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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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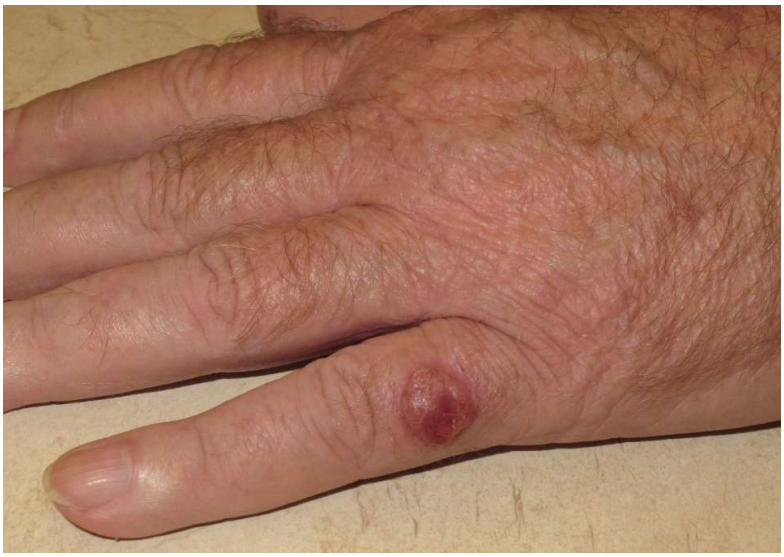


Example of Merkel cell carcinoma on the hand

Table of Contents ***Page***

Background	*3-7*
Diagnosis	*8-11*
Serology	*12-13*
Staging	*14*
Treatment	*15-22*
Prognosis & Follow-Up	*23-27*
Consultation	*28*
How You Can Help	*28*
About Us/Contact Information	*30*
Literature Reference	*32*

Quick summary

What is Merkel Cell Carcinoma (MCC)? (see page 3)

Rare (2,500 cases/year in US) and aggressive skin cancer that arises from uncontrolled growth of cells that share some characteristics with normal Merkel cells of the skin.

What causes MCC? (see page 5)

The exact causes are not known.
Associated factors: age > 65, fair skin, history of extensive sun exposure, chronic immune suppression (though 90% of MCC patients are not immune suppressed), and the **Merkel cell polyomavirus in ~80% cases.**

What is the next step of my MCC care?

- Note: You may not undergo all of these steps or may have extra treatments depending on your medical condition.

Diagnosis/Staging	Treatment	Surveillance
□ Biopsy / WLE □ SLNB □ Scan (CT, PET/CT)	□ Surgery □ Radiation □ Systemic therapy	□ Physical exam □ Scan □ Serology

What is the Merkel cell polyomavirus antibody test? (see page 12)

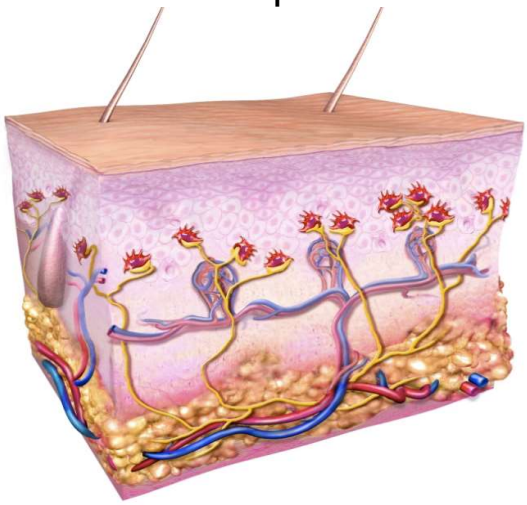
Issues to discuss with your physicians:

What are your concerns and goals?
Is pathologic diagnosis confirmed?
What is the stage? Prognosis?
Further surgery? Sentinel lymph node biopsy?
Radiation therapy to primary site? Radiation therapy to lymph nodes?
Systemic therapy?
Palliative treatment?
Scans? Follow-up?

ABOUT THE DISEASE

What is a Merkel cell?

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



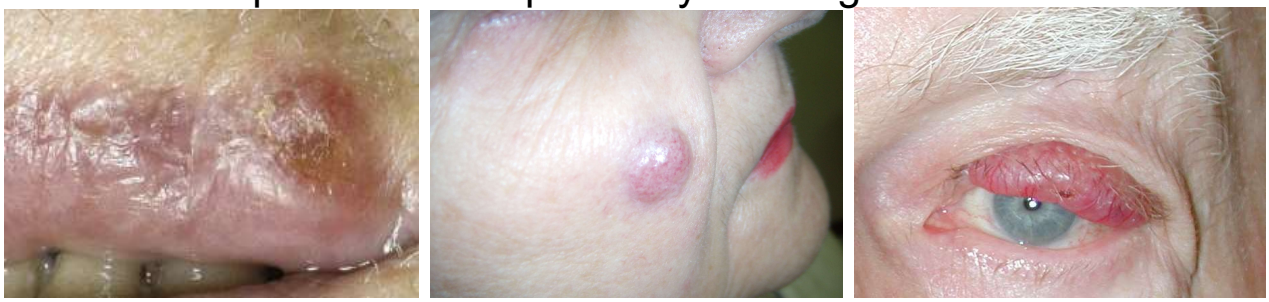
Normal Merkel cells in the skin: in this illustration of a cross-section of skin, normal Merkel cells are shown in red and connect to nerves shown in yellow. The structures drawn include the epidermis (upper third), dermis (middle), and deeper adipose layer containing the fatty tissue. Arteries are depicted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

What is Merkel cell carcinoma?

Merkel cell carcinoma (MCC), sometimes referred to as a neuroendocrine carcinoma of the skin, arises from uncontrolled growth of cells in the skin that share some characteristics with normal Merkel cells of the skin. It is a rare skin cancer with roughly 2500 cases per year in the United States, making it about 30 times less common than melanoma. MCC has the potential to be lethal, and thus prompt aggressive treatment is warranted.

Appearance of Merkel cell carcinoma

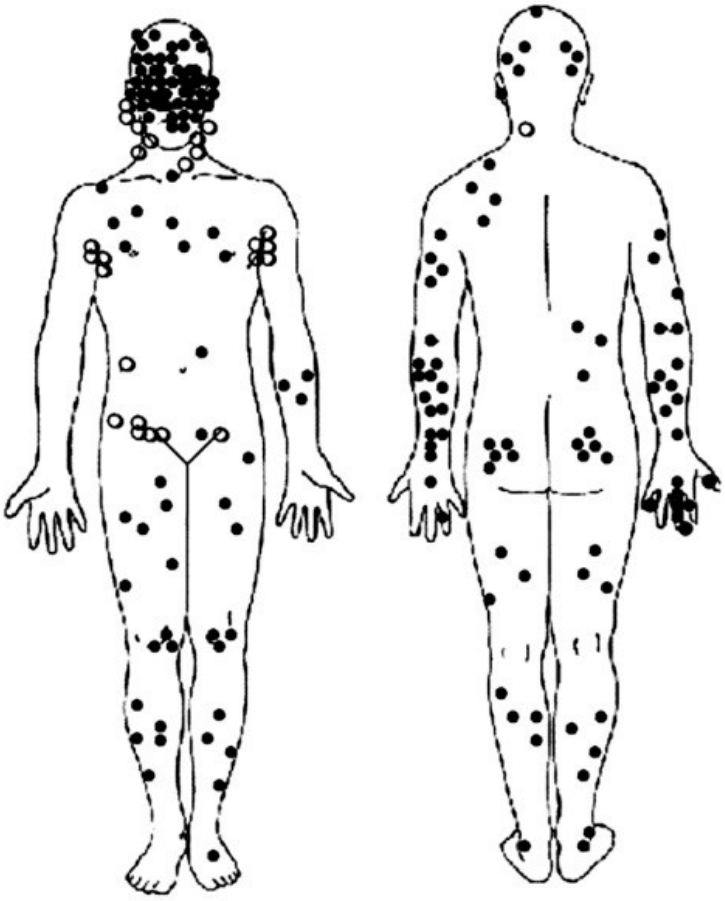
MCC usually develops on sun-exposed skin (e.g., head, neck, arms) as a painless, firm bump that can be red-purple or skin-colored. Patients frequently point out a new MCC to their doctor because a bump is growing rapidly and/or does not look like anything the patient has ever had before. Most MCCs are diagnosed when a skin biopsy is performed to rule out another sun-induced skin cancer or to remove a presumed cyst. In the vast majority of cases, both the doctor and the patient are surprised by the diagnosis of MCC.[1]



Merkel cell carcinoma on the upper lip, right cheek, and eyelid, respectively (Nghiem)

Where does MCC occur on the body?

MCC primarily occurs on highly sun-exposed skin, but it can occur anywhere on the body, including sun-protected areas such as the buttock or the scalp under hair.



Solid circles depict MCC tumors that arose on the skin (86% of these cases). Open circles indicate MCCs that presented in lymph nodes without an associated “primary lesion” (this was the case in 14% of cases). Recent data suggest that patients who present without a primary lesion originally did have a lesion on the skin, but that their immune system eliminated the tumor. Elimination of the primary lesion is associated with less risk for patients that already have the same stage at presentation.

What are the risk factors for Merkel cell carcinoma?

The exact causes of MCC are not known. Factors strongly associated with the development of MCC include age over 65 years, fair skin, history of extensive sun exposure, chronic immune suppression (e.g., kidney or heart transplantation or HIV), and Merkel cell polyomavirus.

