Merkel Cell Carcinoma

Disease Overview

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Disease Overview

MCC is a rare, cutaneous malignancy **more frequently occurring in the elderly** that has a poor prognosis

Clinical Presentation

MCC is diagnosed **more often in men** than women, and its incidence is predicted to increase

Epidemiology

6 **Factors that** may influence outcome and disease burden

Risk Factors

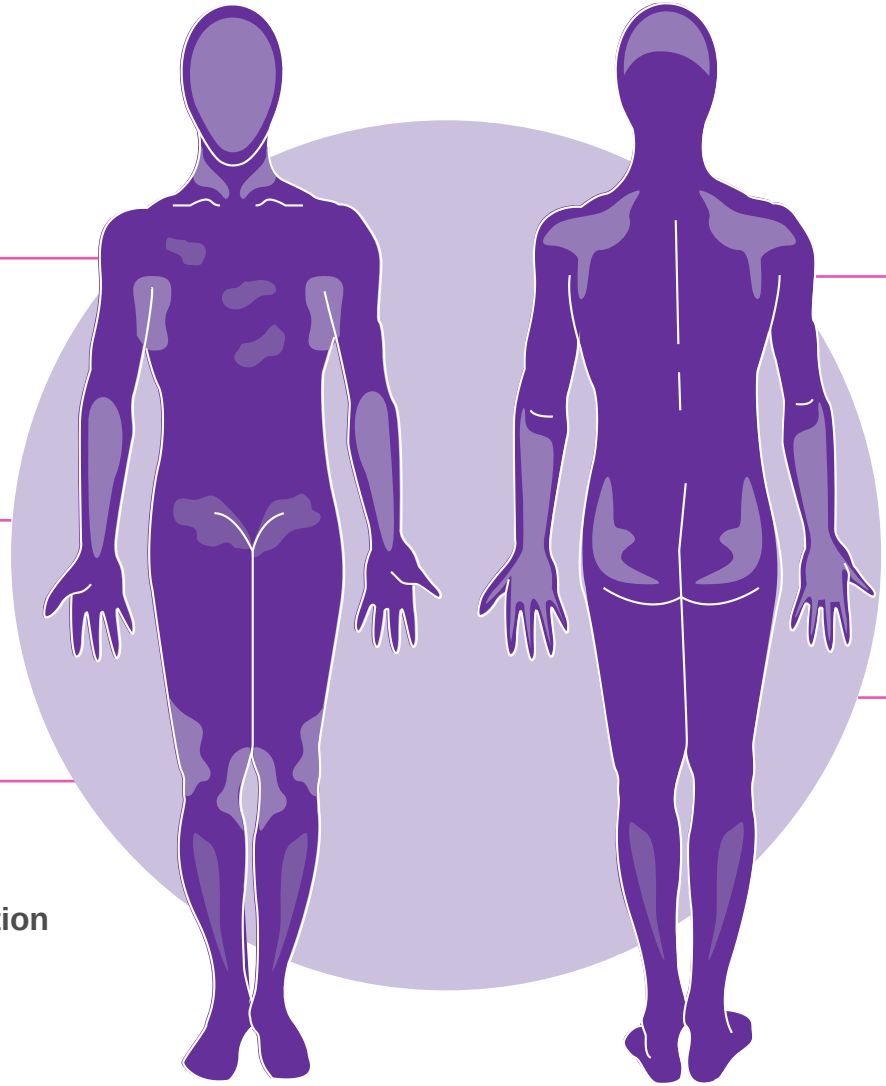
MCC etiology is likely multifactorial

MCPyV infection

Immuno-suppression

Solar radiation

Etiology



MCC is classified in stages

1 to 4

TNM Classification

3.1%

of patients with MCC have distant metastases at diagnosis

53.5%

of patients with MCC are diagnosed at an early stage

Stage/Metastatic Site at Diagnosis

24%

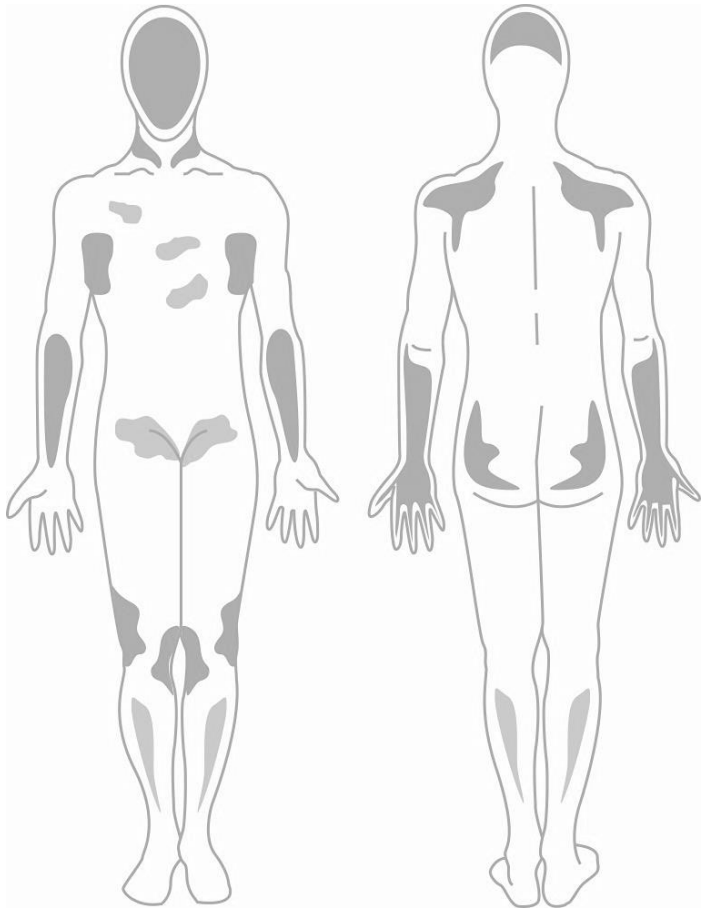
5-year relative survival rate for patients with metastatic disease at diagnosis

Survival

EMD SERONO

Clinical Presentation

ANATOMICAL DISTRIBUTION OF MCC AT PRESENTATION[1]



CLINICAL CHARACTERISTICS OF MCC[1]

The acronym **AEIOU** is often used to summarize the classical clinical characteristics of MCC:

- **A**symptomatic
- **E**xpanding rapidly
- **I**mmune suppression
- **O**lder than 50 years of age
- **U**V exposure on fair skin

- MCC is an ultra-rare neuroendocrine, cutaneous malignancy that occurs more frequently in elderly individuals and has a poor prognosis[2]
- Patients present with a firm, painless, rapidly enlarging, red-violet, cutaneous, dome-shaped tumor nodule[2]
- MCC nodules are often located in **sun-exposed areas** of the head and neck or upper extremities[3]
- MCC commonly occurs on the **face and neck** (40-60%), followed by the trunk (23%), and the extremities (10-20%)[4]

*****MCC distribution evaluated in 195 patients: 168 patients with primary skin lesions and 27 patients with nodal involvement and no known primary lesions.
MCC, Merkel cell carcinoma.

1. Heath M et al. J Am Acad Dermatol. 2018;58(3):375–81; 2. Dellambra E et al. Biomedicines. 2021;9(7):718–41; 3. Smith VA et al. Laryngoscope. 2012;122(6):1283–90; 4. Medina-Franco H et al. Ann Surg Oncol. 2001;8(3):204–8.

