Merkel Cell Carcinoma:

Information for Patients & Treating Physicians
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Much of the information in this document is also at: www.merkelcell.org
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Example of Merkel cell carcinoma on the hand

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BACKGROUND

What is a Merkel cell?

Merkel cells are found in the skin (see diagram below), where their key function is as touch receptors.

![Normal Merkel cells in the skin](image)

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.

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

What is Merkel cell carcinoma?

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 1500 cases per year in the United States, making it about 40 times less common than melanoma. MCC has the potential to be lethal, and thus prompt aggressive treatment is warranted.

How does Merkel cell carcinoma appear on the skin?

MCC does not have a distinctive appearance (see photographs below). It usually develops on sun-exposed skin (e.g., head, neck, arms) as a painless, firm, flesh-colored to red or blue bump. Frequently, patients seek advice from their doctor because the bump is growing rapidly or the overlying skin is breaking 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 (Heath, 2008).

![Merkel cell carcinoma on the skin](image)

Merkel cell carcinoma on the upper lip, right cheek, and eyelid, respectively (Nghiem)
What are the risk factors for Merkel cell carcinoma?

The exact causes of MCC are not known. Factors strongly associated with development of MCC are:

- Age over 65 years
- UV exposed or fair skin
- History of extensive sun exposure
- Chronic immune suppression (e.g., organ transplantation, HIV/AIDS, leukemia/lymphoma)

The best available information on characteristics of patients with MCC comes from a study of 1,034 patients summarized in the table below (Agelli, 2003). The average (median) age of the patients with MCC was 74 years. The most common sites of involvement were head followed by arms (upper limb). At the time of diagnosis, half of the patients had disease localized to the skin, while the other half had MCC that was no longer confined to the skin.

<table>
<thead>
<tr>
<th>Total Number of Patients = 1034</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
</tr>
<tr>
<td>Age groups (years)</td>
</tr>
<tr>
<td>&lt; 65</td>
</tr>
<tr>
<td>65-74</td>
</tr>
<tr>
<td>≥ 75</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Other/Unknown</td>
</tr>
<tr>
<td>Anatomic site</td>
</tr>
<tr>
<td>Head</td>
</tr>
<tr>
<td>Trunk</td>
</tr>
<tr>
<td>Upper limb</td>
</tr>
<tr>
<td>Lower limb</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
</tr>
<tr>
<td>Localized</td>
</tr>
<tr>
<td>Regional</td>
</tr>
<tr>
<td>Distant</td>
</tr>
<tr>
<td>Unstaged</td>
</tr>
</tbody>
</table>

Patient characteristics. Adapted from Agelli, 2003.
**Age & Merkel cell carcinoma**

The number of MCC cases increases with advancing age. The average age for developing MCC is 74 years, with 75% of patients over the age of 65 years. The incidence of MCC (see graph below) is somewhat greater in men (squares) than in women (circles) for each age group. Thus, advancing age and male gender are risk factors for MCC.

![Graph showing incidence of MCC by age and sex](image)

Frequency of MCC by age & sex: men (square) and women (circle). Adapted from Agelli, 2003.

**Sunlight & Merkel cell carcinoma**

It is believed that ultraviolet radiation from the sun plays a significant role in the development of MCC. This cancer is found most commonly on sun-exposed areas of the body (e.g., head, neck, arms) in older Caucasian individuals, who may also have other sun-induced skin cancers. There is more MCC in sunny climates (Hawaii) as opposed to areas with less sun (Connecticut) (see graph below). Thus, a history of extensive sun exposure is a risk factor for MCC, though MCC can also occur on sun-protected skin (such as hair-covered scalp).

![Graph showing frequency of MCC by UV exposure](image)

Frequency of MCC of the head in Caucasians by UV exposure (Agelli, 2003).
**Immune function & Merkel cell carcinoma**

Patients with weakened immune systems (such as those with HIV/AIDS, organ transplant patients or those with autoimmune diseases who are on medications that suppress the immune system, or people with chronic lymphocytic leukemia (CLL) and certain types of lymphoma) are at significantly higher risk of developing MCC. The risk of developing MCC is increased 8-fold in HIV patients (Engels, 2002), 10-fold in organ transplant patients (Penn, 1999), and 34-fold to 48-fold in CLL (Heath, 2008). Long-term suppression of the immune system (for many years) appears to be a risk factor for MCC in some patients. While patients with profound immune suppression are at a higher risk of developing MCC, over 90% of all people who develop MCC in fact have no known immune deficiency (Heath, 2008).

