Merkel Cell Carcinoma:
Diagnosis, Management and Controversies

Forum 542
Sunday, February 3, 2008, 3:00-5:00 PM
American Academy of Dermatology Annual Meeting
San Antonio, TX

Director: Paul Nghiem, MD, PhD, University of Washington, Seattle, WA

Faculty: Christopher Bichakjian, MD, University of Michigan, Ann Arbor, MI
Klaus Busam, MD, Memorial Sloan Kettering Cancer Center, NYC, NY
Bianca Lemos, MD, University of Washington, Seattle, WA
Kevan Lewis, MD, Mayo Clinic, Rochester, MN
Tara Miller, MD, UCSF, San Francisco, CA

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 - *Klaus Busam, MD*
3. Staging & Prognosis - *Bianca Lemos, MD*
4. Role of Radiation Therapy - *Kevan Lewis, MD*
5. Multidisciplinary Management - *Christopher Bichakjian, MD*
6. Challenging Cases & Discussion - *Tara Miller, MD*

Merkel Cell Carcinoma:
Overview and Key Issues

(Revised 11/19/2007)

Prepared by: Paul Nghiem, MD, PhD, and Bianca Lemos, MD, University of Washington, Seattle, WA

OUTLINE OF HANDOUT

1. Impact of Merkel Cell Carcinoma (MCC)
2. Clinical presentation & pathology
3. Staging & Prognosis
4. Treatment
5. Summary
6. Annotated References

See www.merkelcell.org for more info or for a pdf of this handout.

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, 2207) (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 Onco*l, 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)

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

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

At biopsy, most common presumed diagnosis was cyst/acneiform lesion

Benign	***57%***
Cyst/acneiform lesion	**36%**
Lipoma	**6%**
Dermatofibroma	**5%**
Malignant	***34%***
Non-melanoma skin CA	**14%**
Lymphoma	**9%**
Indeterminate	***8%***
"Nodule/mass"	**6%**

All others had 3 or fewer presumptive diagnoses: insect bite, abscess, chalazion, melanoma, neural tumor, appendage tumor. 72 of 138 cases stated a presumed diagnosis at biopsy. Total presumed diagnoses = 100 12 pts had 2 presumed dx, 5 pts had 3 presumed dx, 2 pt had 4 dx. Our unpublished data.

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 Dermatopathal, 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

MCC Stages at Diagnosis (Allen/Coit/Busam/MSKCC, 2005):		% Pts	3 yr survival*
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 updated for 7th edition of the AJCC staging manual. The new system will be very similar to Allen, et al. (2005) system (above) but will differentiate micrscopic (pathologic) vs macroscopic (clinical) method of node staging for stages I-III in the form of substages. This system will be adopted by the AJCC for the 7th Ed. of the staging manual, expected to be published in 2009.

Sentinel lymph node biopsy should be performed routinely in MCC

MCC has much higher LN involvement (~30%) than melanoma (~5%)

Among 122 patients without palpable 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 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

PART 4: TREATMENT

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:

		Event-Free Survival rate			
	N	1 yr	5yrs	HR	P value
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

- HR=Hazard Ratio, the relative likelihood of experiencing a particular event
- 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 minimal:

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)

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 better)

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

6 reasons we do not recommend <u>adjuvant</u> chemotherapy (Garneski & Nghiem):

- 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)
- <u>Trend toward **decreased** survival among patients with nodal disease:</u>

<u>Node Positive pts tx with</u>	**<u>MCC-specific survival</u>**
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, but certainly does not suggest a survival benefit!)