Epidemiology

MCC is a very rare form of skin cancer with an incidence rate of **0.7 cases per 100,000 PYs** in the US in 2013, corresponding to **2488 cases per year**[1]

The number of reported MCC cases is rapidly growing, with **an increase of 95% from 2000 to 2013** according to a study of 6600 patients with MCC registered in the SEER database[1]

Due to aging of the Baby Boomer generation, incidences of MCC in the US are **predicted to climb to 2835 cases per year in 2020 and 3284 cases per year in 2025**[1]

MCC incidence **increases exponentially with age,** from 0.1 to 1.0 to 9.8 (per 100,000 PYs) among age groups 40-44 years, 60-64 years, and ≥85 years, respectively[1]

- Consequently, MCC is primarily a **disease of the elderly** with a **median age of 76 years (1986 to 2004)**[2]

The **incidence of MCC is higher in men than in women,** as shown in a study of 3870 MCC cases identified in the SEER database between 1973 and 2006 (0.41 [95% CI: 0.38-0.43] per 100,000 PYs in men vs 0.18 [95% CI: 0.17–0.19] per 100,000 PYs in women; $p<0.05$)[3]

Patients with MCC are **mostly Caucasian (96.4%),** with African American (1.2%) and people of Asian descent (0.8%) making up a very small portion[4]

MCC, Merkel cell carcinoma; **PY**, person-year; **SEER**, Surveillance, Epidemiology, and End Results Program; **US**, United States.

1. Paulson KG et al. J Am Acad Dermatol. 2018;78(3):457–63.e2; 2. Lemos BD et al. J Am Acad Dermatol. 2010;63(5):751–61; 3. Albores-Saavedra J et al. J Cutan Pathol. 2010;37(1):20–7; 4. Harms KL et al. Ann Surg Oncol. 2016;23(11):3564–71.

Select Risk Factors Influencing Clinical Outcome

TUMOR STAGE

Patients with advanced disease (stage III and stage IV) have an increased risk of MCC-specific mortality compared with patients with stage I tumors[1,2]

TUMOR HISTOLOGY & LOCATION

Lymphovascular invasion, tumor growth pattern, and lymph node number have all been shown to affect disease outcome[1,3-5]

BIOMARKERS

PD-L1, p63, VEGFR-2, MMP, and KIT are predictive of a worse disease prognosis in patients with MCC[2,6-11]

HOST FACTORS

Male sex, advanced age, CD8+ infiltration, vitamin D deficiency, and immunosuppression are prognostic host factors for MCC[12-17]

MCPyV INFECTION

MCPyV-negative MCC may represent a more aggressive subtype and may warrant closer clinical follow-up[18]

SECONDARY MALIGNANCIES

Patients diagnosed with MCC are at risk of developing secondary cancers[19]

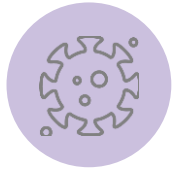
MCC, Merkel cell carcinoma; **MCPyV**, Merkel cell polyomavirus; **MMP**, matrix metalloproteinase; **PD-L1**, programmed death-ligand 1; **VEGFR-2,** vascular endothelial growth factor receptor-2.

1. Andea AA et al. Cancer. 2008;113(9):2549–58; 2. Stetsenko GY et al. Am J Clin Pathol. 2013;140(6):838–44; 3. Iyer JG et al. J Am Acad Dermatol. 2014;70(4):637–43; 4. Ko JS et al. Mod Pathol. 2016;29(2):122–30; 5. Henderson SA et al. J Cutan Pathol. 2014;41(11):846–52; 6. Lipson EJ et al. Cancer Immunol Res. 2013;1(1):54–63; 7. Asioli S et al. Cancer. 2007;110(3):640–47; 8. Asioli S et al. Mod Pathol. 2011;24(11):1451–61; 9. Kukko H et al. Anticancer Res. 2007;27(4C):2587–89; 10. Fernandez-Figueras MT et al. Mod Pathol. 2007;20(1):90–101; 11. Andea AA et al. Hum Pathol. 2010;41(10):1405–12; 12. Chen MM et al. JAMA Otolaryngol Head Neck Surg. 2015;141(2):137–41; 13. Smith VA et al. Laryngoscope. 2012;122(6):1283–90; 14. Paulson KG et al. Am J Clin Pathol. 2014;142(4):452–8; 15. Asgari MM et al. JAMA Dermatol. 2014;150(7):716–23; 16. Paulson KG et al. J Invest Dermatol. 2013;133(3):642–46; 17. Schadendorf et al. Eur J Cancer. 2017;(71):53-69; 18. Shantha E, Nghiem P. Merkel cell carcinoma multicenter interest group: Summary of 10th Annual Meeting. 2015; 19. Saxena A et al. J Skin Cancer. 2014;2014:184245.