The immune system is also very important after diagnosis. Patients whose tumors show a robust immune response with certain T cells tend to do better (Paulson 2014), and patients with MCC without a primary tumor (no original skin lesion) also do better, perhaps because their immune systems are able to eliminate the primary tumor (Deneve 2012.) Conversely, patients on medications that reduce immune function (especially T-cell function) may not do as well.

Researchers are currently investigating ways to help boost the immune response to the tumor (see Therapies-Clinical Trials section below). Meanwhile, it is sensible to eat well, exercise, and get plenty of sleep to promote good immune health. Although not proven in humans, some complementary medical approaches aim to improve immune function (see “Treatment: Complementary and Alternative” section below).

**A virus is involved in Merkel cell carcinoma**

A virus was discovered in 2008 to be frequently involved in MCC. This virus is called Merkel cell polyomavirus (MCPyV) (Feng, 2008). The virus was found in 8 of 10 tumors tested, and was associating with the DNA of the tumor cells in such a way to suggest that it is involved in the development of MCC. Since then, many studies have validated these findings, finding MCPyV in anywhere from 80-97% of MCC patients (Becker 2008, Rodig 2012 and others). Interestingly, studies now show that the majority of people are infected with MCPyV by adulthood (Nicol 2013, others). Also, antibodies to this virus (called the capsid protein VP1 antibody) are found in many people (90% of MCC patients and 60% of healthy people, Carter 2009), but MCC patients whose immune systems have “seen” the virus and make this antibody tend to do better than patients who do not make the VP1 antibody. This also suggests the importance of the immune system in fighting the cancer.
Serology

Our lab has developed a test to detect an antibody that recognizes another part of the MCPyV (the T antigen, or “oncoprotein”, which is necessary for most MCCs to grow.) About 50% of newly diagnosed MCC patients have these antibodies in their blood versus <1% of people without MCC (Paulson, 2010). Importantly, we have also found that levels of these antibodies decrease after the cancer is treated, and rise again if the disease comes back. This test can be sent to the University of Washington (see http://www.merkelcell.org/sero/index.php for details). For the 50% of patients who do not have this antibody, we continue to rely more on scans (CT, PET) for disease monitoring. Although controversial, having an immune response, as measured by making antibodies, tends to be associated with modestly improved survival.

The study of this associated polyomavirus and how it plays a role in MCC is an ongoing, exciting area of research. Research continues into the role of this virus and possible ways to help “boost” the immune system’s ability to fight the cancerous cells.

Proposed mechanism of viral infection and association with MCC development: Most people are infected with MCC earlier in life, and produce capsid antibodies. Other factors including immune system dysfunction and UV damage may lead to development of MCC. At time of diagnosis of MCC, ~50% of patients make antibodies to MCPyV T-antigen (oncogene). These levels fall after treatment but may rise again with disease recurrence or metastasis.
The diagnosis of MCC is made with a skin biopsy, which is examined under the microscope. Special stains are used to distinguish MCC from other forms of cancer, such as small cell lung cancer (SCLC), lymphoma, and small cell melanoma. Each of these cancers has a unique profile as defined by special stains (see table below). MCC will typically stain positive for low molecular weight cytokeratins (CAM 5.2 or AE1/AE3), CK 20 and neuron-specific enolase (NSE) (see photographs below). The majority of tumors also stain positive for αMCPyV T-Ag (the viral oncogene discussed above.) MCC will typically not stain for CK7 or thyroid transcription factor 1 (TTF-1) (positive in SCLC), leukocyte common antigen (LCA) (positive in lymphoma) and S100 (positive in small cell melanoma).

**Microscopic analysis of biopsy of MCC**
MCC as stained by A) hemotoxylin & eosin, B) CAM 5.2, C) CK 20, D) NSE, and E) αMCPyV T-Ag (Goessling, 2002 & Nghiem, 2001 and 2014)

<table>
<thead>
<tr>
<th>Biopsy Characteristics for MCC and Tumors Resembling MCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>MCC</td>
</tr>
<tr>
<td>SCLC</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Melanoma</td>
</tr>
</tbody>
</table>

SCLC = small cell lung cancer
STAGING

*Lymphatic spread*

MCC can spread through the body (metastasize) via the lymphatic system, which is a system of vessels and lymph nodes throughout the body (see diagram below). The lymphatic circulation serves an important function in the immune system. Lymph nodes act as filters to trap cancer cells as they travel through the lymphatic vessels. The lymph nodes that filter the legs are in the inguinal region between the thigh and the abdomen. The lymph nodes that filter the arms are in the armpit (axilla). Those that drain the skin of the face can be under the chin (submandibular), along the neck (cervical), or around the ears (pre/post-auricular).