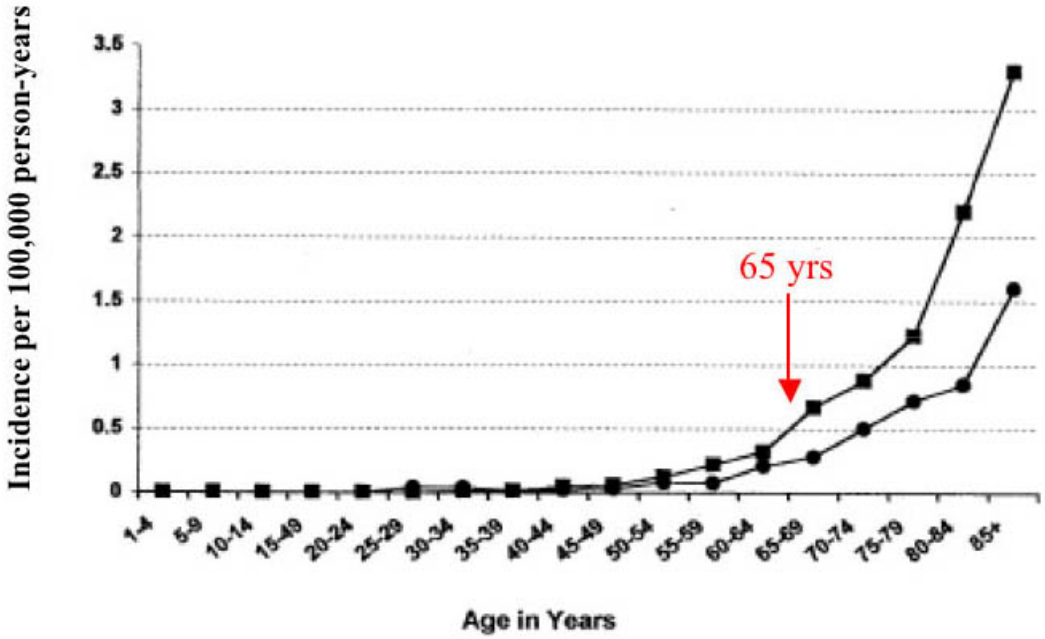
Extensive information on characteristics of patients with MCC comes from a study of 1,034 patients summarized in the table below.[2] The average (median) age of the patients with MCC was 74 years. The most common sites of involvement were head followed by arms (upper limb). At the time of diagnosis, half of the patients had disease localized to the skin, while the other half had MCC that was no longer confined to the skin.

Total Number of Patients Surveyed = 1034		
Median Age of Patient (years)	74	
Age groups (years)	**No.**	**(%)**
< 65	247	(23.9)
65-74	281	(27.2)
>/= 75	506	(48.9)
Race	**No.**	**(%)**
White	968	(93.6)
Black	12	(1.2)
Other	37	(3.6)
Unknown	17	(1.6)
Body site	**No.**	**(%)**
Head	499	(48.3)
Trunk	117	(11.3)
Upper limb	199	(19.3)
Lower limb	165	(16.0)
Other	54	(5.2)
Stage at diagnosis	**No.**	**(%)**
Localized	507	(49.0)
Regional	281	(27.2)
Distant	81	(7.8)
Unknown	165	(16.0)

Patient characteristics. Adapted from Agelli, 2003.

Age & Merkel cell carcinoma

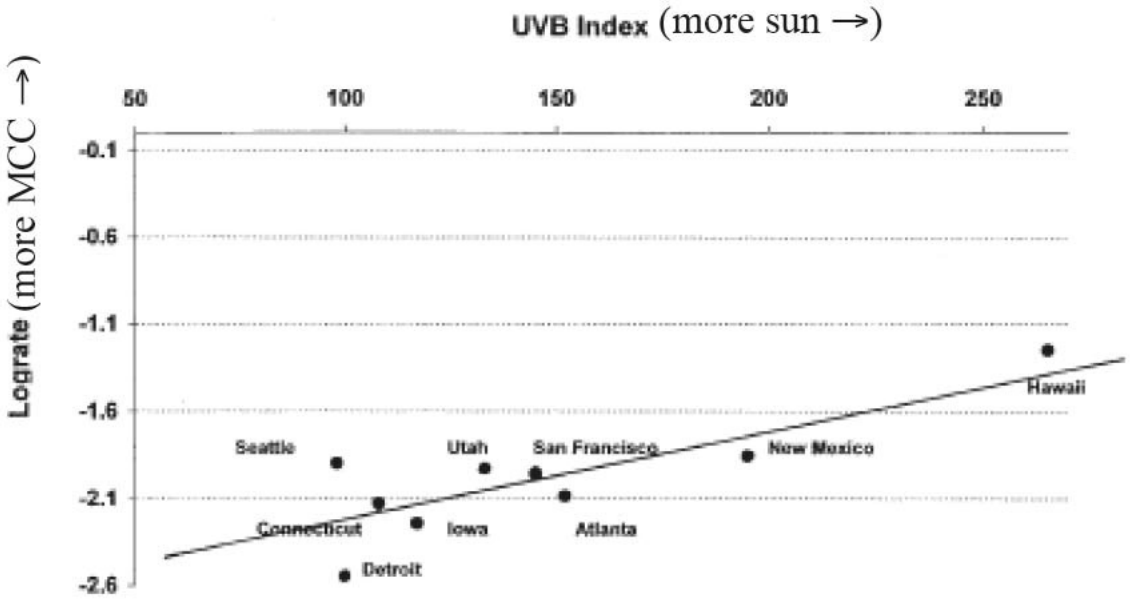
The risk of developing MCC increases with advancing age. 75% of MCC patients are over the age of 65 years at time of diagnosis, with the average age for developing MCC being 74. MCC is slightly more common in men than women for each age group (see graph below).



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. MCC is most commonly found on sun-exposed areas of the body in older Caucasian individuals, who may also have other sun-induced skin cancers. There are more MCC cases in sunny climates (Hawaii) as opposed to areas with less sun (Connecticut) (see graph below). While extensive sun exposure is a risk factor for MCC, MCC can also occur on sun-protected skin, such as a hair-covered scalp.



Frequency of MCC of the head in Caucasians by UV exposure (Agelli, 2003).

Immune function & Merkel cell carcinoma

Patients with weakened immune systems are at significantly higher risk of developing MCC. Conditions associated with weakened immunity include HIV/AIDS, kidney or heart transplantation, and autoimmune diseases requiring medications that suppress the immune system, chronic lymphocytic leukemia (CLL) and certain types of lymphoma. The risk of developing MCC is 8 times greater in HIV patients, 25 times greater in organ transplant patients, and about 40 times greater in CLL.[1,3,4] (Garret JAMA 2016) 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 have no known immune deficiency.[1]

The immune system is also very important after diagnosis of MCC. Patients who show a robust immune response, with certain immune cells present in their tumor (killer T cells), tend to do better.[5] MCC patients without a primary tumor (no original skin lesion) also do better, likely because their immune system was able to eliminate the primary tumor and thus are more likely to be able to fight small amounts of MCC elsewhere in the body as well.[6] In contrast, patients on medications that reduce immune function are at higher risk of having their MCC recur.

Researchers are currently investigating ways to help boost the immune response to MCC. 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 page 22).

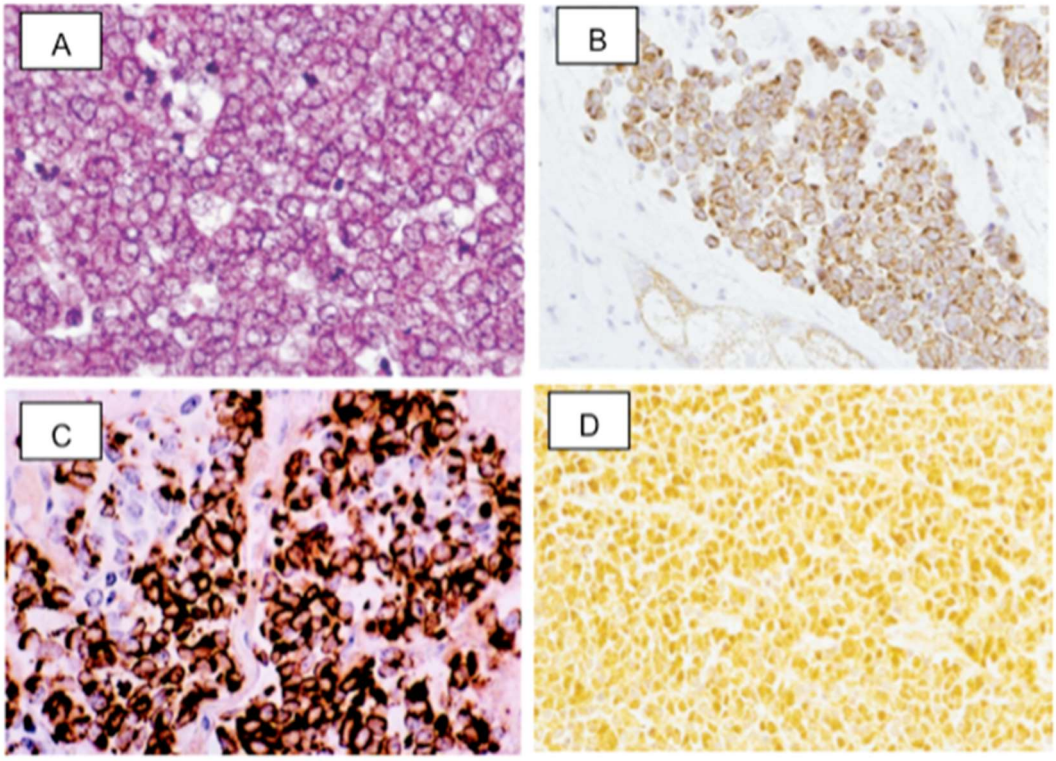
The Merkel polyomavirus is usually involved in Merkel cell carcinoma

In 2008, the Merkel cell polyomavirus (MCPyV) was discovered by the University of Pittsburgh laboratory of Drs. Patrick Moore & Yuan Chang and found to be frequently present in MCC tumors.[7] The virus was found in 8 of 10 tumors tested, and was associated 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 this initial report, finding MCPyV in the vast majority (about 80%) of MCC patients.[8,9] Studies now show that the majority of people have been exposed to MCPyV by adulthood, but it appears that the virus does not cause any symptoms except in the very rare situations in which it leads to MCC.[10]

DIAGNOSIS

Skin Biopsy

The diagnosis of MCC is made with a skin biopsy, which is then examined under the microscope by a pathologist. Common types of biopsy include a punch (a small core is taken) or a shave (part of the top of the lesion is removed with a scalpel). The pathologist will then use special studies (called immunohistochemistry stains), that are used to determine if a lesion is an MCC or another form of cancer, such as small cell lung cancer (SCLC), lymphoma, or melanoma. Each of these cancers has unique characteristics when examined with such special stains. (see table below)



