

**Merkel Cell Carcinoma:
Diagnosis, Management and Controversies
Forum F011; Room: D237
Friday, March 01, 2013, 10:00 – 12:00 pm
American Academy of Dermatology Annual Meeting
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DESCRIPTION

Merkel cell carcinoma (MCC) is a polyomavirus-associated skin cancer with a higher disease-associated mortality (~46%) than melanoma (~15%) and an increasing incidence of ~1600 cases/year in the US. Management is challenging because therapy is different in nature than for other skin malignancies and is controversial within the literature. Multi-disciplinary care involving surgery, radiation, and medical oncology is often indicated. This session will highlight areas of consensus and controversy in the viral etiology, clinical presentation, staging, pathology and evolving management of MCC. Representative and challenging cases will be presented to highlight treatment options and relevant data.

LEARNING OBJECTIVES

Following this forum, the attendee will be able to:

1. Delineate areas of controversy and consensus regarding the risk factors; incidence; clinical, pathologic, and prognostic characteristics of Merkel cell carcinoma.
2. Analyze data linking the Merkel cell polyomavirus and immune evasion by this cancer to outcomes and emerging therapies.
3. Utilize this information to guide the multidisciplinary management of representative cases.

OUTLINE OF SESSION

10:00 - 10:20 a.m. Introduction, Epidemiology, Staging/Dr. Nghiem
10:20 - 10:45 a.m. Pathologic diagnosis, Features and Prognostic implications/Dr. Andea
10:45 - 11:15 a.m. Surgery, Sentinel lymph node biopsy, Radiation & Case examples/ Dr. Bichakjian
11:15 a.m. - 11:40 a.m. Merkel polyomavirus, immunity and future targeted therapies/Dr. Nghiem
11:40 a.m. - 12:00 a.m. Questions and Answers/All faculty

Handout prepared by: Paul Nghiem, MD, PhD, Jayasri Iyer MD, and Amy Bestick, University of Washington, Seattle, WA
See www.merkelcell.org for more info. For a pdf of this handout go to
<http://www.merkelcell.org/usefulInfo/documents/AadMccForumHandout2013.pdf>.

Handout Outline

PART 1: INTRODUCTION, CLINICAL FEATURES & VIRUS

PART 2: PATHOLOGY & PROGNOSTIC FEATURES

PART 3: STAGING & PROGNOSIS

PART 4: MULTIDISCIPLINARY MANAGEMENT AND ROLE OF RADIATION THERAPY

PART 5: SUMMARY

PART 6: ANNOTATED REFERENCES

PART 1: INTRODUCTION, CLINICAL FEATURES & VIRUS

Fatality Rates: (Agelli et al., JAAD, 2003) (Cancer Facts & Figures 2009, American Cancer Society)

Angiosarcoma	3 in 4
MCC	~1 in 2 (46% in Lemos, 2010)
Melanoma	1 in 8
Sq Cell CA	1 in 50
Basal Cell CA	<1 in 10,000

Reported Incidence in SEER database has quadrupled from 1986 - 2006:

1986	0.15 per 100,000 (Hodgson et al., J Surg Oncol, 2005)
2001	0.44 per 100,000 (Hodgson et al., J Surg Oncol, 2005)
2006	0.6 per 100,000 (Albores-Saavedra et al., J Cutan Pathol 2009)

Current Estimate of ~1600 cases/year in US:

- ~950 cases/year in 1997 (Pan et al., Plas & Reconstr Surg 2002, CT Tumor Registry)
- ~1500 cases/year in 2004 (Lemos & Nghiem, JID, 2007, NCDB data)
- ~1630 cases/year in 2006 (Albores-Saavedra et al., J Cutan Pathol 2009, SEER data)

Risk factors will translate to increasing incidence in future:

