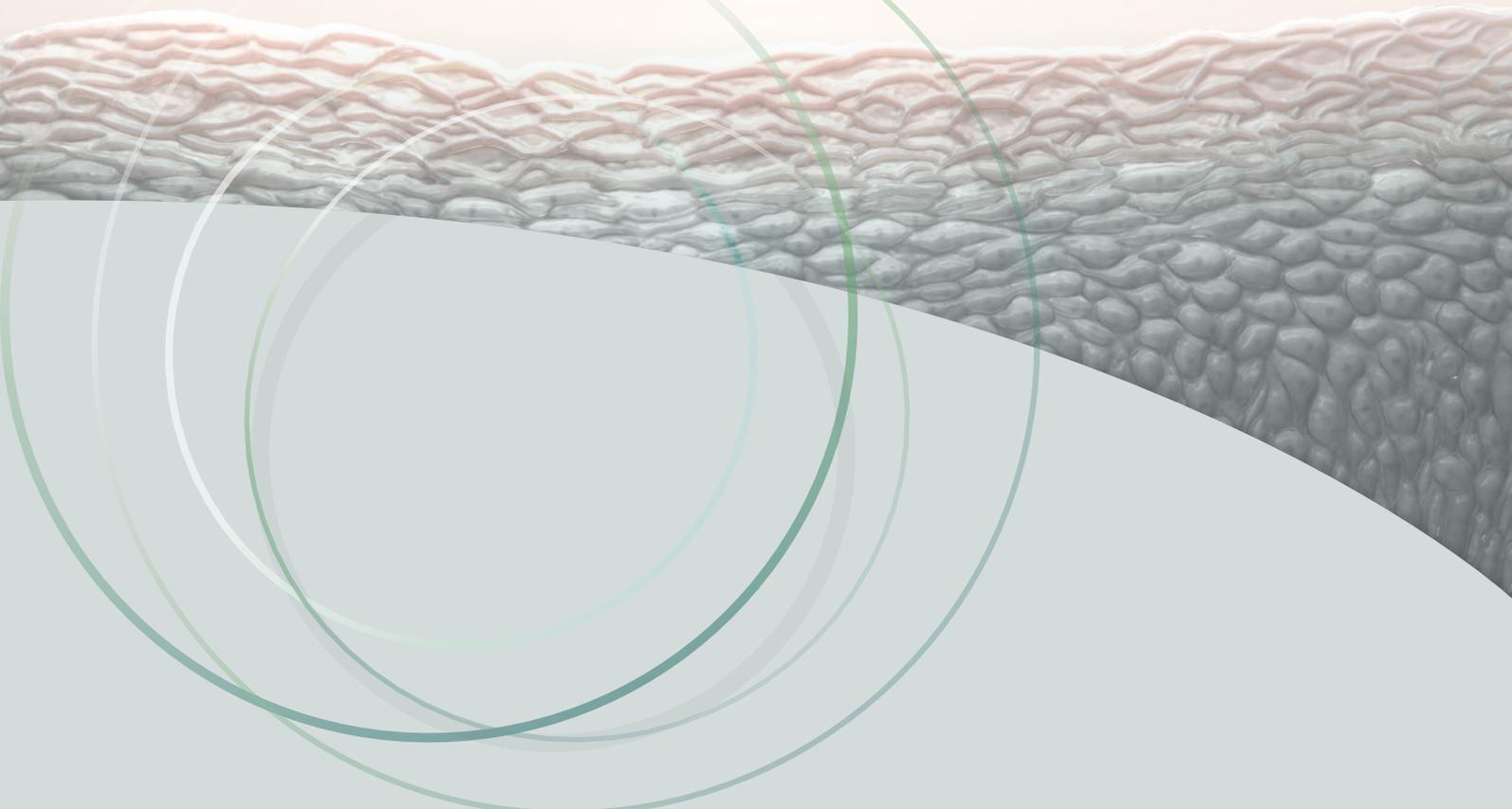


# Information Leaflet for Patients



## **MERKEL CELL CARCINOMA**

### **The aim of this leaflet**

*This leaflet is designed to help you understand more about Merkel cell carcinoma, a type of non-melanoma skin cancer. It tells you what this condition is, what causes it, what it looks like, and what can be done for treatment.*

# MERKEL CELL CARCINOMA

## What is Merkel cell carcinoma?

Merkel cell carcinoma is a rare type of skin cancer. Merkel cell carcinoma has traditionally been thought to arise from the Merkel cells, very specialised cells involved in the sensation of “touch,” located in the basal layer (or deepest layer) of the *epidermis* (the outer epithelial layer of the skin). However, this issue is currently a matter of debate, and research on the exact cells of origin of Merkel cell carcinoma is still going on.

