

**Merkel Cell Carcinoma:
Diagnosis, Management and Controversies
Forum F022
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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
Jayasri Iyer, MD, University of Washington, Seattle, WA
Siegrid Yu, 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 – *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*

Handout prepared by: Paul Nghiem, MD, PhD, and Jayasri Iyer, MD, University of Washington, Seattle, WA

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

Handout Outline

PART 1: IMPACT OF MERKEL CELL CARCINOMA (MCC) AND CLINICAL PRESENTATION

PART 2: PATHOLOGY

PART 3: STAGING & PROGNOSIS

PART 4: MULTIDISCIPLINARY MANAGEMENT AND ROLE OF RADIATION THERAPY

PART 5: SUMMARY

PART 6: ANNOTATED REFERENCES

PART 1: OVERVIEW AND CLINICAL PRESENTATION

IMPACT OF MERKEL CELL CARCINOMA (MCC)

Fatality Rates:

MCC	1 in 3
Melanoma	1 in 8
Sq Cell CA	1 in 50
Basal Cell CA	<1 in 10,000

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

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

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

Current Estimate of ~1600 cases/year in US

~950 cases/year in 1997	(Pan et al., <i>Plas & Reconstr Surg</i> 2002, CT Tumor Registry)
~1500 cases/year in 2004	(Lemos & Nghiem, <i>JID</i> , 2007, NCDB data)
~1630 cases/year in 2006	(Albores-Saavedra et al., <i>J Cutan Pathol</i> 2009, SEER 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)
 - 11-fold increase among patients with AIDS (Engels., *AIDS* 2009)
 - ~ 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)

Associated Merkel cell polyomavirus

2008: Feng, Moore, Chang discovered a new human polyomavirus, the Merkel cell polyomavirus
 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 proteins are present and persistently expressed in 50% of the tumors
 ~60% of US population has specific antibodies to the MCPyV capsid protein (Carter JJ et al., *J Natl Cancer Inst.* 2009)
 ~90% of MCC patients are sero-positive to the MCPyV capsid protein supporting a continuing role for this new virus in most MCC tumors
 Mutation pattern in the large T oncoprotein are highly suggestive of a role in this cancer (N terminal – pro-cell cycle portion is conserved: C terminal – genomic instability generating region is deleted in most tumors) (Shuda et al., *Proc Natl Acad Sci U S A.* 2008)

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
 Chemotherapy in adjuvant setting
 These issues will be detailed below

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	7.8**
O	Age > 50 years	175/195	90
U	UV exposed	136/168	81
	Fair skin	191/195	98

*89% patients had 3 or more features.

** A 16-fold overrepresentation of profound immunosuppression compared with the general population

At biopsy, lesions often thought to be benign; most common presumed diagnosis was cyst/acneiform lesion (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

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

STAIN	MCC	SMALL CELL LUNG CANCER	LYMPHOMA	MELANOMA
CK 20*	+ (perinuclear dot-like pattern)	-	-	-
CK 7	Usually negative	+	-	-
TTF-1	-	+	-	-
LCA	-	-	+	-
CM2B4**	Usually positive	-	-	-
S100	-	-	-	+

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

**The CM2B4 antibody recognizes the Merkel polyomavirus Large T antigen. This antibody is highly specific for MCC but it has a low sensitivity (~60% of MCC tumors are positive). Busam KJ, et al. Merkel cell polyomavirus expression in Merkel cell carcinomas and its absence in combined tumors and pulmonary neuroendocrine carcinomas. Am J Surg Pathol. 2009 Sep;33(9):1378-85.

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 typically definitive

PART 3: STAGING & PROGNOSIS

The New AJCC Merkel cell carcinoma staging system (AJCC Cancer staging Manual, 2009) (Lemos, et al., *JAAD in press*)

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 should be performed routinely in MCC

MCC has much higher LN involvement for an average 1.7 cm MCC (~30%) than melanoma (~1% for average Breslow thickness of 0.63mm). (Gupta et al., *Arch Dermatol*, 2006; Goggins, et al, *Int J Cancer*, 2006; Lens, et al, *Br J Surg*, 2002)

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% disease-free survival 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

New Diagnostic codes for Merkel cell carcinoma (Iyer et al, *Actas Sifilograficus* 2009)

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

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? (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)

Some patients may have inoperable disease.
XRT monotherapy effective in controlling/curing extensive 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)
0% recurrence in 9 patients who received 60 Gray (6000 cG) to primary site +/- node bed with 3 yr f/u (Mortier et al., *Arch Dermatol*, 2003)
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)

Effect of adding XRT to surgery:

- In patients treated with adjuvant radiation therapy, 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)
- For 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 with a median f/u of 18 months). Combining both CLND and radiation therapy does not appear to offer additional benefit for patients with microscopic-only nodal disease but may be indicated for clinically apparent nodal disease (Fang et al., *Cancer*, In press).

	N	Event-Free Survival rate		HR	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

- 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 moderate:

Mild-moderate fatigue, acute erythema, chronic radiation skin changes

Risk of SCCs in those with life expectancy > 20 years

Head/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**
- **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**

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)

Adjuvant nodal therapy: XRT or surgery?

We typically use nodal XRT rather than surgery

Frequency of lymphedema after adjuvant nodal XRT or Surg:

inguinal > axillary > head/neck

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):

- 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:

No adjuvant Chemo (n=53)

Adjuvant Chemo (n=23)

(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!)

MCC-specific survival

60%

40%

Treatment bottom line:

Current management of Merkel cell carcinoma tends to

Underuse:

Sentinel lymph node biopsy

Radiation therapy

Overuse:

Over-aggressive surgery/amputation

Chemotherapy

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 incidence has quadrupled in the past twenty years and it has a higher mortality than other skin cancers.**
- **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 (www.nccn.org)**
- **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*" - # 1 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.

- ***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.***

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. 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.***

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.***

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

Lemos BD, et al., Development of the first American Joint Committee on Cancer staging system for Merkel cell carcinoma based on prognostic factors analysis of 5,823 National Cancer Data Base Cases. *J Am Acad Dermatol*, In press.

- ***Presents data used to derive the MCC staging system that will be adopted in 2010.***

Merkel Cell Carcinoma: Chapter 30, AJCC Cancer Staging Manual (ed Seventh) In Press. Chicago, Springer, 2009

- ***Description of the new MCC Staging System.***