Treatment bottom line:
Current management of Merkel cell carcinoma tends to

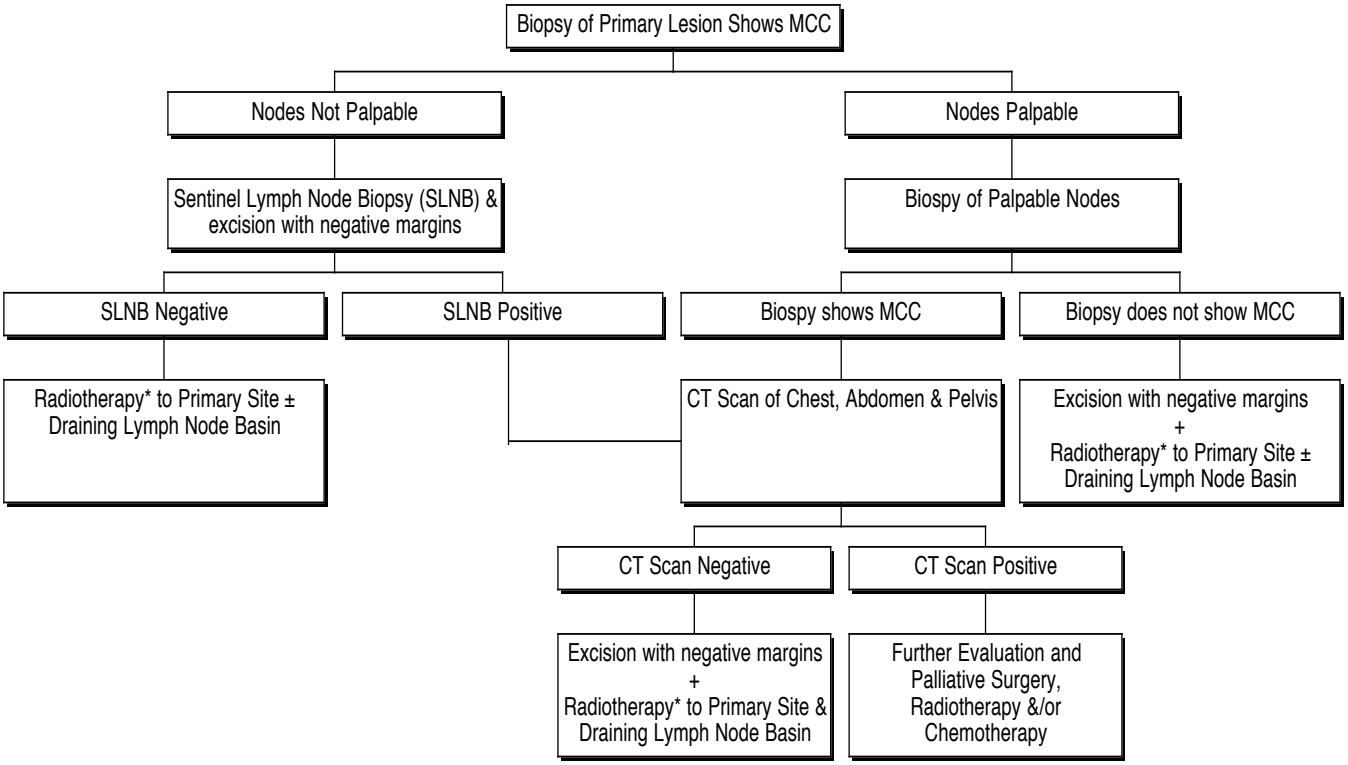
Underuse:

Sentinel lymph node biopsy
Radiation therapy

Overuse:

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

***Schematic of our recommended management:**



---

* **Recommended Radiation Therapy dose** (NCCN Guidelines for MCC, 2006)

45-50 Gy for: Primary site with negative excision margins
Node bed with no palpable disease
55-60 Gy for: Primary site with positive excision margins
Node bed with palpable disease
(XRT given in 2 Gy fractions, 5 times/week over 4-6 weeks)

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.

• The 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)

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 PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. 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.***

Bichakjian CK, Lowe L, Lao CD, Sandler HM, Bradford CR, Johnson TM, Wong SL. Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. Cancer, 110(1):1-12, 2007.
- ***A comprehensive overview of the surgical approach to primary MCC and the use of adjuvant XRT and chemotherapy. Treatment guidelines based on multidisciplinary experience and evidence in the literature are provided.***

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.
- ***A website dedicated to providing easily understood information on MCC causes, prongosis 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 clinically 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 radiotion 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). www.nccn.org.

- ***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, Gilchrest 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 multiauthored textbook of dermatology.***