

# **Merkel Cell Carcinoma: Diagnosis, Management and Controversies**

**Forum F056**

**Sunday, March 8, 2009, 3:00-5:00 PM**

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See [www.merkelcell.org](http://www.merkelcell.org) for more info or for a pdf version of this handout.

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## **DESCRIPTION**

Merkel cell carcinoma (MCC) is a frequently lethal skin cancer with a higher mortality (33%) than melanoma (15%) and evidence of rapidly increasing incidence. Management of MCC is challenging, as therapy is different in nature than for other skin malignancies and is controversial within the literature. Proper care requires coordination between dermatologists, radiation and medical oncologists, and surgeons. In this session, speakers will present the most current data on the clinical presentation, staging, pathology, and 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. Define the risk factors, incidence, clinical, pathologic, and prognostic characteristics of Merkel cell carcinoma.
2. Examine data on wide versus Mohs excision, sentinel lymph node biopsy, radiation and chemotherapy.
3. Utilize this information to guide management of representative cases.

## **OUTLINE OF SESSION**

1. Merkel Cell Carcinoma Overview and Clinical Presentation - *Paul Nghiem, MD, PhD*
2. Pathologic Features – *Jacqueline Junkins Hopkins, MD*
3. Staging & Prognosis – *Jayasri Iyer, MD*
4. Role of Radiation Therapy - *Paul Nghiem, MD, PhD*
5. Multidisciplinary Management - *Christopher Bichakjian, MD*
6. Challenging Cases & Discussion - *Siegrid Yu, MD & Panel*

## PART 1: IMPACT OF MERKEL CELL CARCINOMA (MCC)

### Fatality Rates:

MCC	1 in 3
Melanoma	1 in 6
Sq Cell CA	1 in 50
Basal Cell CA	<1 in 10,000

(Nghiem & Jaimes, 2007) (Agelli et al., *JAAD*, 2003)

### Incidence has tripled since 1986:

1986	0.15 per 100,000
2001	0.44 per 100,000

(Hodgson et al., *J Surg Oncol*, 2005)

### Estimates of 600-1500 cases/year in US

- ~600 cases/year in 1999 (Agelli et al, *JAAD*, 2003, SEER data)
- ~950 cases/year in 1997 (Pan et al., *Plas & Reconstr Surg* 2002, CT Tumor Registry)
- ~1500 cases/year in 2007 (Lemos & Nghiem, *JID*, 2007, NCDB data)

### Risk factors will translate to increasing incidence in future:

- Age >65 yr
- Fair skin / prolonged sun exposure / PUVA therapy
- Profound immune suppression (HIV, solid organ transplant, CLL)
  - 13.4-fold increase among HIV+ pts (Engels et al., *Lancet*, 2002)
  - ~10 fold increase after solid organ transplantation (Miller et al., *Cancer Epidemiol Biomarkers Prev*, 1999, using SEER)
- 7.8% of 195 MCC pts had HIV, CLL, Organ Transplant (at DFCI/MGH/UW/SCCA)

### The Merkel cell polyomavirus

- Discovered by Patrick Moore and Yuan Chang (Pittsburg) (co-discoverers in 1994 of KSHV as well...)
- A new human polyomavirus in same family as BK, JC, SV40, WU, KI
- Present in ~ 80% of MCC tumors.
- Present in ≤ 10% of SCC, BCC, Melanomas, or normal skin.
- Virus mutations & early clonal integration suggest it promotes tumorigenesis in MCC.
- Epidemiology (incidence) of virus not yet described but other polyomaviruses are highly prevalent (>50% of normal population seropositive)
- This virus helps to explain the link between MCC and immune suppression.

### Controversy & bias is abundant

- Lack of balanced information due to no "owner" of MCC
  - "Narrow" literatures are field/expertise biased:
    - Derm/Mohs, Surg, Med Oncol, Rad Tx
- Few MDs are familiar with this disease or its management
  - Often not included in medical school curricula—even today

**MCC management is often not optimal**

- Underused therapies:
    - Sentinel lymph node biopsy
    - Radiation therapy
  - Overused therapies:
    - Over-aggressive surgery/amputation
    - Scans (CT/MR/PET)
    - Chemotherapy
- These issues will be detailed below