- Age >65 yr associated with striking increase in MCC
- Fair skin / prolonged sun exposure / PUVA therapy
- Profound immune suppression (HIV, solid organ transplant, CLL)
 - 2.3-fold increase among patients with AIDS (Engels et al, Int J Cancer, 2010)
 - ~ 5 fold increase after solid organ transplantation (Engels et al., Int J of Cancer, 2009)
 - 15.7-fold increased risk of MCC following CLL diagnosis and 17-fold increased risk of CLL following MCC diagnosis (Koljonen V et al., British Journal of Cancer, 2009)

Merkel cell polyomavirus (MCPyV):

- 2008: Feng, Moore, Chang discovered a new human polyomavirus, the Merkel cell polyomavirus (MCPyV)
- Virus integrates in the genome of most MCC tumors in a clonal pattern (Feng H et al., Science 2008)
- Viral DNA present in ~80% MCC tumors
- MCPyV oncoproteins are present and persistently expressed in 80-90% of MCCs (sT protein expression in 92% of 51 cases; Shuda et al, JCI, 2011)
- Mutation pattern in the large T oncoprotein is highly suggestive of a role in this cancer: N terminal is conserved (needed for cell cycle promotion), C terminal is deleted (would kill cancers due to viral DNA replication at chromosomal integration site) (Shuda et al., Proc Natl Acad Sci U S A. 2008)
- Elimination of T-Ag from tumor cell lines results in inhibited growth or tumor cell apoptosis (Houben, R et al., Journal of Virology, 2010; Houben, R et al., Int J of Cancer, 2011).

Antibodies to the Merkel cell polyomavirus:

Anti-VP1 (capsid protein) antibodies:

- ~60% of US population have antibodies to MCPyV capsid (coat) protein (Carter JJ et al., J Natl Cancer Inst. 2009)
- Children as young as 5 years old are often seropositive (Chen T et al., J Clin Virol 2011)
- ~90% of MCC patients are seropositive for the MCPyV capsid protein

Anti-T-Ag (oncoprotein) antibodies:

- A high level of anti-MCPyV T-Ag antibody is specific for recent MCC disease
- Antibody levels fluctuate dynamically in response to changing disease burden (i.e. increased antibodies → recurrent or progressive disease)
- Increasing antibody titers can thus serve as a biomarker of recurrent disease (Paulson KG et al, Cancer Research 2010)
- Baseline serum (within 3 months) of MCC treatment is critical for determining change over time
- This blood test is currently available, free of charge on a research basis as detailed at <http://www.merkelcell.org/help/participate.php>

MCC management is often not optimal:

Underused therapies:

Sentinel lymph node biopsy

Radiation therapy

Overused therapies:

Over-aggressive surgery/amputation

Chemotherapy in adjuvant setting

CLINICAL PRESENTATION**Non-specific clinical presentation of MCC:**

Firm, red to purple non-tender papule/nodule

Rapid growth within prior 1-3 months

Usually on a sun-exposed location (~15% are not)

Ulceration is very rare

Clinical Features of MCC: *(Heath, et al., JAAD, 2008)*

MCC Clinical Feature*		No.	Percentage
A	Asymptomatic/lack of tenderness	87/89	88
E	Expanding rapidly	57/91	63
I	Immune suppressed	15/193	8**
O	Older than 50	175/195	90
U	UV exposed	136/168	81
	Fair skin	191/195	98

*89% patients had 3 or more of these features.

**8% of MCC patients with immunosuppression (chronic-profound) is 16-fold over-represented relative to general population

Presumed diagnosis at time of biopsy:

(141 presumed diagnoses analyzed from among 106 cases; Heath, et al., JAAD, 2008)

57% "Benign"

(Cyst/acneiform lesion in 36% of all cases)

34% "Malignant"

(Non-melanoma skin CA in 14% of all cases)

8% "Indeterminate"

("Nodule/mass" in 6% of all cases)

PART 2: PATHOLOGY & PROGNOSTIC FEATURES

Merkel cells are mechanoreceptors (fine touch) within basal epidermis

Prior to CK20 antibody (early 1990s) many cases were misdiagnosed as lymphoma, SCLC etc.