Etiology

The etiology of MCC is likely multifactorial, with immunosuppression, UV-induced skin damage, and viral factors contributing to its development[1]

MCPyV INFECTION

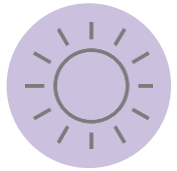


- MCPyV, a DNA virus, is detected in approximately 80% of MCC cases[2]
- Likely to be part of the normal skin flora, MCPyV DNA is nearly ubiquitous in the normal skin of healthy individuals[3]
- Infection likely occurs during childhood, but remains largely asymptomatic in adults[4,5]
- The early gene region of MCPyV encodes ST and LT, both of which are independently required for modulation of the host cell and viral replication[6]
- The oncogenic potential of MCPyV is thought only to occur upon clonal integration into the host genome; spontaneously or through exogenous mutations in the 3' end of the LT[3,7]
- ST appears to be the major transforming oncogene in MCC[7]

IMMUNOSUPPRESSION

- A key factor in the development of MCC, which appears to be associated with a worse prognosis[8,9]
- The relative risk for MCC is approximately 13-fold higher in HIV and about 5-fold higher in solid organ transplantation recipients than the general population[9]

SOLAR RADIATION



- UV-B rays induce mutations in the tumor suppressor p53 and Ha-ras genes, increasing the risk of cancer[8]
- The UV-B index is positively associated with MCC incidence[8]
- MCPyV-negative tumors exhibit a high mutation burden associated with UV-induced DNA damage[10,11]

HIV, human immunodeficiency virus; **LT**, large T antigen; **MCC**, Merkel cell carcinoma; **MCPyV**, Merkel cell polyomavirus; **ST**, small T antigen; **UV**, ultraviolet.

1. Saini AT, Miles BA. Onco Targets Ther. 2015;8:2157–67; 2. Feng H et al. Science. 2008;319(5866):1096–100; 3. Tothill R et al. Am Soc Clin Oncol Educ Book. 2015;e519–26; 4. Martel-Jantin C et al. J Clin Virol 2013;58(1):288–91; 5. Tolstov YL et al. Emerg Infect Dis 2011;17(8):1371–80; 6. Liu W, You J. Annu Rev Virol 2020; 7(1): 289-307; 7. Arora R et al. Curr Opin Virol 2012;2(4):489–98; 8. Ma JE, Brewer JD. Cancers (Basel) 2014;6(3):1328–50; 9. Desch L, Kunstfeld R. J Skin Cancer 2013;2013:327150; 10. Wong SQ et al. Cancer Res 2015;75(24):5228–34; 11. Harms PW et al. Cancer Res 2015;75(18):3720–7.

TNM Classification: MCC Is Classified in Stages I to IV

The **consensus staging system** for MCC was introduced by the AJCC in 2010[1] and updated in 2016 to help clinicians better stratify patients into groups based on their predicted survival, emphasizing the difference between clinically and pathologically determined staging[2,3]

I **STAGE I**
Primary tumor size ≤2 cm

II **STAGE II**
Primary tumor size >2 cm

III **STAGE III**
Positive nodal disease

IV **STAGE IV**
Distant metastasis

CLINICAL STAGE GROUPS (cTNM)

STAGE	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-3	N0	M0
IIB	T4	N0	M0
III	T0-4	N1-3	M0
IV	T0-4	Any N	M1

PATHOLOGICAL STAGE GROUPS (pTNM)

STAGE	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-3	N0	M0
IIB	T4	N0	M0
IIIA	T1-4	N1a(sn) or N1a	M0
	T0	N1b	M0
IIIB	T1-4	N1b-3	M0
IV	T0-4	Any N	M1

Part 1 Part 2

AJCC, American Joint Commission on Cancer; **M**, metastasis; **MCC**, Merkel cell carcinoma; **N**, node; **T**, tumor.