**PART 2: CLINICAL PRESENTATION AND PATHOLOGY**

**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 (but not always)
- May rarely ulcerate

**AEIOU Features of MCC** (Heath, Nghiem: JAAD, 2008) – Derived from 195 patients

<p><b>A: Asymptomatic/lack of tenderness</b>  <b>E: Expanding rapidly</b>  <b>I: Immune suppression</b>  <b>O: Older than 50 years</b>  <b>U: Ultraviolet exposed/fair skin</b></p>	}	<p><b>Consider biopsy if <math>\geq 3</math> features present</b></p>
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AEIOU PARAMETER	No.	Percentage
<b>A: Asymptomatic</b>	<b>78/89</b>	<b>88</b>
<b>E: Expanding rapidly</b>	<b>57/91</b>	<b>63</b>
<b>I: Immune suppressed</b>	<b>15/193</b>	<b>8*</b>
<b>O: Age &gt; 50 years</b>	<b>175/195</b>	<b>90</b>
<b>U: UV exposed</b>	<b>136/168</b>	<b>81</b>
<b>Fair skin</b>	<b>191/195</b>	<b>98</b>

\* 16 fold over representation of immunosuppression as compared with the general US population based on the estimated prevalences of: chronic lymphocytic leukemia 0.029%, HIV 0.4% and living recipients of solid organ transplantaion with viable grafts 0.075%.

**At biopsy, most common presumed diagnosis was cyst/acneiform lesion** (Heath, Nghiem: JAAD, 2008)

- Benign** **57%**
  - Cyst/acneiform lesion 36%
- Malignant** **34%**
  - Non-melanoma skin CA 14%
- Indeterminate** **8%**
  - "Nodule/mass" 6%

**Pathology**

Merkel cells are mechanoreceptors (fine touch) within basal epidermis  
 Three histologic patterns (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

**Immunohistochemistry panel:**

	CK20*	CK7	LCA	S100
Merkel cell carcinoma	+	-	-	-
Small cell lung cancer	-	+	-	-
Lymphoma	-	-	+	-
Melanoma	-	-	-	+

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

**Pathology Summary:**

***"Peri-nuclear dot pattern of cytokeratin" is pathognomonic {favorite boards question!}***  
 Prior to CK20/CK7 (early 1990s) many cases were misdiagnosed as lymphoma, SCLC etc.  
 If immunohistochemistry is done properly, diagnosis is definitive

**PART 3: STAGING & PROGNOSIS**

<b>MCC Stages at Diagnosis (Allen/Coit/Busam/MSKCC, 2005):</b>	<b>% Pts</b>	<b>3 yr survival*</b>
Stage I Localized disease, primary < 2 cm	~30%	~90%
Stage II Localized disease, primary ≥ 2 cm	~30%	~70%
Stage III Nodal disease	~30%	~60%
Stage IV Metastatic disease	~10%	<20%

\*Essentially all MCC-specific deaths occur by 3 yr after dx\*

- A new staging system is currently being prepared for the 7th edition of the AJCC staging manual. The new system will be very similar to the Allen, et al. (2005) system (above) but will differentiate microscopic (pathologic) vs macroscopic (clinical) method of node staging for stages I-III in the form of substages. This system is expected to be published in 2009.

**Sentinel lymph node biopsy should be performed routinely in MCC**

*"The average MCC is thirty times more likely to have occult nodal metastasis than the average melanoma."*

<b>Cancer Type</b>	<b>Median 1° tumor size</b>	<b>+ SLNB with clinically negative nodes</b>
Melanoma	0.63 mm Breslow depth	1%
Merkel cell carcinoma	1.7 cm diameter	30%

(M.B.Lens et al., BJS 2002; Goggins, W et al., Int. J. Cancer 2006; Gupta et al., Arch Dermatol, 2006)

Among 122 MCC patients with clinically negative lymph nodes, 39 (32%) had a positive SLNB  
SLNB-positive patients benefited from adjuvant nodal therapy:

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

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

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

**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 for CT Scans in MCC:**

**For detecting nodal disease: SLNB sensitivity >> CT Scan sensitivity**

**Scans not very useful if small primary or if SLNB is negative**

**Scans ARE useful for SLNB-positive patients to rule out distant spread**

## **PART 4: TREATMENT**

### **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? (no)**

Wide local excision >2.5 cm margins:  
 49% regional recurrence/persistence  
 41 pts (O'Connor, et al 1997)

**Is Mohs excision alone sufficient? (no)**

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? (maybe)**

60 Gray (6000 cG) to primary site +/- node bed:  
 0% recurrence in 9 patients with 3 yr f/u (Mortier et al., *Arch Dermatol*, 2003)

**Effect of adding XRT to surgery:**

	N	Event-Free Survival rate		Haz Ratio	P value
		1 yr	5yrs		
Local recurrence					
Surgery only	418	71%	61%	1.00	
Surgery + RT	169	90%	88%	0.27	<0.001
Regional recurrence					
Surgery only	373	63%	44%	1.00	
Surgery + RT	125	85%	77%	0.34	<0.001