Three histologic patterns of MCC (all with similar prognosis):

Intermediate type (most common type): ddx: small blue cell tumors/melanoma/lymphoma

Small cell type: ddx: small cell lung CA (SCLC)

Trabecular type: ddx: metastatic carcinoid

STAIN	MCC	SMALL CELL LUNG CANCER	LYMPHOMA	MELANOMA
CK 20*	+ (perinuclear dot-like pattern)	-	-	-
CK 7 or TTF1	Usually negative	+	-	-
LCA	-	-	+	-
CM2B4 or Ab3**	Typically positive	-	-	-
S100	-	-	-	+

* 87% of MCC vs 4.6% of SCLC are CK20 positive (*Bobos et al. Am J of Dermatopathol, 2006*)

** CM2B4 and Ab3 antibodies recognize the MCPyV T antigen oncoprotein. Ab3 was described in 2012 (Rodig, et al JCI, 2012) and appears to be more sensitive & specific than CM2B4 (Busam KJ, et al. *Am J Surg Pathol. 2009*)

PROGNOSTIC FEATURES:

- **Lymphovascular invasion (LVI) in primary tumor:** Most MCC path reports do not comment on LVI.
 ** *You need to call the pathologist and request an addendum***
 - **Recurrence and survival** are strongly associated with LVI in the primary tumor in one large cohort:
 - 83 of 162 (51%) LVI-positive patients developed recurrence as compared to 2 of 132 (1.5%) LVI-negative patients (*Fields RC, Cancer 2011*)
 - LVI-positive patients: 15% 2-year cumulative incidence of death from MCC
 - LVI-negative patients: 0% death in 2 years (*Fields RC, et al., Ann Surg Oncol, 2011*).
 - **Nodal involvement** is controversially associated with LVI: One study strongly associated LVI with a positive SLNB (55% of LVI-positive patients (n=75) were SLNB positive compared to 4% of LVI-negative patients (n=69); p<0.01 (*Fields RC, et al., Ann Surg Oncol, 2011*). Another study found no significant association between LVI and nodal spread (LVI-negative cases (n=52) had 39% SLNB positivity; LVI-positive cases (n=38) had a 53% SLNB positivity) *Schwartz JL et al., J Clin Oncol. 2011*
- **CD8 T-cell infiltration and Improved survival:**
 - Patients with robust CD8+ intratumoral infiltration (n=26) had 100% MCC-specific survival as compared to 60% survival among those with sparse or no CD8+ intratumoral infiltration (n=120) (*Paulson K, et al., J Clin Oncol 2011*).
 - CD8+ infiltration predicted excellent survival even for patients presenting with nodal/distant disease
 - These results were validated in two independent cohorts (*Sihto, Clin Ca Res 2012; Paulson K, unpublished*)
- **Viral status and MCC clinical outcome is controversial:**
 - One study of German and Australian MCC cases (n=174) found no link between tumor viral status & survival (*Schrama et al., J Invest Dermatol. 2011*)
 - A Finnish study of 114 MCC patients found that MCPyV DNA in the tumor was associated with improved survival in a multivariate analysis (Hazard Ratio of death of 0.42 for virus-positive vs. virus-negative cases; 95% CI = 0.25 to 0.71, P = .001) (*Sihto et al, J Natl Cancer Inst. 2009*)
- **Immune suppression & survival:**
 - Patients with chronic immune suppression are roughly twice as likely to succumb to MCC as those with normal immune function (*Paulson JID 2013*)