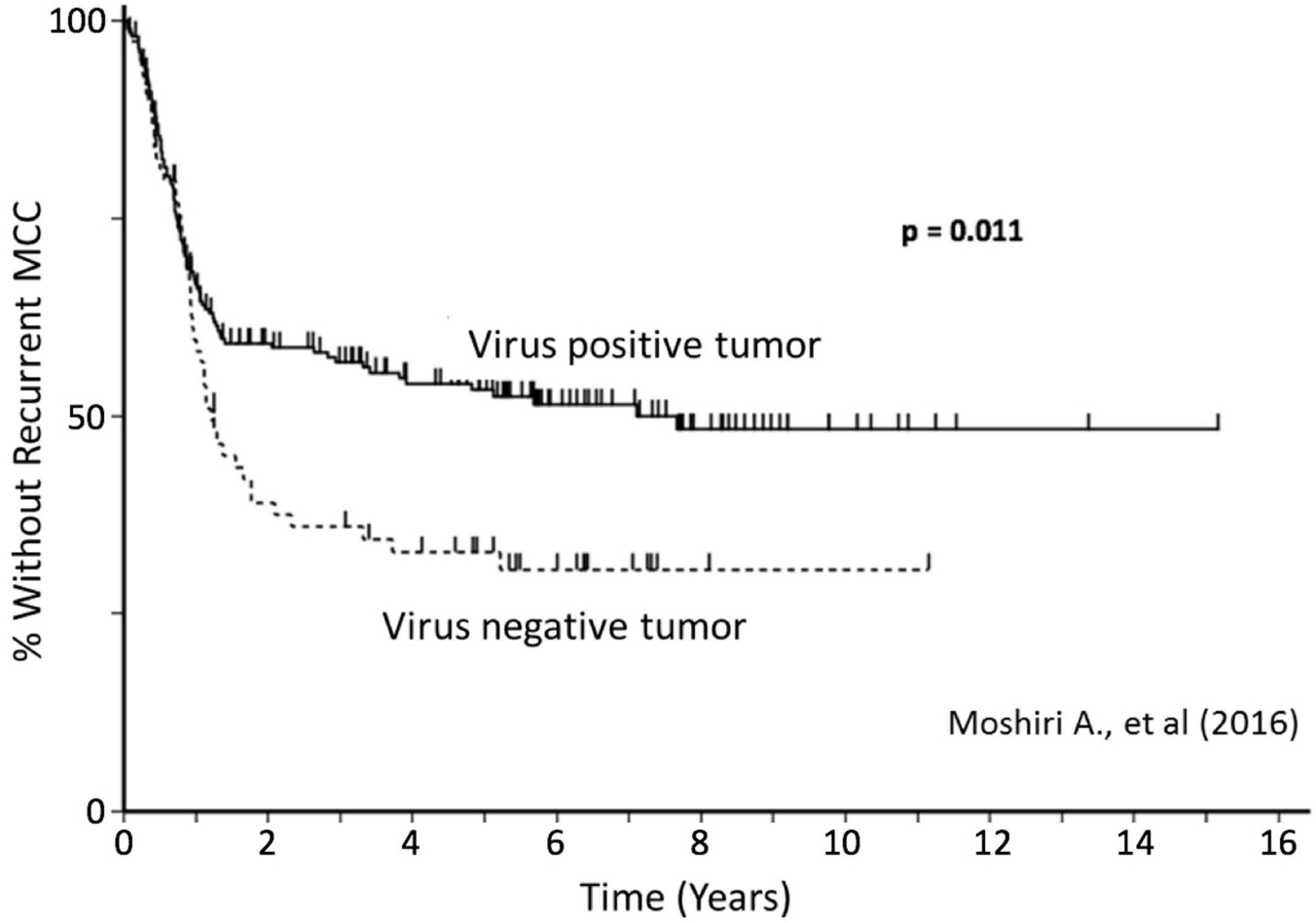
MCC as stained by A) hemotoxylin & eosin, B) CAM 5.2, C) CK 20, and D) NSE. (Goessling, 2002 & Nghiem, 2001)

Biopsy Characteristics for MCC and Tumors Resembling MCC

	Stain					
Tumor	**CAM5.2 or AE1/AE3**	**CK20**	**NSE**	**CK7 or TTF-1**	**LCA**	**S100**
MCC	+	+	+	-	-	-
SCLC	+	-	+	+	-	-
Lymphoma	-	-	-	-	+	-
Melanoma	-	-	+	-	-	+

Determining if an MCC tumor is positive for the Merkel polyomavirus

About 80% of MCCs in the United States contain the Merkel polyomavirus. A study of 282 MCC patients found that the risk of the cancer recurring was higher among patients whose tumors did not contain the virus ("virus-negative MCC tumors"). The typical way to test if the Merkel virus is present in a tumor is by using the CM2B4 antibody which detects if the Merkel polyomavirus oncoprotein is present, and can be performed in many major pathology laboratories. The graph below shows that patients whose tumors are "virus negative" are more likely to have their tumors progress and thus should be followed more closely in order to catch a possible recurrence early (this trend is statistically significant, p = 0.011).

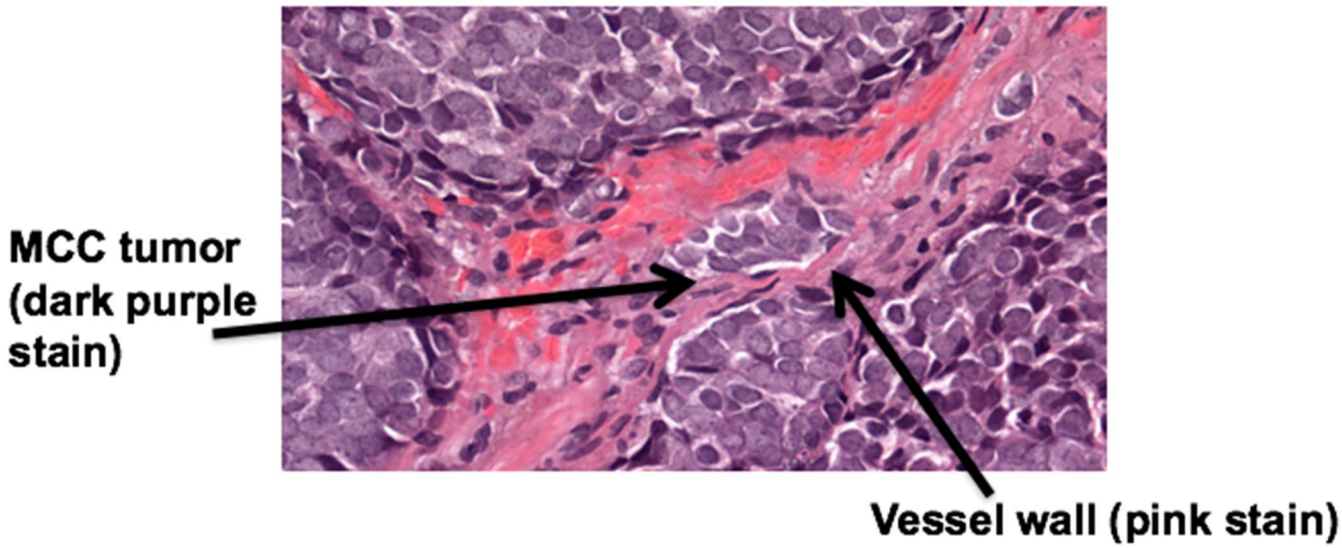


Lymphovascular invasion

In order for a tumor to spread or metastasize, it needs to enter into vessels that carry blood or lymph fluid. Sometimes it is possible to actually see MCC tumor cells that have entered into such vessels within or around the tumor, which is called "lymphovascular invasion (LVI)".

The presence of LVI suggests there may be a higher risk that the cancer has spread. Indeed, several studies suggest that this is true in MCC. However, the presence or absence of LVI has a much smaller effect on risk of recurrence than stage at diagnosis, or even immune suppression. Many pathologists are not

aware of the importance of this feature for MCC and it is often not included in the pathology report. This can be remedied by your physician (or you) contacting the pathologist and requesting that this be evaluated and that a comment be added to the report as to whether or not LVI was seen in the biopsy sample.



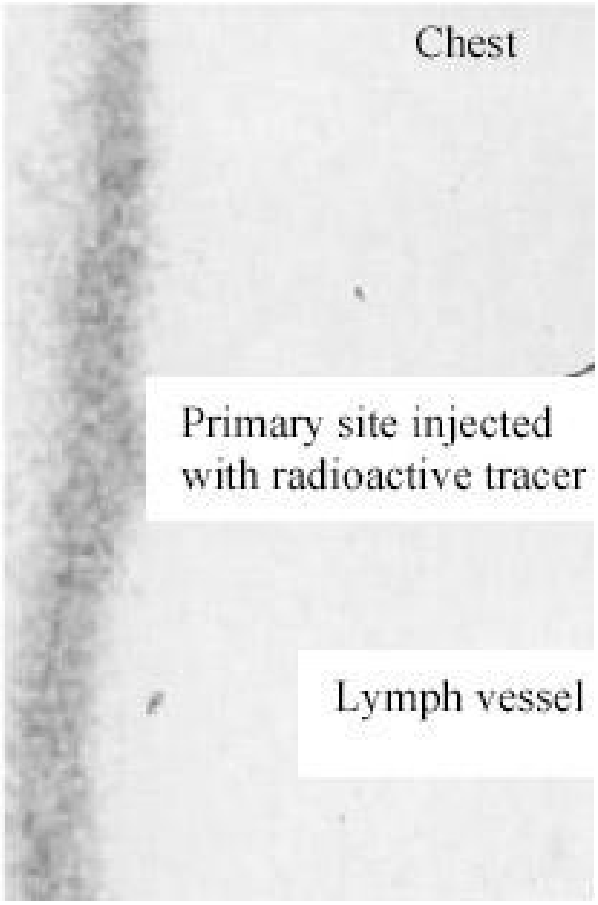
An image of showing lymphovascular invasion, where the vessel wall is stained pink and MCC tumor cells are stained dark purple (nuclei of the cells).