*Schematic representation of the lymphatic system.* MCC cells can travel from the primary site through the lymph vessels to the sentinel (first) lymph node. Note that a MCC on the leg will likely drain to the inguinal (groin) lymph nodes on the same side; a primary on the arm will drain to the armpit (axilla); MCC on the trunk can drain to the closest axilla or inguinal bed, or multiple beds unpredictably; a primary on the face can drain to many different areas (submandibular, pre- and post-auricular, pre- and post-cervical). Adapted from Perrott, 2003.
**Sentinel lymph node biopsy**

MCC can travel from the skin, through the lymphatic vessels, to the sentinel lymph node. The sentinel lymph node is the first lymph node to which MCC would travel. If a lymph node feels enlarged, it may contain MCC (macrometastases). Sometimes, lymph nodes may contain MCC, but not feel enlarged (micrometastases). Lymph nodes should be removed (biopsied) to determine if MCC is present.

There is a technique to identify the sentinel lymph node when it cannot be felt on physical exam. A blue dye and a safe radioactive tracer are injected at the site of the primary lesion. Within 5 to 10 minutes, the dye and tracer travel along the same path that cancer cells would spread through the lymphatic vessels and collect in the sentinel lymph node (see figure below). An instrument that detects the tracer is used to map the path from the skin to the sentinel lymph node. The sentinel lymph node is removed and examined for the presence of MCC. If MCC is not found in the sentinel lymph node, then the chance that it has spread beyond the skin is lower.

The "sentinel lymph node biopsy" technique has a low risk of significant side effects, provides useful information on the chance of spread, helps determine if treatment is needed in the draining node bed, and identifies the lymph node region containing the sentinel lymph node (draining lymph node basin), which is sometimes difficult, especially for lesions on the trunk or head and neck.

**Mapping a sentinel lymph node.**
A radioactive tracer was injected at the site of a skin cancer on the left flank. The tracer traveled along the lymphatic vessels to a lymph node in the left groin and was then photographed using a special x-ray technique. This procedure allows the surgeon to identify the sentinel lymph node and remove it for pathologic analysis. *Adapted from Perrott, 2003.*
Metastases (distant spread)

A physical exam may reveal a new skin lesion, an enlarged lymph node, or an enlarged liver that may signal the spread of MCC. A lesion of metastatic MCC may appear as a 1-3 cm, flesh-colored to red-purple bump that feels firm, is deeper compared to the primary lesion, and grows rapidly over a period of 2-4 weeks. See table below for common sites of MCC metastasis. Blood tests, such as liver function tests (LFTs), may be used to detect the spread of MCC to internal organs, such as the liver. If a doctor is suspicious of distant metastases, he or she may use non-invasive imaging techniques, such as chest X-rays, CT (computed tomography) scans, and PET (positron emission tomography) scans.

<table>
<thead>
<tr>
<th>Metastatic site</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>28</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>27</td>
</tr>
<tr>
<td>Liver</td>
<td>13</td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
</tr>
<tr>
<td>Bone</td>
<td>10</td>
</tr>
<tr>
<td>Brain</td>
<td>6</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>2</td>
</tr>
<tr>
<td>Pleura</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
</tbody>
</table>

Metastatic sites of MCC. Adapted from Voog, 1999.

In patients who are found to make antibodies to the MCPyV oncogene (the T-antigen antibody) at the time of diagnosis, monitoring of the level of antibodies can help detect early recurrence or metastasis.
What are Merkel cell carcinoma "stages"?

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 centimeters, 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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Tumor</th>
<th>Lymph Node</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>In situ primary tumor</td>
<td>No regional lymph node metastasis</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IA</td>
<td>Less than or equal to 2 cm maximum tumor dimension</td>
<td>Nodes negative by pathologic exam (biopsy)</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IB</td>
<td>Less than or equal to 2 cm maximum tumor dimension</td>
<td>Nodes negative by clinical exam* (no pathologic node exam performed)</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IIA</td>
<td>Greater than 2 cm tumor dimension</td>
<td>Nodes negative by pathologic exam</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IIB</td>
<td>Greater than 2 cm tumor dimension</td>
<td>Nodes negative by clinical exam* (no pathologic node exam performed)</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IIC</td>
<td>Primary tumor invades bone, muscle, fascia, or cartilage</td>
<td>No regional lymph node metastasis</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IIIA</td>
<td>Any size tumor (includes invading tumors)</td>
<td>Micrometastasis**</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IIIB</td>
<td>Any size tumor (includes invading tumors)#</td>
<td>Macrometastasis*** -OR- In transit metastasis****</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>IV</td>
<td>Any size tumor (includes invading tumors)</td>
<td>Any lymph node metastasis</td>
<td>Metastasis beyond regional lymph nodes</td>
</tr>
</tbody>
</table>

* 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 tumor 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.