PART 3: STAGING & PROGNOSIS

2010 AJCC staging system for MCC: (AJCC Cancer staging Manual, 2010; Lemos, et al., JAAD, 2010)

Stage	Stage Grouping	Stage Description	1-yr relative survival	3-yr relative survival	5-yr relative survival
Stage 0:	0	Tumor in situ	----*	----*	----*
Stage I: Local, tumor diameter ≤ 2cm	IA	Nodes microscopically negative and not clinically detectable	100	86	79
	IB	Nodes not clinically detectable (no pathologic eval of nodes done)	90	70	60
Stage II: Local, tumor diameter > 2cm	IIA	Nodes microscopically negative and not clinically detectable	90	64	58
	IIB	Nodes not clinically detectable (no pathologic eval of nodes done)	81	58	49
	IIC	Primary tumor invading bone/muscle/fascia/cartilage	72	55	47
Stage III: Regional Nodal Disease	IIIA	Micrometastasis**	76	50	42
	IIIB	Macrometastasis*** (clinically detectable node or intransit metastases****)	70	34	26
Stage IV: Distant Metastatic Disease	IV	Distant Metastatic Disease	44	20	18

* No data are available for in situ MCC tumors, but survival is expected to be excellent

** Micrometastases are diagnosed after sentinel or elective lymphadenectomy

*** Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically by biopsy or therapeutic lymphadenectomy.

**** In-transit metastasis is 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.

Sentinel lymph node biopsy is often indicated in MCC:

Occult nodal disease is much more common in MCC than melanoma.

Average MCC (1.7 cm diameter): ~33% positive SLNB in many studies

Average melanoma (0.63mm Breslow thickness): ~1% positive SLNB

(Gupta et al., *Arch Dermatol*, 2006; Goggins, et al, *Int J Cancer*, 2006; Lens, et al, *Br J Surg*, 2002)

SLNB-positive patients benefitted from adjuvant nodal therapy:

0% recurrence-free survival if no adjuvant tx (n=3)

~60% recurrence-free survival if adj XRT or Surg given (n=26); (p<0.01)

When might SLNB not be indicated?

Some groups pursue SLNB in all MCC cases, but its benefit is less (and Seattle team often doesn't employ) if:

- The draining node bed will be treated regardless of the SLNB result (eg. when the node bed is close to primary) **and** the patient does not value the prognostic information of SLNB
- When SLNB has a higher false negative risk (eg. primary overlies parotid)

CT Scans: Data from Gupta, et al., *Arch Dermatol*, 2006. CT scans in 34 cases, PET scan in 1 case; Gold Standard for presence of disease was pathologic dx within 6 months of CT/PET Scan

- **CT Scans for NODAL DISEASE**

Sensitivity (of scans for nodal disease) 20%
(4 of 20 pts with nodal disease called positive by scans)

Specificity (of scans for nodal disease) 87%
(13 of 15 pts without nodal disease called negative by scans)

- **CT Scans for DISTANT SPREAD**

Sensitivity (of scans for distant sites) 100%
(4 of 4 pts with distant disease called positive by scans)

Specificity (of scans for distant sites) 48%
(16 of 33 pts without distant disease called negative by scans)

CT Scan Summary

CT Scans failed to detect nodal disease in all 7 pts with positive SLNB
(who also received scans)

No true disease detected by scans in SLNB-negative patients.

14 false positive nodal scans per one unique* true positive scan
(*identified by scan only and not by exam/history)

True negative scan for distant spread: 100% (16 of 16 pts)

Bottom line on CT Scans:

- **For detecting nodal disease: SLNB sensitivity >> CT Scan sensitivity**
- **Scans not very useful if small primary or if SLNB is negative**
- **Scans useful for SLNB-positive patients to rule out distant spread and serve as baseline scans for comparison**
- **PET-CT scans are marginally more sensitive & specific than CTs** (Colgan, et al JAAD 2012; Hawryluk, JAAD 2012), **but are more costly and are not as often covered by insurance.**

Diagnostic codes for Merkel cell carcinoma: (Iyer et al, *Actas Dermosifiliogr*. 2009)

MCC is no longer coded as 173.x (malignant neoplasm of skin). Seven MCC-specific diagnostic codes were adopted for use beginning in October 2009. Introduction of these specific codes improves the ability to obtain insurance approval for appropriate procedures/tests for MCC (ICD codes are used by insurance companies to approve/deny coverage) and should improve tracking MCC-associated costs.