## Who is affected by Merkel cell carcinoma?

Merkel cell carcinoma is rare, as it affects less than 5 out of one million inhabitants each year in Europe, even if its incidence is growing. Overall, Merkel cell carcinoma accounts for less than 1% of *non-melanoma skin cancers*. However, it is crucial to recognize and treat this skin cancer rapidly because of its aggressive behavior.

Merkel cell carcinoma mainly affects males or females aged 50 years and older with a fair complexion. Most patients are approximately 75 years old at the time of diagnosis. People who have medical conditions that impair their immunity (e.g. organ transplant recipients, immunosuppressive medications, and hematological diseases) as well as people with a personal history of sun exposure are at increased risk of developing this type of cancer.

## What causes Merkel cell carcinoma?

In 2008, researchers from Pittsburgh (USA) found that a previously unknown virus was detected in most Merkel cell carcinoma tumors. This virus, therefore named the “Merkel cell *polyomavirus*,” belongs to a widespread group of viruses affecting human and animals called *polyomaviruses*. Some *polyomaviruses* were already known to induce cancers in animals. However, the discovery of the Merkel cell *polyomavirus* was the first description of the association between a human *polyomavirus* and cancer.

Since the discovery of the Merkel cell

*polyomavirus*, it has been shown that the majority of healthy adults actually harbor this virus as a “normal” resident of the skin. Therefore, the Merkel cell *polyomavirus* induces skin cancer in a very small minority of people, and these mechanisms are still under investigation. Impaired immunity in elderly people, together with other factors such as sun exposure, may disrupt the balance between the virus and the host and trigger *oncogenic* (tumour-causing) events. Briefly, the virus *genome* (its genetic material) integrates into the *genome* of the *host cells* of the person affected (living cells that are being invaded) and undergoes some molecular changes, thus impacting key regulators of skin cancer development.

## Can Merkel cell carcinoma be inherited or transmitted?

No, there are no reported cases of hereditary or transmitted Merkel cell carcinoma. The viral *genome* of the Merkel cell *polyomavirus* is integrated into the tumour cells and cannot be transmitted.

Infection with the Merkel cell *polyomavirus* takes place during childhood in the majority of healthy people, without any visible symptoms. The virus lives in the skin during one’s lifetime, though the exact mechanisms and physiological role of this chronic infection are still unclear.

## What does Merkel cell carcinoma look like?

Merkel cell carcinoma presents as a rapidly-growing, painless, firm, shiny, flesh-coloured or bluish-red nodule. It can be located in sun-exposed areas (head and neck), limbs, or



**Fig. 1** Merkel cell carcinoma – rapidly-growing red, firm, painless lump on the sun-exposed skin of the forehead of a 85 year-old man



**Fig. 2** Merkel cell carcinoma – rapidly growing, asymptomatic, red-violet, ulcerated lump on the right buttocks of a 77 year-old woman

trunk. In less than 10% of cases, Merkel cell carcinoma is diagnosed in regional enlarged lymph nodes, without evidence of a skin cancer (an “*occult primary*”).

The characteristics of Merkel cell carcinoma have been summarized by the acronym “AEIOU” (A, for asymptomatic/painless; E, for expanding rapidly; I, for immune suppression; O, for older than 50 years; U, for ultraviolet site on a person with fair skin).

### How is Merkel cell carcinoma diagnosed?

As in other skin cancers, an excisional biopsy is mandatory to make the diagnosis. After local anesthesia, the entire skin tumor is removed and examined under the microscope. Beyond routine histopathology some immunohistochemical *biomarkers* (e.g. *Cytokeratin 20*, *chromogranin A*, and *synaptophysin*) are required to confirm the diagnosis of Merkel cell carcinoma.