Adapted from AJCC’s Cancer Staging Manual 2009

# In the upcoming AJCC staging system, stage IIIB may be divided into known and unknown primary tumor

MCC is divided into stages depending on the severity of disease (see Table above). The stage at diagnosis is a major determinant of the chance for spread (metastasis), treatment options, and chance for recovery (see “Prognosis” section below).
PROGNOSIS IN MERKEL CELL CARCINOMA

Overall survival (MCC specific) for 426 Merkel cell carcinoma patients by stage in the University of Washington, Seattle cohort, through June 2014.

Several factors other than stage may affect prognosis.

**Clinical factors**
Though most patients with MCC have a primary (original) skin lesion, almost 20% are diagnosed after the cancer first appears elsewhere, such as in a lymph node or another organ. These cases are called “unknown primary”. Several studies have shown that MCC patients with unknown primaries have increased survival (Foote 2012, Tarantola 2013). In these patients, the immune system may have eliminated the primary tumor, and is “primed” to fight the cancer elsewhere. More research into this association, as well as into therapies to help MCC patients fight the cancer, continues.

**Findings on histology**
Patients with MCC whose tumors show a specific immune response with “tumor infiltrating lymphocytes (CD8 type) tend to do better (Paulson 2014).

Lymphovascular invasion (LVI) is where the tumor is found on histology (or tissue examination under the microscope) to be invading the blood vessels or lymph channels. Though this remains controversial, some studies show that patients with MCC tumors with LVI may do worse than those whose tumors lack this finding (Andea 2008). Researchers continue to investigate.
TREATMENT

Overview
Optimal therapy for MCC remains controversial. The best summary for current recommendations is available via the National Comprehensive Cancer Network (http://www.nccn.org); these guidelines are updated annually and can also be found at www.merkelcell.org/usefulinfo/index.php.)

Treatment is generally based on the stage of the disease. There are four major treatments for MCC: 1) surgical excision of the primary lesion, 2) lymph node surgery, 3) radiation therapy, and 4) chemotherapy. Each will be reviewed below in greater detail. Depending on how well a patient tolerates the treatments, surgery, radiation therapy, and chemotherapy may be given at the same time or one after the other.

For most cases of MCC, excision of the primary lesion with a greater than or equal to 2 cm margin (wide surgical excision) may be a recommended part of care. As discussed above, it is important for almost all cases in which there is no obvious lymph node disease to also undergo sentinel lymph node biopsy at the time of wide surgical excision to determine whether or not microscopic disease is present. When microscopic disease is found, radiation of the affected nodes, or surgical removal of the remaining lymph nodes in a draining lymph node basin (lymph node dissection) may be indicated and often results in a high 'cure' rate for the affected nodal region.

We typically recommend radiation therapy to the site of the primary lesion and to the draining lymph node basin in stage I, II and III disease. Chemotherapy should be reserved for patients with stage IV disease.

Metastatic disease should be treated with radiotherapy and/or chemotherapy. The purpose of treatment in stage IV disease is palliative. Palliative therapy is given to relieve symptoms, such as pain, and to help patients live more comfortably.

It is important to emphasize that optimal care depends on many issues that are highly variable between patients. It is thus important to obtain care from a multi-disciplinary team of physicians with significant experience with this disease and who take into consideration many factors such as: overall health of the patient, immune suppression, node status, tumor size and location, age, and the patient's personal philosophy in making decisions affecting quality vs. quantity of life.

Wide surgical excision

The goal of wide excision is to control local recurrence and lymph node metastases. MCC should be removed with clear margins as judged by pathology examination. As noted below however, even with margins >2cm, surgery alone has a very high recurrence rate - up to 42%, depending on the study. This recurrence rate can typically be cut in half or better by the addition of radiation therapy.

To optimize the appearance and function of your scar, your surgeon may make an excision in the shape of a football (ellipse). The length of your scar will be roughly three times the diameter of the excision around the tumor (when possible, the excision is usually 2 cm beyond the tumor). Therefore, the scar may be up to 8 times as long as the width of the original MCC tumor.