ICD CODE	DISEASE
209.31	Merkel cell carcinoma of the face
209.32	Merkel cell carcinoma of the scalp and neck
209.33	Merkel cell carcinoma of the upper limb
209.34	Merkel cell carcinoma of the lower limb
209.35	Merkel cell carcinoma of the trunk
209.36	Merkel cell carcinoma of other sites including buttocks and genitals
209.37	Secondary Merkel cell carcinoma (presenting in nodal or visceral sites without known primary)
V10.91	Personal history of malignant neuroendocrine tumor (should be used when seeing a patient more than 5 years after an MCC tumor was last treated)

PART 4: MULTIDISCIPLINARY MANAGEMENT AND ROLE OF RADIATION THERAPY:

Surgery and Radiation in MCC:

Can MCC be treated like BCC? (no)

Simple excision with 0.5 cm margins:

100% recurrence in 38 pts (*Meeuwissen, et al 1995*)

Can MCC be treated like SCC/Melanoma? (only in selected low risk cases--see page 9)

For wide local excision >2.5 cm margins:

49% regional recurrence/persistence; n=41 pts (*O'Connor, et al 1997*)

Is Mohs excision alone sufficient? (only in selected low-risk cases--see page 9)

Mohs excision +/- "safety margin" of 1 cm:

16% recurrence in 25 patients (*Boyer et al., JAAD, 2002*)

Mohs + XRT:

0% recurrence in 20 patients (*Boyer et al., JAAD, 2002*)

Can MCC be treated by XRT only? (in some cases)

XRT monotherapy is effective in treating extensive/inoperable local disease (*Multiple examples in our series and in the literature: Mortier et al., Arch Dermatol, 2003, Veness et al., Int. J. Radiation Oncology Biol. Phys, 2009*)

43 patients treated with radiation monotherapy in a retrospective analysis had 75% loco-regional/in-field control rates at 39 months median f/u. (*Veness et al., Int. J. Radiation Oncology Biol. Phys, 2009*)

2 of 25 patients treated with RT alone (median dose 65 Gy) to primary site + node bed had regional nodal recurrence as compared to 4 of 25 patients treated with surgery + RT (median 55 Gy) to primary + node bed at 3 yr f/u. No difference in overall or disease-free survival between patients who received RT alone or those that received RT + surgery (*Mortier et al., J Am Acad Dermatol, 2011*)

Adjuvant Radiation:

• Local:

Among all MCC cases:

- Local recurrences at 5 years diminished by 3.7-fold with the addition of XRT (40% to 13%) (*Lewis et al., Arch Dermatol, 2006*)

In high-risk cases: (large primaries, positive surgical margins, presence of LVI, increasing stage)

- Need to be treated with adjuvant RT.
- High-risk tumors receiving adjuvant RT had a local recurrence of 3% (n= 75)(*Fields et al, Cancer 2011*)

• Nodal disease:

Microscopic Node-positive MCC:

- Either completion lymph node dissection (CLND) or radiation therapy can offer excellent regional control rates (100% regional control rates in 19 patients treated with definitive RT and 7 patients with CLND; median f/u of 18 months).
- Combining both CLND and XRT does not offer additional benefit & should likely be avoided due to morbidity/lymphedema

Clinically Apparent Nodal Disease:

- Combination of surgery (debulk at least) and XRT likely indicated (*Fang et al., Cancer, 2009*)

• Overall survival:

- In patients treated with adjuvant RT, a retrospective analysis of SEER cases (1,487 patients) found significant survival, particularly in larger tumors > 2cm (overall median survival improved from 21 to 50 months with the use of adjuvant RT) (*Mojica et al, J Clin Oncol. 2007*)

Is XRT indicated in most cases? (Yes--typically)

XRT markedly decreases local recurrence and is indicated except in very low risk tumors, as defined below)

XRT side effects?