### Are additional imaging studies necessary?

Yes, if the diagnosis of Merkel cell carcinoma is confirmed on skin biopsy, then additional imaging is necessary. Indeed, at the time of diagnosis, Merkel cell carcinoma is limited to the skin in about 2/3 of patients, but

there are already lymph nodes involved or even distant metastases in 1/3 of patients. Your clinician will check your entire skin and lymph nodes during the clinical examination.

Ultrasound imaging of the regional lymph node area will detect any abnormal lymph nodes. A whole body imaging (either CT [Computed Tomography]-scan or PET [Positron Emission Tomography]-CT scan) is also useful to exclude any distant *metastasis* (spreading of the cancer) to internal organs. Such imaging is necessary for classification of the disease, according to the AJCC (American Joint Cancer Classification) staging system. Briefly, the AJCC staging distinguishes stages I-II (cancer limited to the skin), stage III (regional *metastatic* lymph nodes), and stage IV (distant *metastases*).

### What is the treatment of Merkel cell carcinoma?

Treatment of Merkel cell carcinoma depends on the AJCC staging. Most stages (I and II) are treated with skin surgery alone. Stage III patients are treated with skin and nodal surgery eventually combined with radiotherapy; besides, adjuvant immunotherapy has been proposed. Patients with stage IV disease undergo either systemic treatments (chemotherapy or better immunotherapy).

# MERKEL CELL CARCINOMA

## Surgery

In most cases (AJCC stages I, II, and III), the skin tumor should be removed with wide “margins” (1-2 cm of surrounding normal tissue) whenever possible. Depending on the size and the location of the skin tumour, your surgeon will choose the optimal way to close the wound (e.g. direct wound closure, skin graft, etc.).

If the pre-operative staging showed any abnormal lymph nodes in the regional drainage area (AJCC stage III disease), your surgeon will also remove all lymph nodes in the area, whether *metastatic* or not.

If the pre-operative staging has NOT shown any abnormal lymph nodes, there can still be microscopic *metastases* (called *micrometastases*) in about 1/3 of cases. Your surgeon will therefore perform a *sentinel lymph node biopsy* to assess this issue. The “first” lymph node of the regional area to receive drainage from the tumour will be identified, collected, and examined under the microscope during the surgical process. If there are any *micrometastases* in this lymph node, complete lymph node removal of the area will be performed. If the *sentinel lymph node biopsy* does not reveal any *micrometastases*, the biopsy wound will be closed with no further surgery of the lymph node area.

## Radiotherapy

After radical surgery, additional radiation can be eventually recommended on the site of nodal surgery. Radiation of the regional lymph node area is discussed on a case-by-case basis, depending on the characteristics of your primary skin cancer, results of the *sentinel lymph node biopsy*, and above all complete lymph node dissection.

## Systemic treatments

To date, there are no recommended systemic treatments in patients with stages I or II disease. However, such treatments can be proposed for patients with stage III or IV disease.

These treatments traditionally include *cytotoxic* (meaning toxic to cells) chemotherapy, mostly a combination of platinum and etoposide administered by infusions, which may be extremely toxic.

Recent advances show that immunotherapy (treatments that stimulate the immune response against cancer) yield promising results in patients with stage III (clinical trials) and IV Merkel cell carcinoma. Immunotherapy with anti-PD-L1 or anti-PD-1 drugs has been proposed as a first-line treatment in such cases with acceptable toxicity.

## Are clinical trials available for Merkel cell carcinoma?

There are many recent advances in the field of Merkel cell carcinoma regarding the understanding of the disease, the role of the Merkel cell *polyomavirus*, and increasing evidence for the role of immunity. Participating in clinical trials will help improve understanding of this rare cancer and can give you the opportunity to get access to innovative treatments. You may ask your clinician about currently available clinical trials in this field.

## What is the recommended follow-up schedule?

Patients with Merkel cell carcinoma should be regularly checked because of the risk of disease recurrence, especially during the three years following initial treatment. Most of the time, a clinical follow-up every 3-6 months for two years and then every 6-12 months thereafter is recommended. The exact periodicity of follow-up as well as additional imaging studies (e.g. ultrasonography, CT scan, PET-CT scan) depends on the AJCC staging at the time of diagnosis and the initial treatment modalities. ■

*While every effort has been made to ensure that the information given in this leaflet is accurate, not every treatment will be suitable or effective for every person. Your own clinician will be able to advise in greater detail.*

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