Schematic of wide surgical excision with MCC shown in gray.
Depending on a patient’s general health and the location of the MCC, surgery may not be possible. In that case, radiation therapy may be used alone. A recent study suggests that radiation therapy alone may be as effective as both radiation therapy and surgery (Mortier, 2003.)

Finally, no evidence exists that extremely wide excision margins improve overall survival. Overly aggressive surgical treatment (such as amputation or wide margins in cosmetically sensitive areas like the eyelid) does not appear to improve outcomes and may cause post-operative complications and lead to delay in radiation treatment.

**Mohs micrographic surgery**

Cutaneous neoplasms that develop on the head & neck are more likely to recur and metastasize via lymphatics to regional lymph nodes. It may not be possible to excise some MCCs on the face with a margin of at least 2 cm. For these reasons, sometimes doctors may recommend Mohs micrographic surgery. Mohs micrographic surgery allows for conservation of skin to maintain function and appearance of sensitive areas of the body (such as the face). Complete removal of the MCC is evaluated under the microscope during surgery. Our analysis of published studies on the treatment of MCC suggests that as in wide local excision (discussed above), radiation therapy needs to be added to Mohs micrographic surgery to optimize control of the disease. Addition of radiation therapy to Mohs micrographic surgery appears to reduce recurrence by roughly one-half (see table below, adapted from Longo & Nghiem, 2003).

**Radiation therapy**

Radiation therapy, also referred to as radiotherapy or XRT, is the treatment of cancer with penetrating beams of energy waves or streams of particles that can destroy cancer cells. Radiation therapy is delivered to the cancer cells and a small margin of surrounding normal tissue, sometimes referred to as the radiation field. Radiation therapy damages the genetic material of cancer cells making them unable to grow. Radiation therapy also damages healthy cells in the field of radiation. Adjuvant radiation therapy is radiotherapy that is used to destroy any cancer cells that may remain after surgery and/or chemotherapy.

We typically recommend radiation therapy to the primary site in the vast majority of cases as well as to the draining lymph node basin (for stage III disease). This recommendation is based on numerous studies showing marked improvement in control of disease at the primary site and in the draining lymph node basin when radiation therapy is added (Lewis, 2006).

<table>
<thead>
<tr>
<th>Treatment (n)</th>
<th>Local Recurrence</th>
<th>% Nodal Recurrence</th>
<th>Distant Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery only (429)</td>
<td>24.5%</td>
<td>44.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Surgery + Radiotherapy (156)</td>
<td>9.6%</td>
<td>13.2%</td>
<td>6.8%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>.62</td>
</tr>
</tbody>
</table>

Adapted from Lewis, 2006.
Local recurrence is 3.7 times more likely in MCC patients treated with surgery only vs those treated with radiation and surgery (Adapted from Lewis, 2006)

Our analysis of the available literature and our experience caring for patients with MCC suggest that radiotherapy (XRT) is associated with a statistically significant improvement in local and nodal recurrence. Where wide excision of the primary is not feasible, XRT alone may be considered (Mortier 2003). Additionally, if surgical treatment of nodal disease is not possible, XRT alone may be as effective as completion lymphadenectomy and radiation (Fang, 2010). Overall, data supports a role for XRT to the primary site and draining lymph node basin in most cases of stage I, II, and III disease.

XRT is measured in units called Gray (Gy). The total dose of radiation therapy should be greater than or equal to 50 Gy. Radiation therapy is usually administered in a doctor's office in divided doses for 10-15 minutes, 5 days a week (e.g., Monday - Friday) over a set number of weeks (e.g., 5 weeks).

**Low-risk MCC patients who may benefit less from adjuvant radiation**

Patients who have very low risk disease, as defined by having all of the favorable features below, may be likely to benefit less from adjuvant radiation therapy. However, research is ongoing in this area. At this time, we recommend a careful discussion with patients regarding the risks and benefits of radiation in these cases.

**Favorable features**

1) Primary tumor ≤ 2 cm in largest dimension
2) Negative sentinel lymph node biopsy
3) No chronic immune suppression (HIV disease, leukemia/lymphoma, organ transplant)
4) No lymphovascular invasion in the primary tumor (a pathologist may need to go back to the original biopsy and specifically comment on this feature's presence or absence).
5) Confidently negative microscopic margins after excision

In our lab, we have found that in these “low risk” patients, radiation to the site of the primary tumor and surrounding area after surgery may reduce risk for local recurrence. Out of 61 patients, 0/36 who underwent radiation and surgery developed recurrence, while 4/25 (16%) of patients who only had surgery and did not receive radiation developed recurrence. Thus, as above, we recommend discussion with the patient and treatment team regarding XRT therapy in these cases.
**Possible side effects of radiation therapy**

Possible side effects of radiation therapy in the area being treated include loss of hair, skin irritation (like a sunburn), and changes in the color and texture of the skin. If given in the face/neck, decreased saliva or tear production, altered taste sensations and transient ulcers are common and significant side effects. Radiation to a draining lymph node basin may cause swelling of the arm or leg on the same side that may be long lasting in unusual cases. A frequent side effect is fatigue, which usually resolves soon after the radiotherapy is stopped. Accordingly, it is important to eat a well-balanced diet and get plenty of rest. A radiation oncologist may adjust the dose or schedule of radiation therapy based on these side effects.

