal Merkel cells are shown in red and connect to nerves shown in yellow. The structures drawn include the epidermis (upper third), dermis (middle), and deeper adipose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

Harms, P.W. 2017.

“Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous neuroendocrine malignancy. Merkel cell polyomavirus, a tumorigenic DNA virus, is present in most MCC tumors, with implications for tumor biology, diagnosis, and management. Merkelcell polyomavirus-negative tumors have a high burden of UV-signature mutations, similar to melanoma. The histopathologic diagnosis of MCC requires immunohistochemistry to exclude morphologically similar entities. Therapies for advanced disease are currently lacking. The features of MCC are reviewed, including recent molecular discoveries with implications for improved therapy for advanced disease.”

Incidence of Merkel Cell Carcinoma (MCC) in South Africa

The National Cancer Registry (2014) 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.

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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.

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.

Cogshall, K., Tello, T.L., Norht, J.P. & Yu, S.S. 2018.

"Merkel cell carcinoma (MCC) is an uncommon primary cutaneous neuroendocrine cancer. It most commonly presents as an indurated plaque or nodule on sun-damaged skin in elderly patients and is characterized by high rates of local recurrence and nodal metastasis. Survival at 5 years is 51% for local disease and as low as 14% for distant disease, which underscores the aggressive nature of this tumor and challenges in management. Advances in immunology and molecular genetics have broadened our understanding of the pathophysiology of MCC and expanded our therapeutic arsenal. With this comprehensive review, we provide an update of MCC epidemiology, pathogenesis, clinical presentation, diagnostic evaluation and prognostic markers."

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

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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.

Cassler, N.M., Merrill, D., Bichakjian, C.KI. & Brownell, I. 2016.

“Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin. Early-stage disease can be cured with surgical resection and radiotherapy (RT). Sentinel lymph node biopsy (SLNB) is an important staging tool, as a microscopic MCC is frequently identified. Adjuvant RT to the primary excision site and regional lymph node bed may improve locoregional control. However,

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newer studies confirm that patients with biopsy-negative sentinel lymph nodes may not benefit from regional RT. Advanced MCC currently lacks a highly effective treatment as responses to chemotherapy are not durable. Recent work suggests that immunotherapy targeting the programmed cell death receptor 1/programmed cell death ligand 1 (PD-1/PD-L1) checkpoint holds great promise in treating advanced MCC and may provide durable responses in a portion of patients. At the same time, high-throughput sequencing studies have demonstrated significant differences in the mutational profiles of tumors with and without the Merkel cell polyomavirus (MCV). An important secondary endpoint in the ongoing immunotherapy trials for MCC will be determining if there is a response difference between the virus-positive MCC tumors that typically lack a large mutational burden and the virus-negative tumors that have a large number of somatic mutations and predicted tumor neoantigens. Interestingly, sequencing studies have failed to identify a highly recurrent activated driver pathway in the majority of MCC tumors. This may explain why targeted therapies can demonstrate exceptional responses in case reports but fail when treating all comers with MCC. Ultimately, a precision medicine approach may be more appropriate for treating MCC, where identified driver mutations are used to direct targeted therapies. At a minimum, stratifying patients in future clinical trials based on tumor viral status should be considered as virus-negative tumors are more likely to harbor activating driver mutations.”

Ultentuis, S.E., Louwman, M.W.J., van Akkooi, A.C.J. & Bekkenk, M. 2019.

BACKGROUND: Merkel cell carcinoma (MCC) is a rare and potentially lethal skin-cancer. MCC is known for its potential rapid growth and its propensity to metastasise.

OBJECTIVE: To describe the incidence, treatment and survival of MCC in a population-based setting.

METHODS: All MCC's diagnosed in the Netherlands between 1993 and 2016 were selected from the Netherlands Cancer Registry. Patient and tumour characteristics, therapy and vital status were obtained. Cox' proportional hazards were computed and relative survival analyses were performed.

RESULTS: Our cohort included 1977 patients with MCC. Incidence increased from 0.17/100,000 person-years in 1993 to 0.59/100,000 in 2016. The mean age at diagnosis was 75.5. Most MCC's (59.8%), were treated with surgery alone. Relative five-year survival was low (63.0%) and did not improve. Mortality was higher among males (HR: 1.24, 95%CI: 1.11-1.39), higher age (HR 1.07, 95%CI: 1.06-1.07) and nodal (HR1.26, 95%CI: 1.08-1.48) and distant spread of disease (HR2.44, 95%CI: 1.99-2.99).

LIMITATIONS: We lacked data on cause of death, comorbidity and pathological margins, which may have led to misinterpretation of the data.

CONCLUSION: This study shows continuously increasing incidence rates of MCC in the Netherlands. Survival after MCC diagnosis remained low. Our results emphasise the need for implementation of new therapies.

Drusio, C., Becker, J.C., Schadendorf, D. & Ugurel, S. 2019.