Acute: acute erythema, Mild-moderate fatigue, Head/Neck: ulcers, pain (acute), dry mouth/taste changes

Chronic: chronic radiation skin changes, risk of SCCs in those with life expectancy > 20 years

When is XRT to the primary site not indicated (or less beneficial)?

The benefit of XRT is less for low-risk tumors, although *where to draw the line is controversial!* We typically do not irradiate if all these low-risk features are present:

- **Small primary (usually <1cm)**
- **No lymphovascular invasion (*you may need to ask path to comment on this...*)**
- **No immune suppression (HIV, CLL, solid organ transplant recipient)**
- **SLNB result negative**
- **Margins confidently clear both clinically and pathologically**
- MCC patients whose tumors have no LVI, small tumor size, clinically negative LN and lower stage have a low local recurrence rate (3.8% at 2 years) with adequate surgery (including SLNB) and no adjuvant radiation (*Fields et al, Cancer 2011*)

Adjuvant nodal therapy benefit depends on SLNB status:

Among **SLNB-positive** patients:

Node therapy improves disease-free survival ($p < 0.01$)

- Adjuvant XRT: 0% (n=3)

+ Adjuvant XRT: 60% (n=26)

Among **SLNB-negative** patients:

Non-significant trend for improved disease-free survival after nodal therapy

- Adjuvant XRT: 70% (n=19)

+ Adjuvant XRT: 90% (n=24)

(*Gupta et al., Arch Dermatol, 2006*)

Chemotherapy:

Most commonly used agents: Carboplatin or Cisplatin + Etoposide (VP-16)

Useful in palliative setting for symptomatic disease:

Most patients will have a significant initial response

6 reasons we do not recommend adjuvant chemotherapy (*Garneski & Nghiem, JAAD 2007*):

- Mortality: 4-7% deaths due to adjuvant chemo in MCC
(*Tai et al., J Clin Oncol, 2000; Voog et al., Cancer, 1999*)
- Morbidity: neutropenia (60% of pts) fever and sepsis (40%)
(*Poulsen et al., Int J Radiat Oncol Biol Phys, 2001*)
- Decreased quality of life: fatigue, hair loss, nausea/vomiting
- MCC that recurs after chemo is less responsive to later palliative chemo
- Chemo suppresses immune function (important in fight against MCC)
- Trend toward **decreased** survival among patients with nodal disease:

Node Positive pts tx'ed with:**MCC-specific survival**

No adjuvant Chemo (n=53)

60%

Adjuvant Chemo (n=23)

40%

(*Allen et al., J Clin Oncol, 2005; p=0.08*, not a randomized trial, referral bias is likely an issue, but certainly does not suggest a survival benefit!)

Treatment of Distant Metastatic / Stage IV Disease:

- There are no FDA-approved agents, and Tx is typically palliative in nature
- Response to cytotoxic chemotherapy (usually etoposide + cisplatin or carboplatin) is significant (>50% of patients with good response) but usually not durable, lasting only a few months.
- Median survival is ~9 mos after developing metastatic disease, but ~15% of patients survive >5 years. (Miller)
- Fractionated and single-dose XRT can be used to shrink problematic lesions.
- Numerous immune therapies are in development with encouraging results.