Sentinel lymph node biopsy

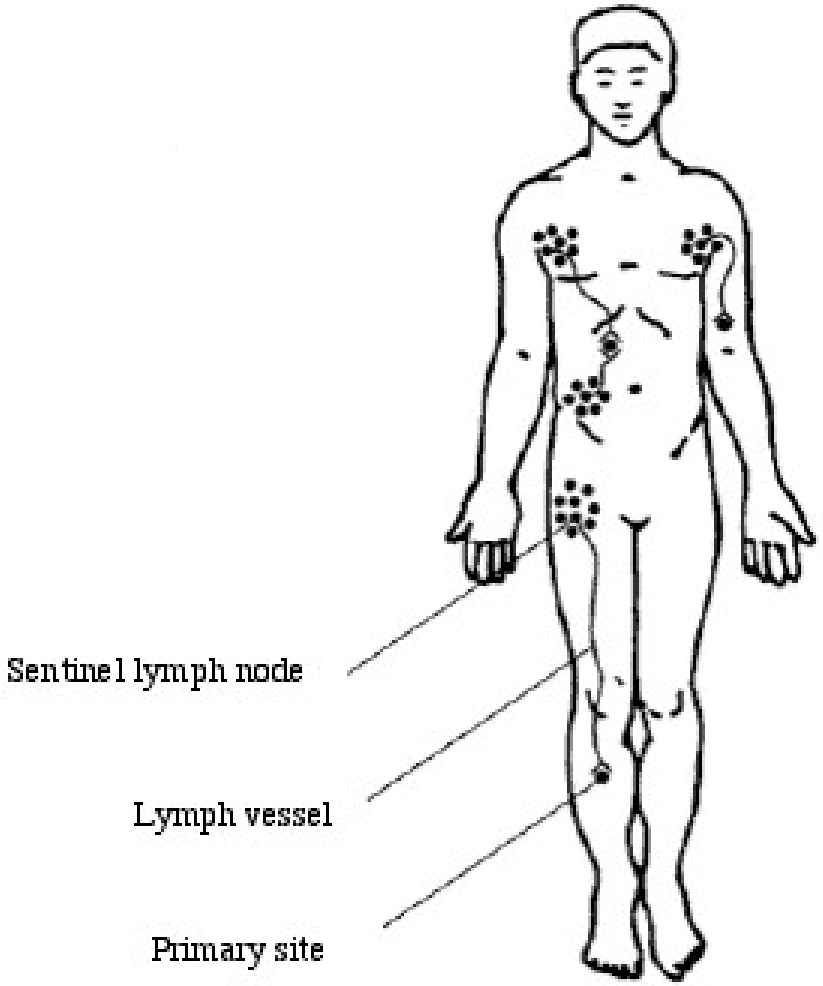
Merkel cell carcinoma cells can travel from the skin, through the lymphatic vessels, to the sentinel lymph node. The sentinel lymph node is the first lymph node that connects with the part of the body where the cancer arose. If a lymph node feels enlarged, it may contain MCC (macrometastases). Sometimes, 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 or a 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. 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 under a microscope. If MCC is not found in the sentinel lymph node, then the chance that it has spread elsewhere in the body is lower than if MCC is present.

This technique has a low risk of significant side effects, provides useful information on the chance of spread, 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.



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, with permission.



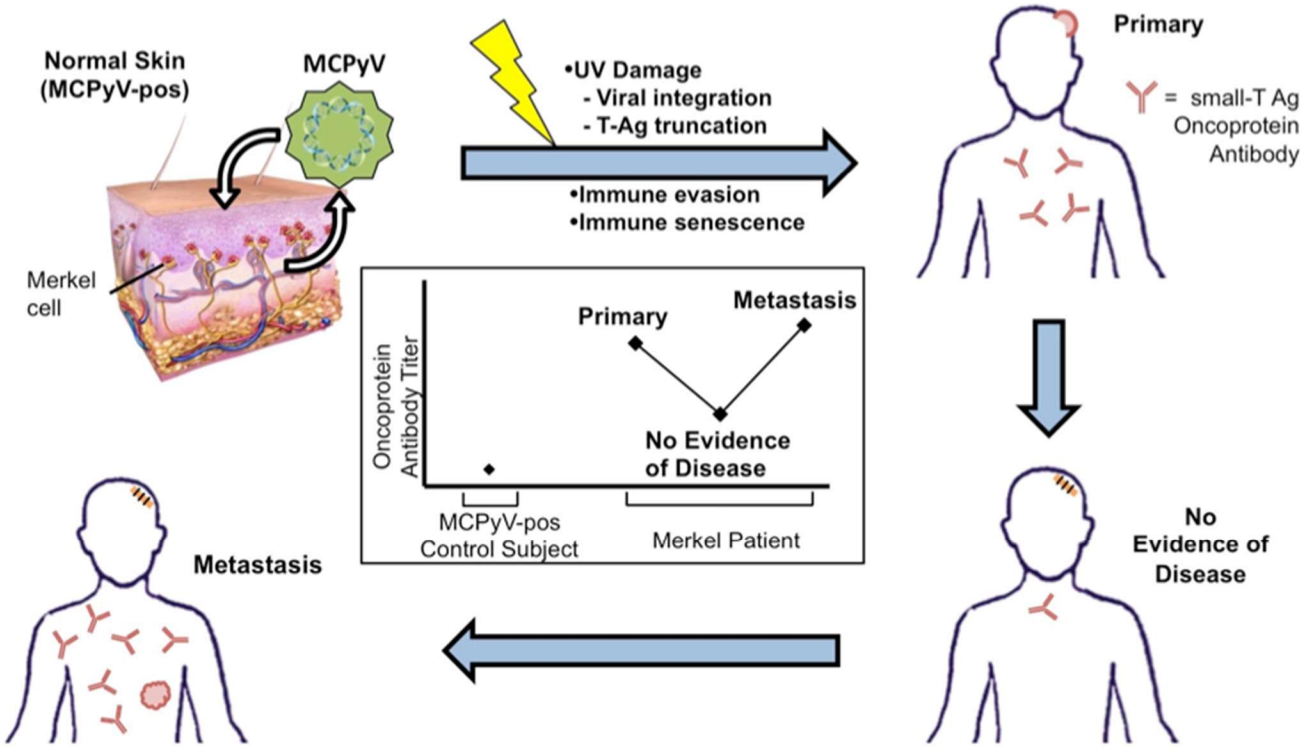
Schematic representation of the lymphatic system. MCC cells can travel from the primary site, through the lymph vessels to the sentinel lymph node. Note that MCC on the leg will likely drain to the inguinal lymph nodes on the same side; an MCC on the arm will drain to the axilla (armpit); MCC on the trunk can drain to the closest axilla or inguinal bed, or multiple beds unpredictably; a primary on the face may drain under the chin (submandibular) or in front of the ear (pre-auricular). Adapted from Perrott, 2003, with permission

Serology

The Merkel polyomavirus serology test is a blood test that is helpful in managing MCC patients by detecting possible disease recurrence early, when it can be most effectively treated. A baseline oncoprotein antibody test (ideally within 2-3 months of when a patient had evidence of disease) is useful for all MCC patients. This is because patients who do not produce antibodies are at higher risk of having a recurrence and will need to be followed closely by imaging scans. In contrast, patients who produce oncoprotein antibodies can be followed over time using this test which decreases the need for imaging scans.

A portion of the Merkel polyomavirus–the "oncoprotein"–is present in about 80% of all MCC tumors. This portion of the virus is critical for most MCC tumors to grow. In 2010, we reported that antibodies that recognize this oncoprotein are present in the blood of 50% of newly diagnosed MCC patients. In contrast, oncoprotein antibodies are almost never present in people who have not had MCC.

After treating a patient with Merkel cell carcinoma, if oncoprotein antibodies had been present, they decrease rapidly in the blood. Typically, antibody levels fall by about 90% by one year after treatment, and continue to fall after that. On the other hand, if the cancer returns in a patient who previously had these antibodies, blood antibody levels increase rapidly. By comparing blood antibody levels at two time points, we can see if the cancer is in remission or returning.



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.

Merkel Polyomavirus Serology Test:
a blood test to help manage patients with Merkel cell carcinoma

Merkel cell carcinoma (MCC) is an aggressive skin cancer associated with the Merkel cell polyomavirus (MCPyV). About 50% of people with MCC make antibodies to the oncoprotein portion of this virus. In patients that make these antibodies, it is possible to monitor for recurring MCC by determining the "titer" amount of antibodies in their blood. Oncoprotein antibody titers fall steadily in patients without recurring MCC, while titers increase rapidly in patients with MCC recurrences. Testing for oncoprotein antibodies every 3 months is recommended in MCC patients who make them. This test, known as "AMERK," is now clinically available and can be ordered as a send-out test from your local hospital.

First Merkel virus Serology Test Results:

The first serology test should be done within 3 – 6 months of when a patient was initially treated for MCC. These results will indicate if the patient is positive or negative for oncoprotein antibodies.

A **positive test** for oncoprotein antibodies (titer>150) means that the serology test can be used to track the disease, and we would expect antibody titers to decrease after the cancer is successfully treated.

A **negative test** (titer< 75) for oncoprotein antibodies indicates that the patient does not produce antibodies and the serology test will not be useful in detecting new recurrences. Being negative for oncoprotein antibodies does not change the patient's treatment plan; instead, the patient may be recommended to have more frequent scans which can also detect MCC recurrences.

A **borderline test** (75-150) is inconclusive on the status of oncoprotein antibody production. The effectiveness of monitoring through the serology test is unclear in such patients.

Subsequent Results:

Patient's that initially test positive for oncoprotein antibodies should receive this serology test every three months. The results will contain the antibody titer level, as well as the percentage change from your previous test.

If the antibody titer is decreasing, this suggests that patient's MCC cancer is in remission.

However, *if the antibody titer is increasing, the patient could have a new MCC tumor* and we advise scheduling an appointment with the physician managing your MCC to evaluate if a scan and further treatment is indicated.

Results:

Results will be emailed within a month of receiving the sample. If you do not hear from us by then, please contact Krista Lachance (kcs27@uw.edu / 206-221-4594).

For more information about the AMERK serology test, please visit our website:
https://merkelcell.org/testing-and-diagnosis/serology/

Staging

Physicians determine the stage of cancer by performing physical exams and tests. Stages describe the extent of cancer within the body, especially whether the disease has spread (metastasized) from the primary site to other parts of the body.

Determining the stage of Merkel cell carcinoma

MCC is divided into stages depending on the size of the primary tumor and extent of disease in the lymph nodes and elsewhere in the body (metastasis). 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.

The stage at diagnosis is the major determinant of the chance for later spread (metastasis) and treatment options.

