Cancer Association of South Africa (CANSA)

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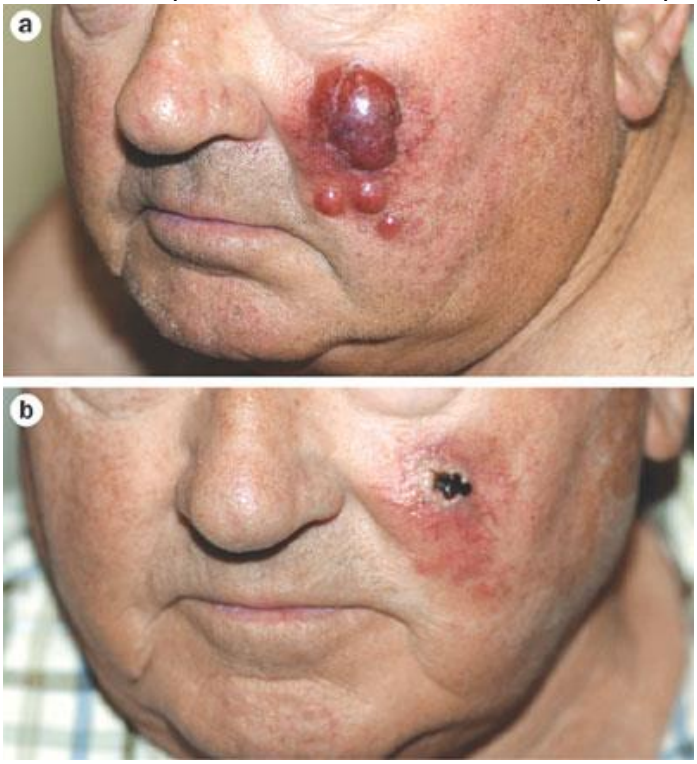
Fact Sheet
on
Merkel Cell Carcinoma

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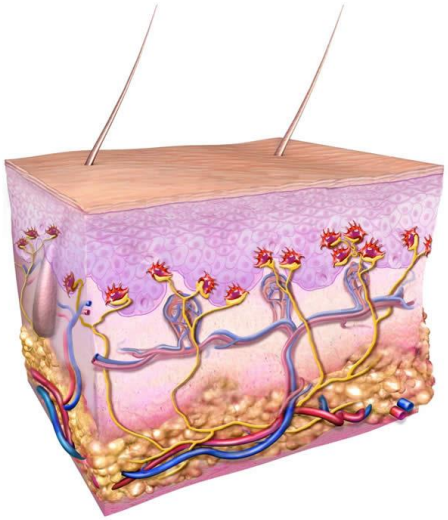
Normal Merkel cells in the skin: In this illustration of a cross-section of skin, normal Merkel cells are shown in red and connect to nerves shown in yellow. The structures drawn include the epidermis (upper third), dermis (middle), and deeper adipose layer containing the fatty tissue. Arteries are depicted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

Incidence of Merkel Cell Carcinoma (MCC) in South Africa

The National Cancer Registry (2012) 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.
(National Cancer Institute; Merkel Cell Carcinoma.Org; Colebunders, *et al*.).

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.

(Mayo Clinic).

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.

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.
(Memorial Sloan Kettering Cancer Center).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.
Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is

processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received. In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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