NCCN Guidelines for MCC:

- The National Comprehensive Cancer Network (NCCN) publishes a comprehensive multi-disciplinary treatment guideline for MCC that is updated annually and contains detailed management algorithms.
- The NCCN guideline reflects care offered at major US Cancer centers.
- The treatment guideline can be freely accessed after registering at the NCCN website: (http://www.nccn.org/professionals/physician_gls/PDF/mcc.pdf)
- Guidelines can be directly accessed via “useful links” category in: <http://www.merkelcell.org/usefullInfo/index.php>

PART 5: SUMMARY

- MCC reported incidence has quadrupled in the past twenty years, and MCC has a higher mortality than melanoma.
- SLN Bx, surgery, and radiation are indicated in most cases.
- NCCN publishes comprehensive Tx guidelines updated annually (www.nccn.org)
- CT scans are not indicated for early stage patients with negative SLN Bx but are recommended if even microscopic node involvement is present.
- Over-aggressive surgery and adjuvant chemotherapy have high morbidity and no proven benefits.
- The www.merkelcell.org website is a practical reference for patients & MDs in determining therapy and prognosis.
(Easy to find via Google or Bing search of "Merkel cell carcinoma" – usually a top hit in both)

PART 6: ANNOTATED REFERENCES (Most can be downloaded via www.merkelcell.org)

Allen, P. J., Bowne, W. B. Jaques, D. P., Brennan, M. F., Busam, K., Coit, D. G. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *Journal of Clinical Oncology*, 23(10):2300-9, 2005.

Andea AA, Coit DG et al., Merkel cell carcinoma: Histologic features and prognosis. *Cancer*. 2008.

Feng H et al: Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 319:1096-100, 2008.
Description of a newly discovered virus in Merkel cell carcinoma.

Gupta S, Wang L, Nghiem P. (website) Merkel cell carcinoma: Information for patients and their physicians: www.merkelcell.org.

A website dedicated to providing easily understood information on MCC causes, prognosis and therapy.

Gupta SG, Wang LC, et al., Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. *Archives of Dermatology*, 142:771-4, 2006.
32% of patients with clinically local-only disease clinically were found to have microscopic nodal disease by SLNB.

Heath ML, Jaimes N, Lemos B, et al: Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol* 58:375-81, 2008.

Lemos B, et al., Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: Analysis of 5,823 cases as the basis of the first consensus staging system for this cancer. *J Am Acad Dermatol*, 63:751-61, 2010.

Lewis K et al., Adjuvant local irradiation for Merkel cell carcinoma. *Archives of Dermatology*, 142:693-700, 2006.
Local and regional recurrences much less likely if XRT given in addition to surgery.

Mortier L, et al., Radiotherapy alone for primary Merkel cell carcinoma. *Archives of Dermatology*, 139:1587-90. 2003.
Radiation mono-therapy is very effective in managing MCC (esp if surgery not an option).

Paulson KG, et al. Antibodies to Merkel cell polyomavirus T-antigen oncoproteins reflect Merkel cell carcinoma tumor burden. *Cancer Res*. 70:8388-97, 2010.

This test is currently available as detailed at www.merkelcell.org/help/participate.php

Paulson KG, et al. Transcriptome-wide studies of Merkel cell carcinoma and validation of intratumoral CD8+ lymphocyte invasion as an independent predictor of survival. *J Clin Oncol*. Apr 20;29(12):1539-46, 2011

Fields RC et al., Recurrence after complete resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma. *Cancer*. 2011.

Low-risk MCCs (no LVI, small tumor size, clinically negative LN) have excellent outcomes with surgery only.

Sihto H et al., Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. *J Natl Cancer Inst*. 2009 Jul 1;101(13):938-45. Epub 2009

Fields RC, Busam KJ, et al., Recurrence and Survival in Patients Undergoing Sentinel Lymph Node Biopsy for Merkel Cell Carcinoma: Analysis of 153 Patients from a Single Institution. *Ann Surg Oncol*. 2011

Schwartz JL et al., Features predicting sentinel lymph node positivity in Merkel cell carcinoma. *J Clin Oncol*. 2011 Mar 10;29(8):1036-41.

Even small MCC tumors have a significant risk of microscopic nodal spread at diagnosis