8th Edition MCC Staging System Table

(Adapted from AJCC's Cancer Staging Manual 2016)

Stage		Primary Tumor	Lymph Node	Metastasis
0		In situ (within epidermis only)	No regional lymph node metastasis	No distant metastasis
I	Clinical*	≤ 2 cm maximum tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
I	Pathological**	≤ 2 cm maximum tumor dimension	Nodes negative by pathologic exam	No distant metastasis
IIA	Clinical	> 2 cm tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIA	Pathological	> 2 cm tumor dimension	Nodes negative by pathological exam	No distant metastasis
IIB	Clinical	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIB	Pathological	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by pathologic exam	No distant metastasis
III	Clinical	Any size / depth tumor	Nodes positive by clinical exam (no pathological exam performed)	No distant metastasis
IIIA	Pathological	Any size / depth tumor	Nodes positive by pathological exam only (nodal disease not apparent on clinical exam)	No distant metastasis
		Not detected ("unknown primary")	Nodes positive by clinical exam, and confirmed via pathological exam	No distant metastasis
IIIB	Pathological	Any size / depth tumor	Nodes positive by clinical exam, and confirmed via pathological exam OR in-transit metastasis***	No distant metastasis
IV	Clinical	Any	+/- regional nodal involvement	Distant metastasis detected via clinical exam
IV	Pathological	Any	+/- regional nodal involvement	Distant metastasis confirmed via pathological exam

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

**Pathological detection/confirmation of nodal disease may be via sentinel lymph node biopsy, lymphadenectomy, or fine needle biopsy; and pathological confirmation of metastatic disease may be via biopsy of the suspected metastasis

***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

TREATMENT

Overview

There are multiple treatments used for MCC, and treatment is generally based on stage of the disease and many issues that are highly variable between patients. It is best to obtain care from a multi-disciplinary team of physicians with significant MCC experience who take into consideration many clinical factors.

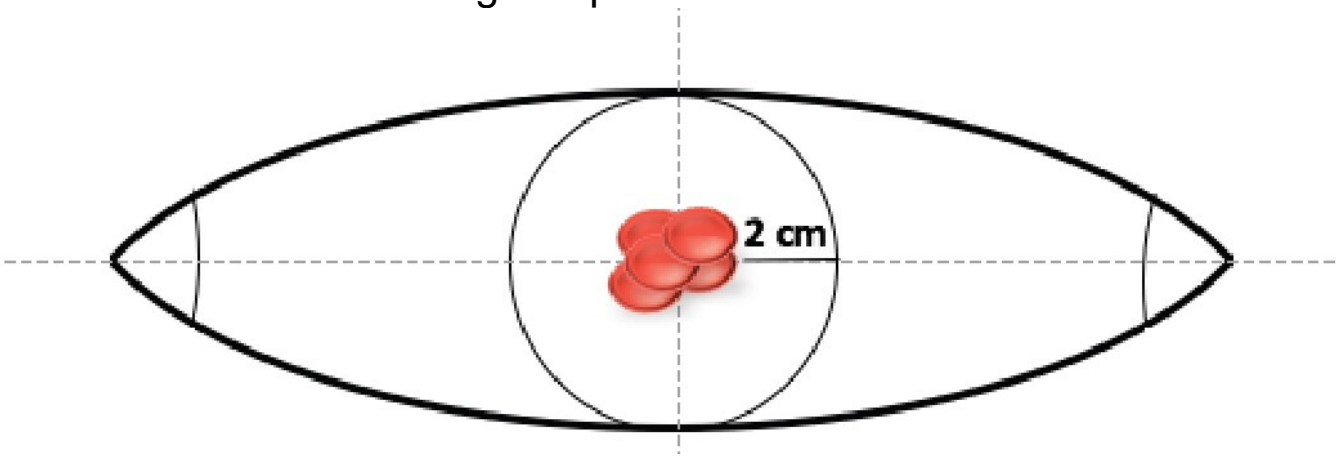
There are three major treatments for MCC:
1) surgical excision of the primary lesion or lymph node,
2) radiation therapy, and
3) systemic therapy including immunotherapy and chemotherapy.
Each will be reviewed below in greater detail.
In relatively low risk MCC tumors, surgery alone can be sufficient. In other cases, surgery may not be possible and a MCC specialist may recommend radiation therapy or another form of treatment. Depending on your general health and the location and size of the MCC, more than one treatment option may be used.

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 https://www.merkelcell.org/wp-content/uploads/2017/11/NCCN-Evidence-Blocks-Clinical-Practice-Guidelines-In-Oncology-Merkel-Cell-Carcinoma-Version-1.2018-October-6-2017.pdf

Surgical excision

The goal of surgical excision for MCC is to remove the MCC so that it does not recur near the primary site or in the nearby lymph nodes. The primary MCC tumor should ideally be removed with clear margins (no microscopic tumor at edge of excision) as judged by pathology examination. As noted below however, even with margins >2 cm, surgery alone can have a high recurrence rate near the primary MCC site of up to 42%, depending on the study. The chance of local recurrence after surgical excision of the primary tumor is far higher for MCC than for the more common types of skin cancer (basal cell carcinoma, squamous cell carcinoma or even melanoma) because MCC more often “jumps” discontinuously to adjacent normal-appearing skin, with recurrences happening quite commonly up to several centimeters away from the edge of the primary tumor. The local recurrence rate can be as high as 20-40% depending on the study, and can typically be cut to less than 5% by the addition of radiation therapy. Importantly, if radiation will be used at the primary site, it is not required for the surgeon to obtain clear margins because radiation kills isolated tumor cells in the radiation field which usually extends at least 5 cm beyond where the tumor was. See the

Radiation therapy below for guidelines about how to decide whether or not radiation should be used for a given patient.



Schematic of wide surgical excision: An excision taken with wide margins, generally approximately 1 cm or greater in an attempt to surgically remove a cancer. with MCC shown in gray.

To optimize the appearance and function of the scar, the surgeon may make an excision in the shape of a football (ellipse). The length of the 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 eight times as long as the width of the original MCC tumor.

In relatively low risk MCC tumors, surgery alone can be sufficient. Among a large series of cases from the literature, the addition of adjuvant radiation to surgery decreased the risk of local recurrence by several folds.

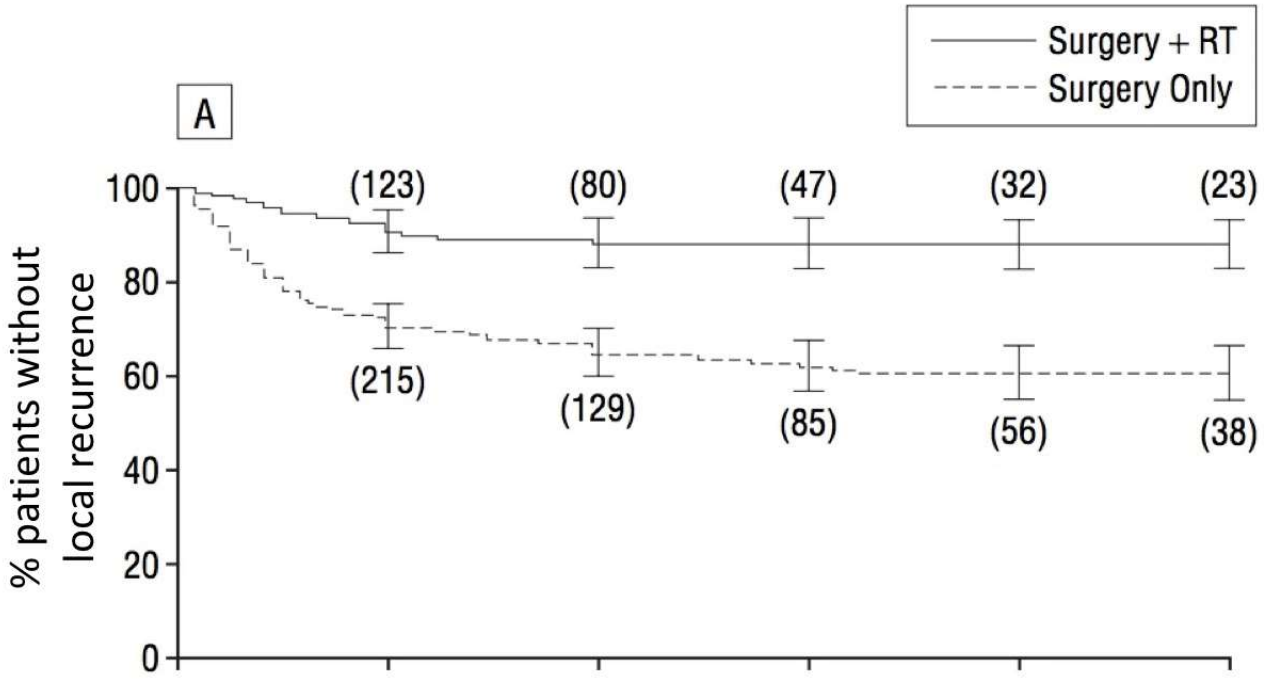
Mohs micrographic surgery

It may not be possible to excise some MCCs on the face with a margin of more than 1 cm. For these reasons, a doctor may refer a patient to 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). Local removal of the MCC is evaluated under the microscope during surgery. Our analysis of published studies on the treatment of MCC suggests that radiation therapy needs to be added to Mohs micrographic surgery to optimize control of the disease, as MCC often “jumps” several centimeters to nearby skin. Addition of radiation therapy to Mohs micrographic surgery appears to cut recurrence by roughly one-half. A challenge of using Mohs micrographic surgery for MCC is that a sentinel lymph node biopsy almost always needs to be done at a separate appointment (prior to having the primary tumor fully removed by Mohs surgery), so this makes scheduling inconvenient.

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 margin of surrounding apparently normal tissue, 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 has removed all of the tumor that is visible.

Our analysis of the available literature and our experience caring for MCC patients since 1999 show that radiotherapy is associated with a statistically significant improvement in local and nodal recurrence. Some studies also suggest that adding radiation may improve a patient's chance of survival, but this is more controversial.[11] Where wide excision is not possible, a recent study suggests that radiotherapy alone may be nearly as effective as both radiotherapy and surgery. These data suggest a role for radiotherapy for many patients with stage I, II & III disease.



Local recurrence is 3.7 times more likely if treated with surgery only

We typically recommend patients receive radiation if they have a significant risk of local-nodal recurrence (typically >15%), are generally healthy, want to maximize the chance of not having the cancer come back in the areas at risk, and can travel daily to a local radiation therapy facility for the 5-6 week treatment period.

Patients who have very low risk disease, as defined by having all of the favorable features below, are likely to benefit very little from adjuvant radiation therapy. We are currently not routinely recommending radiation therapy for such low-risk cases. Features include:

- Primary tumor ≤1 cm in largest dimension
- Negative sentinel lymph node biopsy
- No chronic immune suppression (HIV disease, leukemia/lymphoma, transplant of heart or kidney or liver)
- No lympho-vascular invasion in the primary tumor (pathologist may need to be asked to go back to the original biopsy and specifically comment on this feature's presence or absence).
- Confidently negative microscopic margins after excision

The dose of radiotherapy 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 through Friday) over a set number of weeks (most commonly for 5 weeks).