**Chemotherapy**

Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. These drugs target cells that divide quickly, including cancer cells that grow and multiply without control as well as healthy cells that divide rapidly. Chemotherapy drugs may be given intravenously or orally on certain days of the week over a set number of weeks. For example, a patient may receive chemotherapy Monday, Wednesday and Friday on weeks 1, 4, 7 and 10.

Combination chemotherapy is when two or more drugs are given at the same time because they are more powerful in combination than either individual drug. MCC has similarities to other neuroendocrine carcinomas, such as small cell lung cancer. For this reason, a medical oncologist may use drugs that have shown effectiveness against small cell lung cancer. Etoposide and carboplatin is one such regimen.

Information on treatment with chemotherapy (etoposide and carboplatin) comes from a study of 53 patients that demonstrated a 76% overall survival at 3 years in patients treated with both chemotherapy and radiotherapy (Poulsen, 2003). It is not possible to determine from this study whether adjuvant chemotherapy improves outcomes because 1) the survival was essentially unchanged from that expected for a group of similarly staged patients and 2) it was not randomized.

The decision to use chemotherapy should be made after careful discussion with the oncologist and medical team as its benefits may not be clear. In one study of 76 MCC patients with lymph node disease, there appeared to be a difference in outcome in those who were treated with chemotherapy versus those who were not. This trend was not statistically significant and the study was not randomized, but the study suggests chemotherapy may not positively affect survival (Allen, 2005).

![Comparison of disease-specific survival in patients with lymph node disease who either received (23 patients) or did not receive (53 patients) chemotherapy. Adapted from Allen, 2005.](image)
Generally chemotherapy is reserved for patients with metastatic (Stage IV) disease where surgery and radiation therapy cannot be used. Often, the use of chemotherapy is palliative, meaning that the goal is to make a patient feel better and not for a complete cure.

You may also ask your medical oncologist about promising new medications for MCC (clinical trials). You may wish to visit the NIH Clinical Trials for Cancer website: www.cancer.gov/clinicaltrials

**Possible side effects of chemotherapy**

Possible side effects, also referred to as toxicities, of chemotherapy result from harm to healthy cells, particularly those that divide rapidly. Most patients experience some degree of hair loss, nausea, vomiting and fatigue. A serious side effect may be suppression of the bone marrow's ability to make blood cells. This can lead to lower blood counts, causing anemia, as well as decreased ability of the immune system to fight infection. However, healthy cells usually repair themselves once the chemotherapy drug is stopped. A doctor will monitor these side effects and adjust the dose and schedule of the treatment accordingly. The better a patient’s general health is, the more easily the body will be able to tolerate the side effects of chemotherapy.

**The following are reasons that adjuvant chemotherapy may not be routinely recommended. In the absence of definitive data, the decision to use chemotherapy should be customized to each situation and should be discussed with your medical team.**

"Adjuvant" chemotherapy is used to destroy any cancer cells that may remain after surgery and/or radiation therapy have cleared all detectable cancer cells.

1. Mortality (deaths): Two studies showed an acute death (mortality) rate of 4-7% in MCC patients treated with chemotherapy. This is partly due to the fact that MCC patients are often elderly and less able to tolerate side effects such as increased infection risk (Voog 1999; Tai 2000).

2. Morbidity (side effects): Neutropenia (low white blood cell count) occurs in 60% of patients and can lead to fever and sepsis (infection in the blood) in 40% of patients (Poulson 2001).

3. Decreased quality of life: this can be quite severe in older patients, causing symptoms such as fatigue, hair loss, and nausea/vomiting.

4. Resistance to chemotherapy: Merkel cell carcinoma that recurs after chemotherapy is less responsive to later palliative chemotherapy.

5. Immunity: chemotherapy suppresses immune function, which is known in general to be very important in preventing and controlling MCC. The fact that a virus has been found to be associated with MCC further highlights the especially important role of the immune system in controlling MCC.