“Merkel cell carcinoma is a rare, highly aggressive skin tumor with neuroendocrine features found in older people. The pathogenesis is associated with immunosuppression, chronic UV light exposure and the Merkel cell polyomavirus. Clinically, Merkel cell carcinoma presents as a solitary, cutaneous or subcutaneous, red to bluish node. Due to early lymphogenic metastasis, locoregional metastases are already present in approximately 30% of cases at the time of diagnosis. The frequent local recurrences as well as the regional and distant metastases usually appear within the first 2-3 years after the initial diagnosis. The first treatment after diagnosis consists of complete surgical removal of the primary tumor with wide safety margins as well as a sentinel lymph node biopsy. Subsequently, adjuvant irradiation of the primary site should be performed. By additional radiotherapy of the

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regional lymph node stations, the rate of locoregional recurrence can be reduced. For systemic therapy of advanced Merkel cell carcinoma checkpoint inhibitors targeted against the PD-1/PD-L1 axis have proven to be highly and durably effective. In contrast the formerly frequently used chemotherapy shows moderate to good response rates but they are as a rule very short-lived.”

Del Marmol, V. & Lebbé, C. 2019.

PURPOSE OF REVIEW: Merkel cell carcinoma (MCC), a rapidly progressing skin cancer, has poor prognosis. We reviewed the epidemiology, pathogenesis, diagnosis and treatment of MCC, with a focus on recent therapeutic advancements.

RECENT FINDINGS: Risk factors for MCC, such as old age, immunosuppression, polyomavirus infection and exposure to UV radiation have already been identified, but the underlying mechanisms leading to carcinogenesis still need clarification. On the basis of recent advances, immunotherapy - in particular, inhibition targeting the programmed cell death protein 1/programmed death-ligand 1 (PD1)/PDL1 immune checkpoint blockade - is currently being investigated in the treatment of metastatic MCC. Avelumab, an anti-PDL1 antibody, was the first drug to be approved internationally as second-line monotherapy for patients with advanced MCC, based on results from the JAVELIN Merkel 200 clinical trial. Avelumab has also recently been approved as first-line treatment for advanced MCC in Europe. Pembrolizumab (anti-PD1) in first-line and nivolumab (anti-PD1) in first-line and second-line treatments are two other checkpoint inhibitors that are under investigation, and showing promising results. New innovative therapies are also in development.

SUMMARY: New insights concerning advances in MCC diagnosis and treatment have been highlighted. Immunotherapy for metastatic MCC constitutes a recent breakthrough in an unmet medical need, but alternative therapies should continue to be investigated.

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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Sources and References Consulted or Utilised

Cassler, N.M., Merrill, D., Bichakjian, C.KI. & Brownell, I. 2016. Merkel Cell carcinoma therapeutic update. *Curr Treat Options Oncol.* 2016 Jul;17(7):36. doi: 10.1007/s11864-016-0409-1.

Coggshall, K., Tello, T.L., Norht, J.P. & Yu, S.S. 2018. Merkel cell carcinoma: an update and review: pathogenesis, diagnosis, and staging. *J Am Acad Dermatol.* 2018 Mar;78(3):433-442. doi: 10.1016/j.jaad.2017.12.001. Epub 2017 Dec 9.

Colebunders, R., Bottieau, E., Van den Brande, J., Colpaert, C. & Van Marck, E. 2004. Merkel cell carcinoma and multiple basal cell carcinoma in an African albino woman with HIV infection. *HIV Medicine* (2004), 5, 452–454.

Del Marmol, V. & Lebbé, C. 2019. New perspectives in Merkel Cell carcinoma. *Curr Opin Oncol.* 2019 Jan 28. doi: 10.1097/CCO.0000000000000508. [Epub ahead of print]

Drusio, C., Becker, J.C., Schadendorf, D. & Ugurel, S. 2019. Merkel Cell carcinoma. *Hautarzt.* 2019 Jan 30. doi: 10.1007/s00105-019-4360-5. [Epub ahead of print]

Harms, P.W. 2017. Update on Merkel Cell carcinoma. *Clin Lab Med.* 2017 Sep;37(3):485-501. doi: 10.1016/j.cl.2017.05.004. Epub 2017 Jun 13.

Mayo Clinic

<http://www.mayoclinic.org/diseases-conditions/merkel-cell-carcinoma/basics/risk-factors/con-20026875>

Memorial Sloan Kettering Cancer Center

<http://www.mskcc.org/cancer-care/adult/merkel-cell-carcinoma/diagnosis-treatment-msk>

Merkel Cell Carcinoma

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<http://www.merkelcell.org/aboutDisease/index.php>

Merkel Cell Carcinoma.Org

<http://www.merkelcell.org/aboutDisease/index.php>

<http://www.merkelcell.org/staging/index.php>

MCC

<http://www.nature.com/nrclinonc/journal/v6/n9/images/nrclinonc.2009.109-f1.jpg>

National Cancer Institute

<http://www.cancer.gov/cancertopics/pdq/treatment/merkelcell/Patient/page1>

<http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials>

Skin Cancer Foundation

<http://www.skincancer.org/skin-cancer-information/merkel-cell-carcinoma>

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Wikipedia

http://en.wikipedia.org/wiki/Merkel_cell_carcinoma

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