- Haz Ratio = the relative likelihood of experiencing a particular event (recurrence)
- **Local recurrences at 5 years were diminished by 3.7-fold with the addition of XRT (40% to 13%)**  
 (Lewis et al., *Arch Dermatol*, 2006)

**Is XRT indicated in most cases? YES!**

XRT markedly decreases local recurrence and thus morbidity  
 XRT link to survival is less strong, but trend found in many studies.  
 XRT side effects are usually moderate:  
     Mild-moderate fatigue, acute erythema, chronic radiation skin changes  
     Risk of SCCs in those with life expectancy > 20 years  
     Nead/Neck: ulcers, pain (acute), dry mouth/taste changes (chronic)

**When is XRT not indicated?**

We do not irradiate MCCs with **ALL** of the following favorable features\*:

- <1cm primary tumor diameter
- No lymphovascular invasion noted on path exam of primary lesion
- No profound immune suppression (HIV, CLL, Solid organ transplant recipient)
- SLNB result: negative
- Margins "confidently" clear both clinically and pathologically

(Based in part on published data (Allen 2005) & unpublished data (U of Michigan – Bichakjian, U of Washington, Seattle – Nghiem)).

**XRT as monotherapy**

Some patients may have inoperable disease.  
 XRT monotherapy effective at controlling/curing extensive local disease  
 (Multiple examples in our series and in the literature: Mortier et al., *Arch Dermatol*, 2003)

### Adjuvant nodal therapy benefit depends on SLNB status

- Among **SLNB-positive** patients:  
Improved 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  
- Adjuvant XRT: 70% (n=19)  
+ Adjuvant XRT: 90% (n=24)  
(Gupta et al., *Arch Dermatol*, 2006)

### Adjuvant nodal therapy: XRT or surgery?

- We typically use nodal XRT rather than surgery  
(We believe side effects are less and efficacy is at least equivalent)  
Frequency of lymphedema after adjuvant nodal XRT or Surg:  
inguinal > axillary > head/neck

### Chemotherapy

- Most commonly used agents: Carboplatin + Etoposide (VP-16)  
Useful in palliative setting for symptomatic disease:  
Most patients will have a response  
“Adjuvant” therapy: given for high risk disease to patients with no clinically detectable disease.

### 6 reasons we do not recommend adjuvant chemotherapy

- (Garneski & Nghiem, *JAAD* 57:166,2007):
- 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:

<u>Node Positive pts tx'ed with</u>	<u>MCC-specific survival</u>
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No adjuvant Chemo (n=53)	60%
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Adjuvant Chemo (n=23)	40%
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(Allen et al., *J Clin Oncol*, 2005;  $p=0.08$ , not a randomized trial, but certainly does not suggest a survival benefit!)

### Treatment bottom line:

#### Current management of Merkel cell carcinoma tends to

##### Underuse:

- Sentinel lymph node biopsy
- Radiation therapy

##### Overuse:

- Over-aggressive surgery/amputation
- Scans (CT/MR/PET)
- Chemotherapy

For Detailed MCC Management Guidelines see:

NCCN Guidelines for MCC: (see the website for comprehensive treatment guidelines for MCC)  
[http://www.nccn.org/professionals/physician\\_gls/PDF/mcc.pdf](http://www.nccn.org/professionals/physician_gls/PDF/mcc.pdf)

- Updated annually
- Represents consensus management across nation and disciplines

## PART 5: SUMMARY

- MCC incidence is rising and it has a higher mortality than melanoma.
- SLN bx, surgery and radiation are indicated in almost all cases.
- CT Scans have poor sensitivity for nodal disease (20%) and poor specificity for distant disease (48%).
- Over-aggressive surgery and adjuvant chemotherapy have high morbidity and no proven benefits.
- NCCN publishes comprehensive Tx guidelines updated annually  
([http://www.nccn.org/professionals/physician\\_gls/PDF/mcc.pdf](http://www.nccn.org/professionals/physician_gls/PDF/mcc.pdf))
- The [www.merkelcell.org](http://www.merkelcell.org) website is a practical reference for patients & MDs in determining therapy and prognosis.  
(Easy to find via Google search of *Merkel cell carcinoma*)

## PART 6: ANNOTATED “REFERENCES”

(Most can be downloaded via [www.merkelcell.org](http://www.merkelcell.org))

Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *Journal of the American Academy of Dermatology*, 49:832-41, 2003.