6. Apparent poorer outcomes: In one study of 53 patients with nodal disease, survival was higher in patients who did not receive chemotherapy (60% survived, versus 40% of MCC patients who did receive adjuvant chemotherapy (Allen 2005)). While this was not a randomized trial and was not statistically significant, it certainly does not suggest a survival benefit for administering adjuvant chemotherapy.
**Follow-up care**

Merkel cell carcinoma is optimally cared for by a team of doctors from dermatology, surgery, medical oncology, and radiation oncology. Most recurrences of MCC and most deaths from this disease occur within the first 3 years.

Patients should have regular appointments for skin and lymph node examinations every 3-6 months for the first 3 years. CT or PET scans are sometimes performed every 6 months for a few years after a high-risk diagnosis. For patients who are found to make antibodies to the MCPyV T-antigen oncoprotein, serial monitoring of the blood antibody levels may also be useful. Unfortunately, by the time MCC is visible on imaging, curative treatment is often not possible, so scans are not always recommended for every patient. However, in appropriate cases, early detection of recurrence allows prompt discussion of treatment and potentially better control of metastases or recurrent disease.

If MCC has not recurred or metastasized in the first three years, it may not be necessary to visit a doctor as often. However, you should contact your doctor immediately if you have any unusual lesions or symptoms.

**Future directions**

There are several exciting clinical trials in development for MCC, and many groups are looking at better methods for detection and treatment of MCC, including medications to boost the immune response to the cancer. For instance, our group will soon have a trial for a medication called pembrolizumab (Keytruda), a drug that may boost the immune response to the tumor. Other medications are under investigation as well. You may wish to ask your oncologist about these new therapies as well as available clinical trials. Please also see the NIH website for clinical trials (below).

**Other Resources**

Many of our patients have found useful information on our website, which we keep updated with current data and referral center availability.

Http://www.merkelcell.org

*A copy of this handout in an easy-to-print PDF format can be found on the website as well.*

You may also wish to read about available clinical trials in MCC:

www.clinical trials.gov

(Search for “Merkel Cell Carcinoma” or “Merkel Cell Cancer”)
Complementary & Alternative Therapies

Patients often ask what complementary & alternative approaches to traditional therapies are available for MCC. No studies have been done to test these approaches, but some of our patients have used alternative therapies and are very happy with them. We also routinely encourage our patients to augment their physical activity through daily participation in their favorite forms of exercise. Please remember that this information alone can't take the place of health care or human services you may need. **Because of possible adverse side effects and drug interactions, we strongly encourage you to consult your primary physician and oncologist before starting any new treatment regimen and to notify your doctors and pharmacists of any supplements you are taking.**

Consultation with a Naturopathic Physician

**Dr. Daniel Rubin of Scottsdale, AZ,** has cared for several of our MCC patients and employs an integrated approach to diet and nutritional supplementation that he has customized for neuroendocrine carcinomas such as MCC. **We have no financial links with Dr. Rubin.** He is able to do phone consultations for those who cannot travel to Arizona. Please visit our website for a downloadable information sheet. His office phone is 480-990-1111.

Optimizing Fruit & Vegetable Intake

It is universally agreed that eating fresh fruits and vegetables and having a healthy diet is good for general health including immune system function. It is, however, often difficult to get enough fruits and vegetables in a standard diet. Several of our patients are attempting to optimize their fruit and vegetable intake through "juicing." Visit our website for a downloadable pdf sample regimen from one of these patients: [http://www.merkelcell.org/treatment/documents/JuicingGuidelines10Jul08.pdf](http://www.merkelcell.org/treatment/documents/JuicingGuidelines10Jul08.pdf).

Nutritional Supplements

Several of our patients take supplements to improve their nutritional status and augment the immune system. Animal data exists that certain medicinal mushrooms can augment some aspects of immune function. Some of the supplements patients have told us about include Host Defense MyCommunity Capsules (available from [http://www.fungi.com/](http://www.fungi.com/)) and ImmunoPower pills and powder supplements. **Please note that we are not recommending or endorsing these products but are passing along information that our patients have used and liked. Please consult with your physician prior to beginning any nutritional supplementation program as some supplements can interact with certain medications.**
CONSULTATION

Referral Center:
Paul Nghiem, MD, PhD
Seattle Cancer Care Alliance
825 Eastlake Ave E.
Seattle, WA 98109
Telephone: (206) 288-1024
http://www.seattlecca.org/

(For other centers, please see an updated list at http://www.merkelcell.org/referral/index.php)

HOW YOU CAN HELP

Whether you are a patient, family member or physician, please let us know if this information has played a role in your management of this disease. Your written note to the Seattle address above or to pnhiem@u.washington.edu will be helpful in assessing the impact of these educational efforts. Please indicate what you found most useful as well as ways we can improve this information resource.