In some cases, especially if MCC has spread beyond the local-nodal area, we have successfully used a single, larger dose (8 Gy) of radiation to shrink and sometimes eliminate a given metastatic lesion. This approach has relatively few side effects and may work nicely together with systemic immune stimulation therapy. We described this approach in a 2015 report on 93 tumors treated in 26 patients.[12]

Common 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. Radiation to a draining lymph node basin may cause swelling of the arm or leg on the same side that may be long-lasting, and is more likely if extensive nodal surgery has also been carried out. A frequent side effect is fatigue, which usually resolves within a month or two 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 the side effects. Localized radiation therapy typically does not lead to nausea, vomiting, or hair loss outside of the irradiated area.

Immunotherapy

Immunotherapy is a branch of medicine that uses therapies to augment the body's own immune cells' ability to recognize and destroy tumor cells. Immunotherapy is rapidly becoming a preferred systemic therapy in several cancer types, especially because responses to immunotherapy (when they occur) are generally long-lasting. The durability of immunotherapy responses places this approach in stark contrast to chemotherapy, which was previously considered the standard option for patients with metastatic MCC. (See chemotherapy section)

MCC Immune Checkpoint Inhibitors (ICI)

While there are several therapies that can stimulate the immune system, the most promising emerging option includes a class of drugs called the immune checkpoint inhibitors (ICIs). Tumor cells escape the immune system by pressing "brakes" (like the PD-1 protein) on the surface of the killer immune cells. The ICIs block these brakes from getting pressed and allow immune cells to function better. There are several ICIs currently being investigated/approved in MCC.

Avelumab (brand name Bavencio) is a type of ICI that works by blocking the PD-1 pathway (it binds to a ligand of PD-1 called PD-L1). It has been FDA-approved in 3/2017 to treat patients with metastatic MCC, irrespective of prior therapy based on a promising trial results. The trial tested avelumab in 88 patients with metastatic MCC who had previously been treated with chemotherapy, and whose tumors had then come back. These patients thus had especially difficult-to-treat tumors. Of the 88 patients treated, 28 (32%) responded with significant tumor shrinkage. The responses appeared to be strikingly more durable than chemotherapy responses, with over 80% of patients who initially responded to avelumab having impressively durable responses continuing beyond a year (Kaffuman, 2016). It is currently being investigated in patients with metastatic disease that have not been previously treated with chemotherapy.

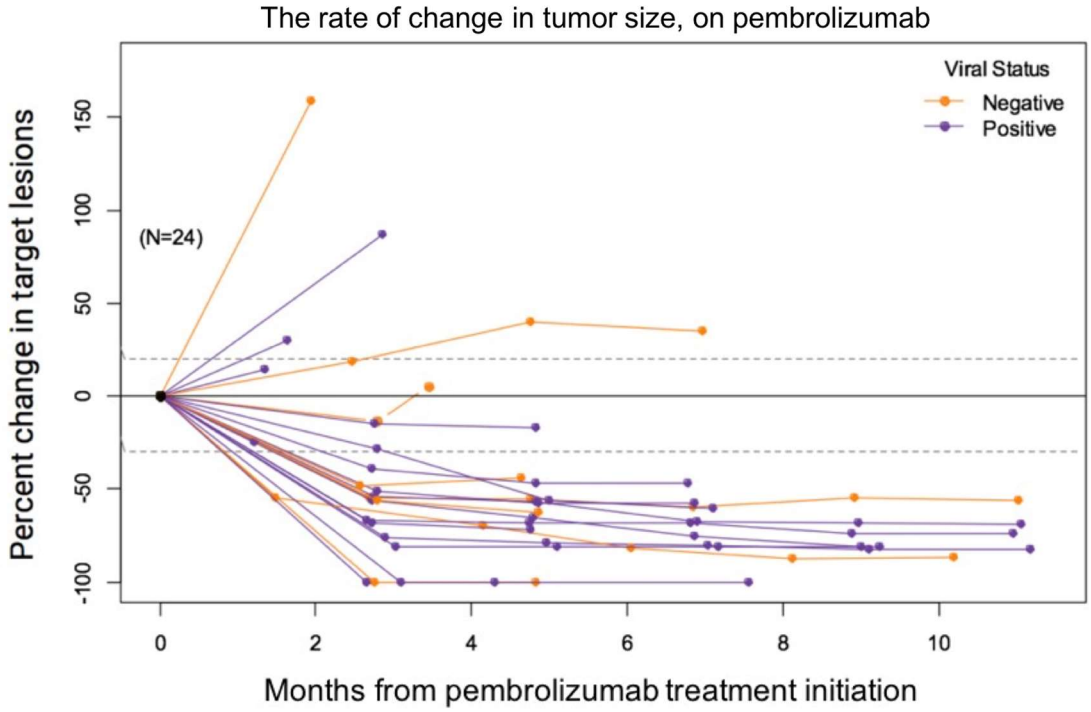
Another study looked at a type of ICI called pembrolizumab (brand name Keytruda). The drug was administered as an intravenous infusion every three weeks in the outpatient clinic to 26 patients with metastatic MCC, who had not received any prior systemic therapy. Of those patients, 56% had impressive shrinkage of their tumors. Patients with both virus-positive and virus-negative tumors responded to the treatment. Importantly, 86% of those who initially responded had long lasting responses, which were strikingly more durable than the chemotherapy responses (Nghiem et al, 2016). Based on this data, pembrolizumab along with avelumab, nivolumab (introduced below) were recently listed as a preferred treatment option for patients with metastatic MCC in the 2018 NCCN guideline.

Other ICIs, including nivolumab (brand name Opdivo) and ipilimumab (brand name YERVOY) are also in clinical trials in advanced MCC. In addition, there are several other immunotherapy approaches being investigated for MCC in clinical trials, including intra-tumoral injection approaches and infusion of immune cells (e.g. T-cells). Initial results suggest a promising future for immunotherapies in the treatment of MCC.

Patients with advanced MCC, such as those with distant metastases (stage IV) or MCC that cannot be removed surgically, could benefit from those agents, but patients who have a suppressed immune system, which could be due to another

cancer, uncontrolled HIV, prior organ transplant, or serious autoimmune disease that requires immunosuppressive drugs, might not benefit from ICI as much as the immunocompetent patients do.

Common side effects for immune checkpoint inhibitors include, but are not limited to, fatigue, cough, nausea, and itching. The vast majority of patients report good quality-of-life while receiving these drugs, which typically do not cause hair loss, nausea, vomiting, infections, etc., in striking contrast to the older chemotherapy options. However, ICIs can sometimes cause severe, life-threatening side-effects, related to immune attack against normal body organs. These include colitis (diarrhea), hepatitis (liver injury), pneumonitis (lung inflammation), hormone changes, nerve damage, etc. Close follow-up and contact with the treating oncologist is critical to avoid serious injury.



Rapid and durable shrinking was observed in most patients (Nghiem, et al, NEJM, 2016)

Chemotherapy

Chemotherapy targets cells that divide quickly, such as cancer cells that grow and multiply without control as well as healthy cells that divide rapidly. MCC is usually initially responsive to chemotherapy, leading to significant shrinkage. However, MCC often quickly gains resistance, and the tumor can start to grow again despite receiving chemotherapy drugs. Adjuvant chemotherapy is chemotherapy that is used to destroy cancer cells that may remain after surgery and/or radiation therapy have cleared the readily detected cancer cells. 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 as they work better together than alone. 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. A combination of etoposide (VP16) and carboplatin (or cis-platin) is one such regimen that will shrink MCC tumors in more than half of cases. A recent study of 62 MCC patients who received chemotherapy to treat distant metastatic disease showed that nearly 60% of patients had their tumors shrink initially. On average, however, MCC tumors began to grow again by only 90 days after the chemotherapy was first started.[15] When MCC returns after chemotherapy, there are two problems that make controlling it more challenging: the immune system is somewhat suppressed by the chemotherapy and the MCC tumor cells have learned how to evade the effects of chemotherapy drugs. For patients who do not have problems with their immune system (no auto-immune disease and no major immunosuppressive medications), it is typically recommended to first try an immune stimulating therapy (such as an immune checkpoint inhibitor), prior to using chemotherapy.

Adjuvant chemotherapy is not typically indicated in treating Merkel cell carcinoma

The following are reasons that adjuvant chemotherapy is 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 a medical team.

- Mortality: There is a 4 to 7% acute death rate due to adjuvant chemotherapy in MCC partly due to the fact that these patients are often elderly.[16,17]
- Morbidity: Neutropenia (low white blood count) occurs in 60% of patients with fever, and sepsis in 40%.
- Decreased quality of life: This is quite severe in this older population, including fatigue, hair loss, nausea and vomiting.
- Resistance to chemotherapy: Merkel cell carcinoma that recurs after chemotherapy is less responsive to later palliative chemotherapy.
- Immunity: Chemotherapy suppresses immune function and this is known in general to be very important in preventing and controlling MCC.
- Apparent poorer outcomes: In a recent study of 6908 patients captured in the National Cancer Database, there was no benefit (or detriment) of giving adjuvant chemotherapy to patients with high risk disease (MCC that had spread to the nodes).[11]

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 expand their physical activity through regular participation in their favorite forms of exercise. Please remember that this information alone can't take the place of the traditional health care that patients may need. Because of possible adverse side effects and drug interactions, we strongly encourage patients to consult with their primary physician and oncologist before starting any new treatment regimen and to notify their pharmacist of any supplements they are taking.

High quality information about what natural medicines are likely to be safe and effective can be found at this website.
(http://naturaldatabase.therapeuticresearch.com/)

Several of our patients take supplements to improve their nutritional status and augment the immune system. These include Host Defense® MyCommunity Capsules (available from Fungi Perfecti). 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 a physician prior to beginning any nutritional supplementation program as some supplements can interact with certain medications.

PROGNOSIS & FOLLOW UP

Disease recurrence and survival are two critical measures of prognosis (how a patient will do after a cancer diagnosis). Recurrence refers to whether the cancer ever comes back; survival rate refers to the chance of death from the cancer.

Knowing a patient's prognosis will help their medical team select the best treatment plan to minimize risk of recurrence and detrimental side effects. This information is also very helpful to determine how closely a patient needs to be followed for recurrence.

Recurrence risk and survival rate varies greatly based on the stage of disease at the time it is initially diagnosed and treated. The following figures show how MCC stage affects the chance of MCC recurrence.

Signs and symptoms of a recurrence

A recurrence of the cancer can appear as a skin lesion, enlarged lymph nodes or via imaging studies that detect new tumors within the body.