1. Edge SB et al. AJCC Cancer Staging Manual. 7th ed. 2010; 2. Harms KL et al. Ann Surg Oncol. 2016;23(11):3564–71; 3. American Joint Committee on Cancer. Merkel Cell Carcinoma. In: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017:549.

TNM Classification: MCC Is Classified in Stages I to IV, cont'd

The **consensus staging system** for MCC is classified by tumor, node, and metastasis criteria

T	N		M
Tx, primary tumor cannot be assessed	cNx, regional lymph nodes cannot be clinically assessed (eg, previously removed for another reason, body habitus)	pNx, regional lymph nodes cannot be assessed (eg, previously removed for another reason) or not removed for pathological evaluation	M0, no distant metastasis
T0, no primary tumor	cN0, no regional lymph node metastasis by clinical or radiological evaluation	pN0, no regional lymph node metastasis detected on pathological evaluation	M1, distant metastasis
Tis, in situ primary tumor	cN1, clinically detected regional nodal metastasis	pN1a(sn), clinically occult nodal metastasis identified only by sentinel lymph node biopsy	M1a, metastases to distant skin, distant subcutaneous tissue, or distant lymph nodes
T1, primary tumor ≤2 cm	cN2, in-transit metastasis without lymph node metastasis	pN1a, clinically occult regional lymph node metastasis following lymph node dissection	M1b, metastasis to lung
T2, primary tumor >2 cm but ≤5 cm	cN3, in-transit metastasis with lymph node metastasis	pN1b, clinically or radiologically detected regional lymph node metastasis, pathologically confirmed	M1c, metastasis to all other visceral sites
T3, primary tumor >5 cm		pN2, in-transit metastasis without lymph node metastasis	
T4, primary tumor invades fascia, muscle, cartilage, or bone		pN3, in-transit metastasis with lymph node metastasis	

AJCC, American Joint Commission on Cancer; **c**, clinical; **M**, metastasis; **MCC**, Merkel cell carcinoma; **N**, node; **p**, pathologic; **T**, tumor.

Harms KL et al. Ann Surg Oncol. 2016;23(11):3564–71.

Stage at Diagnosis and Sites of Metastasis

MCC

Percentage of patients with MCC per clinical stage, as presented at diagnosis[1,*]

STAGE	PATIENTS, %
I	53.5
II	21.4
III	13.8
IV	**3.1**
Unknown	8.2

- MCC develops at an exponential rate on chronically sun-damaged skin, with a doubling time of 5 days to 12 days[2,3]
- MCC grows in an infiltrating manner in the initial stages of disease, and satellite metastases may occur early in development of the disease[4]

METASTATIC MCC

Common metastatic sites of MCC[5,6]

METASTATIC SITE	PATIENTS, %
Lymph nodes	**60**
Skin	30
Lung	23
CNS	18
Bone	15

- Progression to metastatic disease is a frequent phenomena post locally advanced disease and typically observed within the first 2 years following diagnosis[7]
- Recurrence in MCC is high, particularly in patients with a positive SLNB[8]

*Based on 159 patients with a median age of 75 years treated for MCC between 2002 and 2020 at a single institution.