Research

Our efforts to provide optimal care for patients will greatly benefit by better data. Where possible, please participate in clinical trials and or participate in databases that allow researchers to follow your progress and know what therapies you have had. You can get information to participate in our studies at:


Financial Gifts

The generation of our website and this handout, payment of monthly server fees, payment of fees to publishers whose data we reprint altogether cost several thousand dollars. We are also generating a database of MCC patients and are conducting laboratory studies on MCC. Your financial gift to support these endeavors would be most appreciated and help us to carry out these activities that we feel will benefit many people as they search for high quality, interpretable information on this rare, dangerous disease.

If you are interested in supporting our efforts with a financial contribution, please contact Dr. Nghiem's office at 206-221-4594. Your contribution will help make these and future efforts possible. Your contribution is fully tax deductible, and 100% of your donation will go directly to our research and educational efforts.

Please visit our website for more information: http://www.merkelcell.org/help/index.php
DISCUSSION POINTS

*Issues to discuss with your physicians:*

Is pathologic diagnosis confirmed?

What is the clinical stage?

Prognosis?

Further surgery?

Sentinel lymph node biopsy?

Radiation therapy to primary site?

Radiation therapy to lymph nodes?

Chemotherapy?

Scans?

Follow-up?
ABOUT US

Why did we write this?

We have assembled this information to answer frequently asked questions about Merkel cell carcinoma (MCC). Since MCC is an uncommon cancer, few patients are familiar with the disease and few doctors are familiar with its treatment. Easy access to understandable information is often difficult to obtain. In this resource, we have combined our review of the best available literature and our experience caring for over 1000 patients with MCC at the Dana-Farber Cancer Institute and the Seattle Cancer Care Alliance. This information is designed to facilitate key therapeutic decisions that need to be made within days to weeks of the initial diagnosis of MCC. Please discuss any questions that you may have about the information presented below with your doctor, or feel free to share a copy of this document with your medical team.

Who created this handout?

Sheela Gupta, MD. Dr. Gupta graduated from Boston University School of Medicine and from Harvard/Massachusetts General Hospital Dermatology Residency Program in 2009. She has a faculty appointment at Brigham and Women's Hospital and Harvard Medical School.

Linda Wang, MD, JD. Dr. Wang is on staff at the Brigham and Women's Hospital and the Dana-Farber Cancer Institute in Boston, serving as the Clinical Director of the Cutaneous Oncology Disease Center at the Dana-Farber Cancer Institute. She is the Principal Investigator for the MCC database project at the DFCI and is an Assistant Professor of Dermatology at Harvard Medical School.

Erica Shantha, MD. Dr. Shantha completed her internship in Seattle at Virginia Mason and is a clinical research fellow in Dr. Nghiem's lab with an interest in dermatology.

Teresa Fu, MD. Dr. Fu is completing her dermatology residency at Stanford University and worked with Dr. Nghiem to learn more about MCC and other high-risk cutaneous malignancies.

Jayasri Iyer, MD. Dr. Iyer trained as a dermatologist in India and moved to Seattle in 2008, where she worked in Dr. Nghiem’s lab on the immune response to MCC and the MCPyV.

Bianca Lemos, MD. Dr. Lemos was a research fellow with Dr. Nghiem from 2006-2009 and completed her residency in dermatology at Emory University in Atlanta.

Paul Nghiem, MD, PhD. Dr. Nghiem is a dermatologist/scientist who moved 'back home' in 2006 from the Dana-Farber Cancer Institute to the Seattle Cancer Care Alliance. He specializes in skin cancers with a particular interest in optimizing the management of patients with Merkel cell carcinoma. He has cared for over 400 patients with MCC and has read, lectured, and written about this uncommon and challenging disease. Dr. Nghiem conducts basic science research on cancer biology at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle. His publications on MCC can be viewed at http://pnlab.org/clinical/MerkelCellCarcinoma.php. With a goal of defining more optimal treatment for MCC, he is maintaining a clinical database and tumor bank to better analyze this rare disease using funding from the American Cancer Society and the National Institutes of Health. In addition, he is leading genetic studies to further understand the biology of MCC. He has also founded the MCC Multicenter Interest Group (MMIG), with representatives from over 30 institutions to pool resources and expertise on this challenging cancer.
LITERATURE REFERENCES


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