A physical exam may reveal those lesions 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. The AMERK serology test can be an inexpensive, safe and sensitive approach to detect early recurrence. 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-ray, CT (computed tomography) scans, and PET (positron emission tomography) scans. In most cases, a biopsy of a new lesion will be required to be certain if the lesion represents MCC or not.

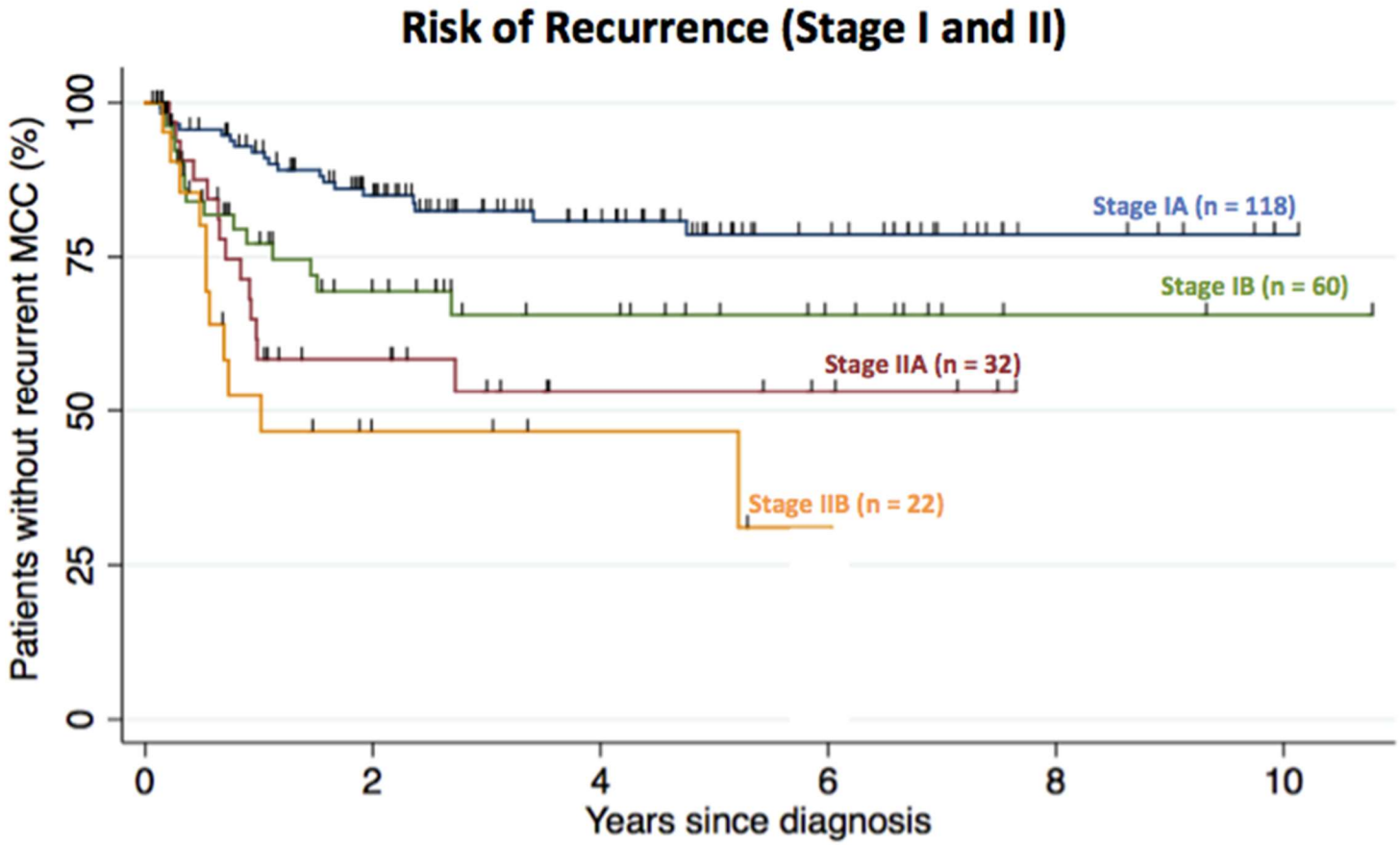
Reading Kaplan-Meier curves

"Kaplan-Meier" curves are a standard way to depict both recurrence-free survival and MCC-specific survival over time starting from diagnosis. In the Kaplan-Meier curves, each tick mark indicates a patient who was "censored" at that point and is no longer included in the data to the right of that point. Reasons for "censoring" include no follow up available beyond that date, or death from a non-MCC cause.

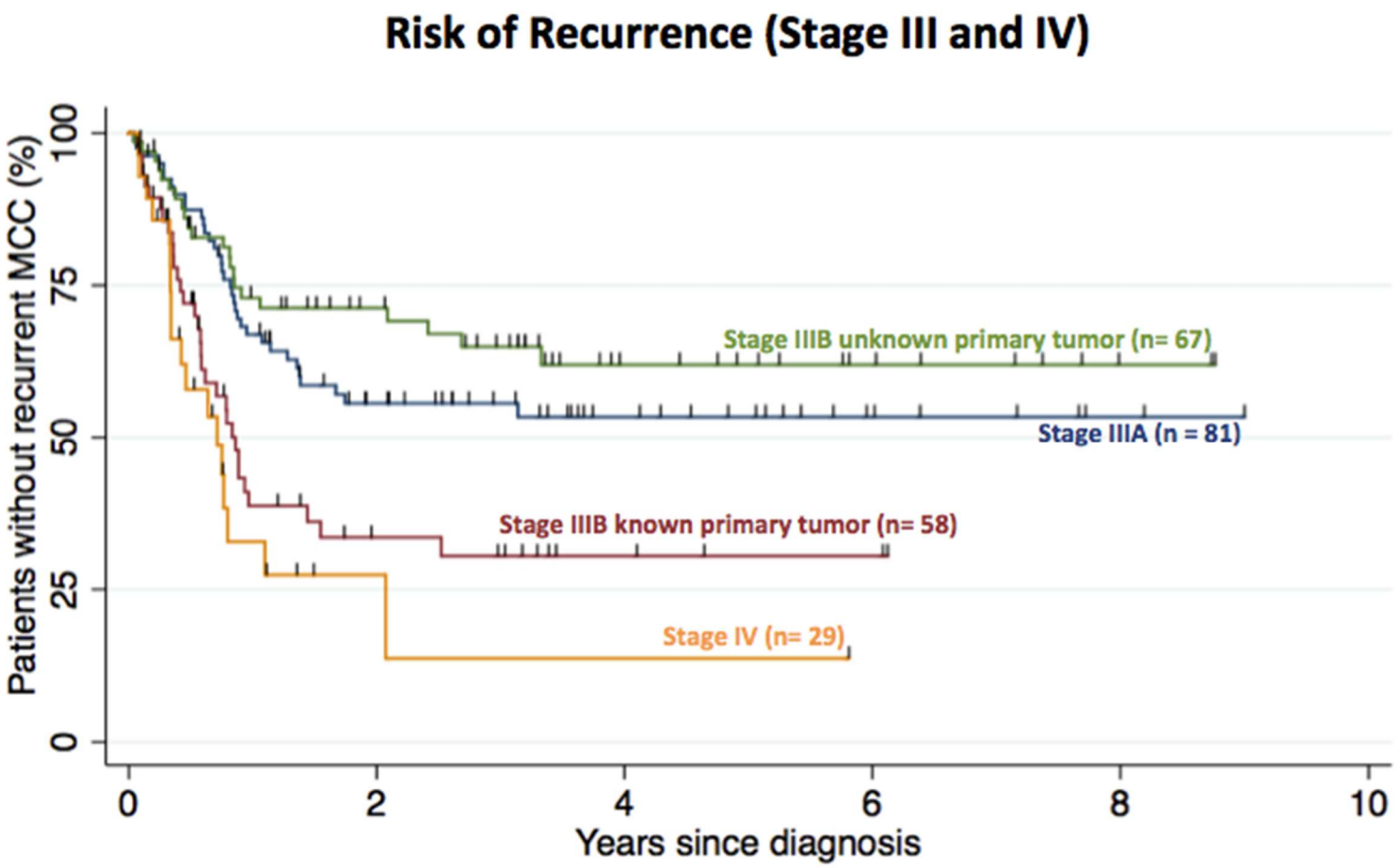
Recurrence risk after MCC

Recurrence-free survival is the chance that MCC has not recurred at a given time after diagnosis. Recurrence-free survival varies by stage, as shown below, but about 80% of all MCC recurrences occur in the first two years after diagnosis.

These graphs can be very helpful in determining how closely a patient needs to be followed. For example, after 2-3 years, the frequency of visits, blood tests and scans can typically start to decrease.