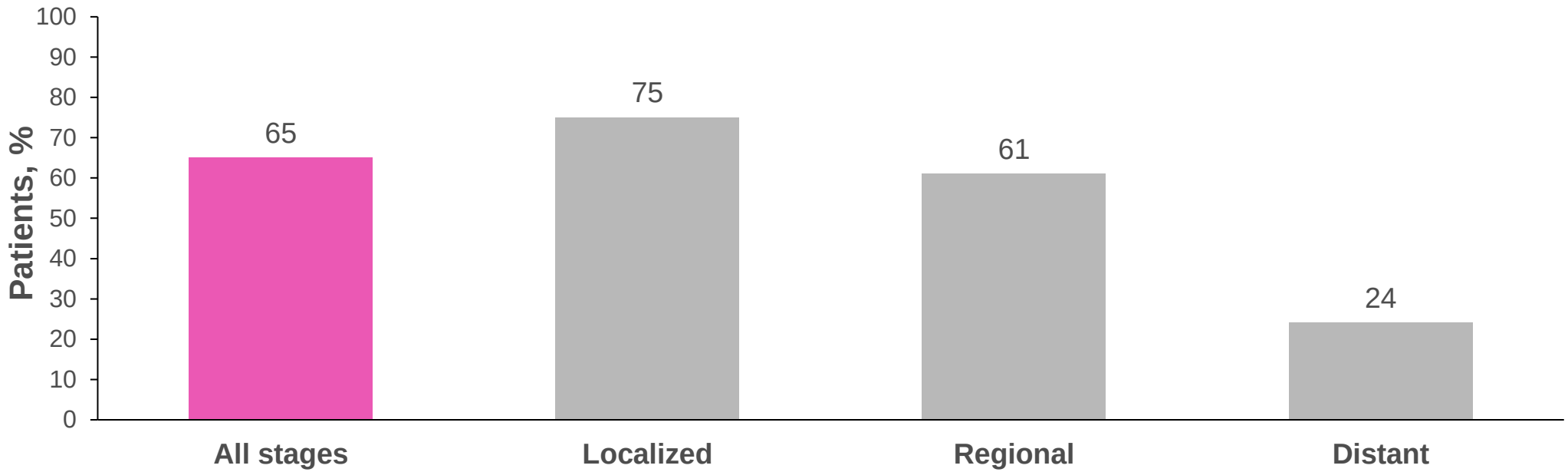
CNS, central nervous system; **MCC**, Merkel cell carcinoma; **SLNB**, sentinel lymph node biopsy.

1. Esposito A et al. Ann Surg Oncol. 2022;29(1):415–24; 2. Poulsen M. Drugs Aging 2005;22(3):219–29; 3. Swann MH, Yoon J. Semin Oncol 2007;34(1):51–6; 4. Becker JC. Ann Oncol 2010;21(suppl 7):vii81–5; 5. Medina-Franco H et al. Ann Surg Oncol 2001;8(3):204–8; 6. Voog E et al. Cancer 1999;85(12):2589–95; 7. Allen PJ et al. J Clin Oncol 2005;23(10):2300–9; 8. Gupta SG et al. Arch Dermatol 2006;142(6):685–90.

5-Year Survival by Stage at Diagnosis

- MCC exhibits aggressive clinical features and is associated with a poorer prognosis and lower survival compared with other aggressive skin malignancies, such as melanoma[1-4]
- According to an analysis of data from the SEER database between 2012 and 2018, tumor stage significantly affects survival, with higher mortality rates with more advanced disease[5]

FIVE-YEAR RELATIVE SURVIVAL BY MCC STAGE AT DIAGNOSIS, 2012-2018[5]



MCC, Merkel cell carcinoma; **SEER**, Surveillance, Epidemiology, and End Results Program.

1. Saini AT, Miles BA. Onco Targets Ther 2015;8:2157–67; 2. Chen MM et al. JAMA Otolaryngol Head Neck Surg 2015;141(2):137–41; 3. Smith VA et al. Laryngoscope 2012;122(6):1283–90; 4. Grabowski J et al. Clin Med Oncol 2008;2:327–33; 5. American Cancer Society. Survival Rates for Merkel Cell Carcinoma. Accessed December 8, 2023. https://www.cancer.org/cancer/types/merkel-cell-skin-cancer/detection-diagnosis-staging/survival-rates.html