- ***Largest study (1034 pts) of survival after MCC diagnosis via SEER data. Essentially all deaths due to MCC occur within three years of dx. No data on treatments included.***

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.

- ***Study of 251 patients from Memorial Sloan-Kettering Cancer Center's MCC database, between 1970-2002. Conclusions: 1) Pathologic nodal staging identifies a group of patients with excellent long-term survival. 2) After margin-negative excision and pathologic nodal staging, local and nodal recurrence rates are low. 3) Adjuvant chemo for Stage III patients showed a trend (p=0.08) to decreased survival compared with Stage II patients that did not receive chemo.***

Garnski K, Nghiem P. Merkel cell carcinoma adjuvant therapy: Current data support radiation but not chemotherapy. *Journal of the American Academy of Dermatology*, 57:166-9, 2007.

- ***Review and discussion of literature on adjuvant chemotherapy and radiation in MCC showing a reduction in recurrence with radiation therapy but no survival benefit with chemotherapy.***

Gupta S, Wang L, Nghiem P. Merkel cell carcinoma: Information for patients and their physicians:

[www.merkelcell.org](http://www.merkelcell.org).

- **A website dedicated to providing easily understood information on MCC causes, prognosis and therapy. 20 page color pdf can be downloaded from the site.**

Gupta SG, Wang LC, Penas PF, Gellenthin M, Lee SJ, Nghiem P. 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.

- **Evaluation of 122 MCC patients (61 from the Dana-Farber and 92 from the literature). Findings: 32% of patients with clinically local-only disease were found to have microscopic nodal disease by SLNB. Three-year recurrence rate was 3 times higher in this group (+SLNB vs - SLNB). Relapse free survival was improved with the use of adjuvant XRT in patients with a positive SLNB. CT scans had a low sensitivity and poor specificity for detecting nodal disease that was not readily clinically apparent.**

Lewis K, Weinstock M, Weaver A, Otley C. Adjuvant local irradiation for merkel cell carcinoma. Archives of Dermatology, 142:693-700, 2006.

- **Meta-analysis demonstrating reductions in local and regional MCC recurrence in patients treated with surgery plus XRT as compared to those treated with surgery alone.**

Mojica P, Smith D, Ellenhorn, J. Adjuvant radiation is associated with improved survival in Merkel cell carcinoma of the skin. Journal of Clinical Oncology, 25(9):1043-47, 2007.

- **Retrospective analysis of SEER (1,487 patients) found improved survival in patients treated with adjuvant radiation therapy, particularly in larger tumors (>1 cm).**

Mortier L, Mirabel X, Fournier C, Piette F, Lartigau E. Radiotherapy alone for primary Merkel cell carcinoma. Archives of Dermatology, 139:1587-90. 2003.

- **French study of stage I MCC that found no difference in overall survival in treatment with radiation therapy alone (9 patients) compared with surgery and radiation therapy (17 patients).**

National Comprehensive Cancer Network (NCCN). Merkel cell Carcinoma Treatment Guidelines (updated annually). [http://www.nccn.org/professionals/physician\\_gls/PDF/mcc.pdf](http://www.nccn.org/professionals/physician_gls/PDF/mcc.pdf)

- **Consensus recommendations for MCC management from 20 different cancer centers in the US.**

Nghiem P, Jaimes N. Merkel cell carcinoma. In Wolff K, Katz S, Goldsmith L, Gilchrist B, Leffell D, Paller A (Eds), Fitzpatrick's Dermatology in General Medicine. 7th edition. McGraw-Hill, NY, NY, pp. 999-1006, 2007.

- **Comprehensive chapter on MCC in a multi-authored textbook of dermatology.**

Feng H, Shuda M, Chang Y, 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.**

Heath ML, Jaimes N, Lemos B, Mostaghimi A, Wang L, Penas P, Nghiem P. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 58:375-81, 2008.

- **This study is the first to define the clinical features that may serve as clues in the diagnosis of MCC.**

Lemos B, Nghiem P. Merkel cell carcinoma: more deaths but still no pathway to blame. J Invest Dermatol 127:2100-3, 2007.

Goggins W, Daniels GH, and Tsao H Elevation of thyroid cancer risk among cutaneous melanoma survivors. Int. J. Cancer: 118, 185-188, 2006

M.B.Lens, M.Dawes, J.A.Newton-Bishop\* and T. Goodacre. Tumor thickness as a predictor of occult lymph node metastasis in patients with stage I and II melanoma undergoing sentinel lymph node biopsy. BJS: 89, 1223-1227, 2002.