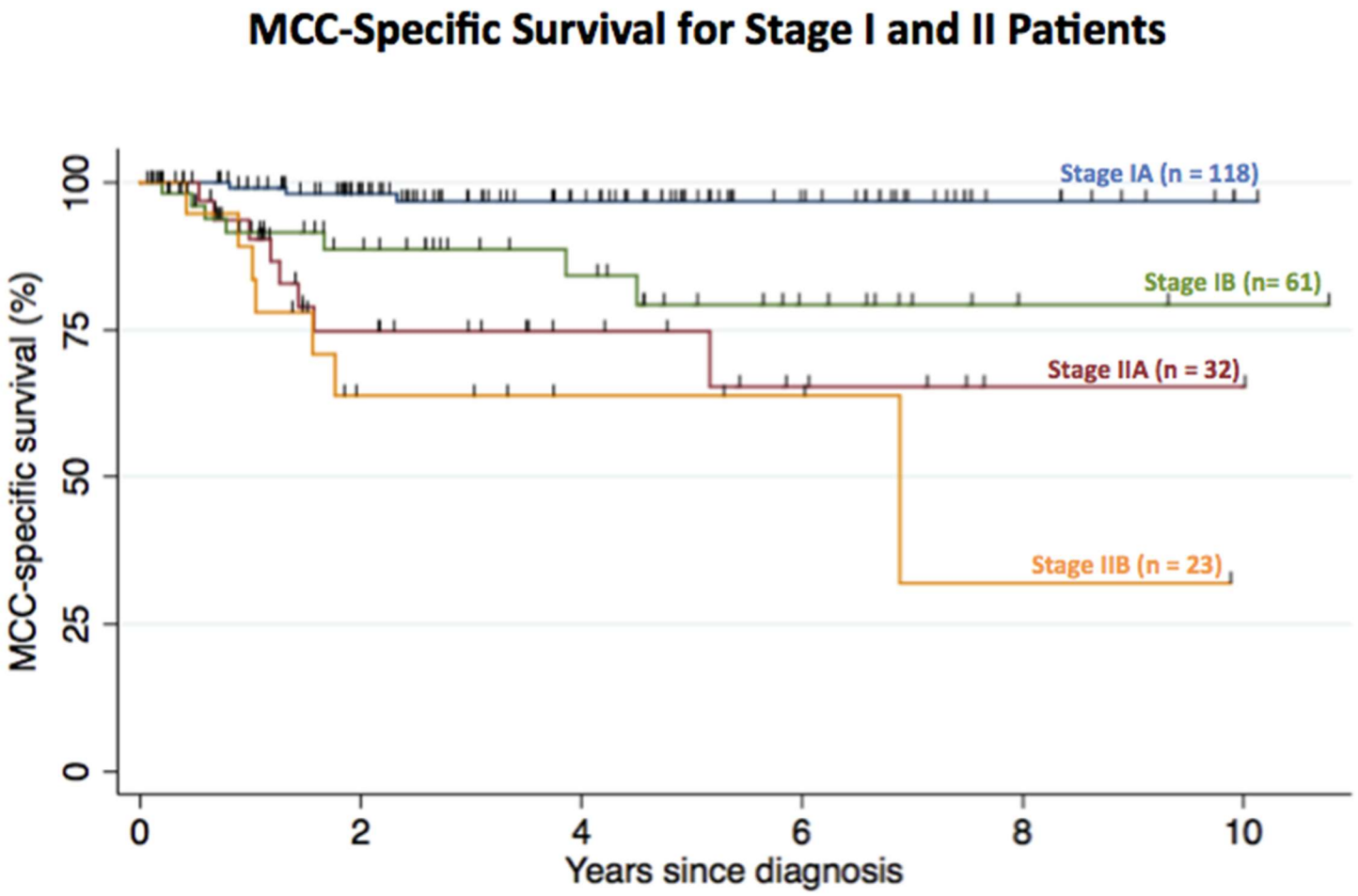
Recurrence free survival for 232 patients with stage I or II MCC. These data are from the patients with stage IA (n=118), stage IB (n=60), stage IIA (n=32) and stage IIB (n=22) enrolled in the Seattle based MCC cohort through December 2015. Staging was per AJCC 7th Edition system.



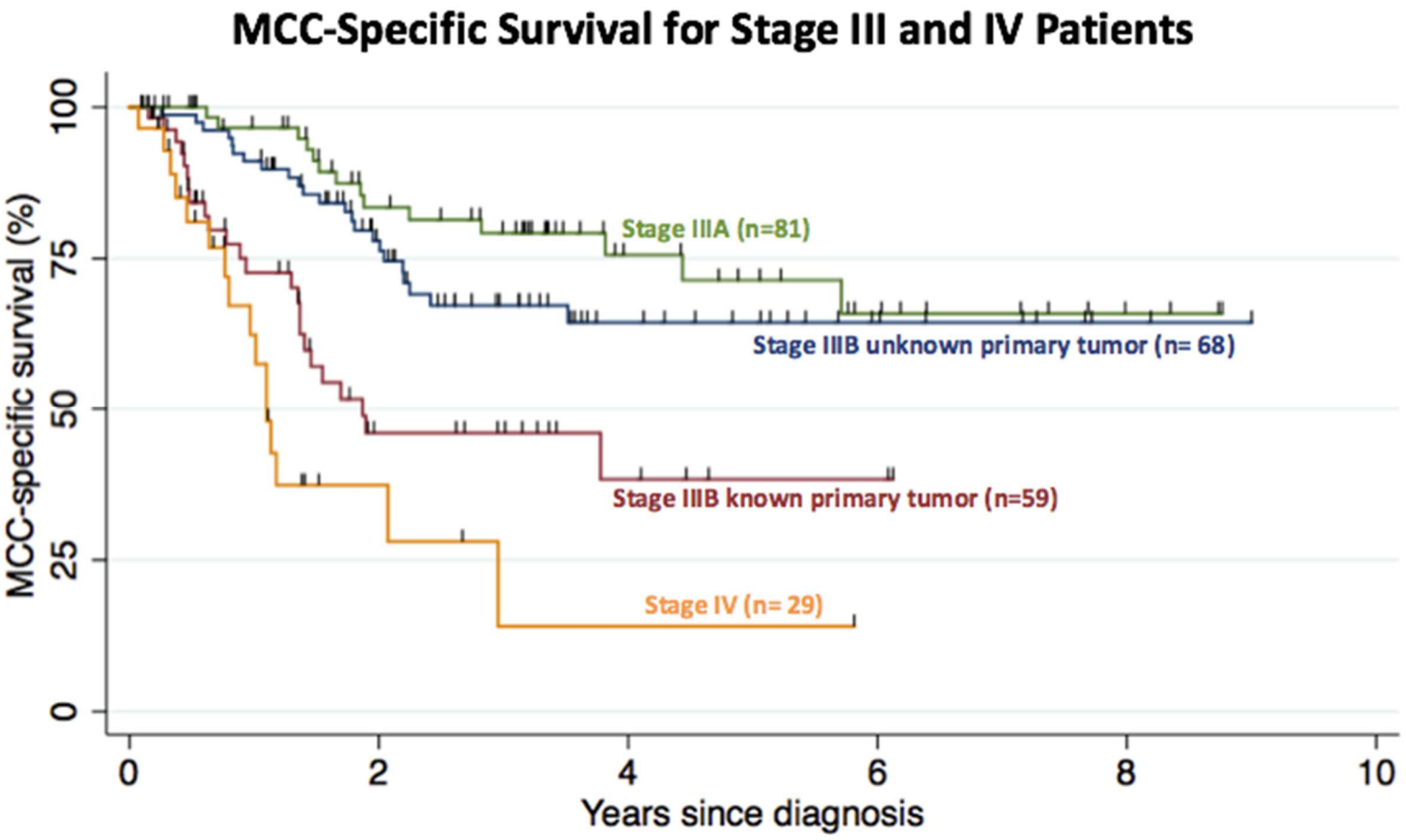
Recurrence free survival for 235 patients with stage III or IV MCC, breaking down stage IIIB known and unknown primary tumors. Some patients present without an identifiable primary MCC tumor (lesion) on the skin. These patients are referred to as having an “unknown primary tumor” and often present instead with an enlarged lymph node containing MCC. Unknown primary Stage IIIB patients have a lower risk of MCC recurrence relative to Stage IIIB patients with known primary tumors. These data are from patients with stage IIIA (n=81), stage IIIB known primary tumors (n=58), stage IIIB unknown primary tumors (n=67) and stage IV (n=29) enrolled in the Seattle based MCC cohort through December 2015. Staging was per AJCC 7th Edition system.

MCC survival rates

MCC-specific survival relates to the percent of patients that will not have died of MCC at various times after diagnosis. In general, patients with local or nodal disease have improved survival compared to patients with distant metastatic disease. Most deaths from MCC occur in the first three years after diagnosis.



MCC-specific survival for 234 patients with stage I or II MCC. These data are from patients with stage IA (n= 118), stage IB (n= 61), stage IIA (n= 32) and stage IIB (n= 23) MCC enrolled in the Seattle-based MCC cohort through December 2015. Staging was per AJCC 7th Edition system.



MCC-specific survival for 237 patients with stage IIIA, stage IIIB with known or unknown primary tumors and with stage IV. Some patients present without an identifiable primary MCC tumor (lesion) on the skin. These patients are referred to as having an "unknown primary tumor" and often present instead with an enlarged lymph node containing MCC. Stage IIIB patients with a known primary tumor have a poorer outcome relative to Stage IIIB patients with an unknown primary tumor. At three years, MCC specific survival for unknown primary tumor is about 80% versus 45% in known tumor patients, 80% stage IIIA, and 15% in stage IV. These data are from patients with stage IIIA (n=81), stage IIIB known primary tumors (n=59) and stage IIIB unknown primary tumors (n=68) and stage IV (n= 29) enrolled in the Seattle based MCC cohort through December 2015. Staging was per AJCC 7th Edition system.

Follow-up care

Merkel cell carcinoma is optimally cared for by a team of doctors from dermatology, surgery, medical oncology, and radiation oncology.

After your initial treatment, you will need to be followed closely by a physician to do regular skin and lymph node exams and take a thorough history. Visits should be approximately every 3 months for year 1 and then every 3-6 months for year 2, and then annually after that.

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 https://merkelcell.org/resources/find-a-specialist/)

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 pnghiem@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: https://merkelcell.org/join-the-fight/participate-in-research-studies/

Donation

All gifts will be used to advance three main goals related to Merkel cell carcinoma: Educating new Merkel cell carcinoma patients and their physicians about this serious and uncommon disease, maintaining and developing serology test to monitor disease status and understanding and reversing immune evasion mechanism of MCC.

While portions of our research endeavors can be very expensive, all contributions help make a difference. For example, our website is exclusively supported by donors. Funds are used for server fees, updates and website maintenance, and we are now also working towards increasing the visibility of our website so that newly diagnosed patients and their physicians may find us early after diagnosis — the most critical time.

Your donation to our Merkel cell carcinoma research effort would be tax deductible, and 100% of your donation would go directly to our research and educational efforts. The family will also receive an acknowledgement letter when a donation is made “in honor” or “in memory” of an MCC patient.

If you are interested in supporting these efforts, please make your donation below using the University of Washington’s secure donation form on our website: https://merkelcell.org/join-the-fight/donate/
Alternately, you can make your tax-deductible donation by writing a check payable to: “University of Washington MCC Research”
and sending it to:

Paul Nghiem, MD, PhD
University of Washington, Dermatology
850 Republican St.
Brotman Building – Room 242, Box 358050
Seattle, WA 98109

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?

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

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.

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. She is now training in UW Dermatology Residency Program.

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 800 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.

Song Park, MD. Dr. Park trained as a dermatologist in Korea and moved to Seattle in 2016, where she is working in Dr. Nghiem's lab as clinical research fellow.

Erica Shantha, MD. Dr. Shantha completed her internship in Seattle at Virginia Mason and served as clinical research fellow in Dr. Nghiem's lab in 2014-2016. She is now training in UW Dermatology Residency Program.

Hannah Thomas, BS. Ms. Thomas worked as an assistant while an undergraduate at UW, and afterwards began working as a research coordinator.

Linda Wang, MD, JD. Dr. Wang was 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.

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.

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