

# **Merkel Cell Carcinoma**

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**AAD Focus Session**

**New Orleans, LA**

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

## **Outline of Presentation**

1. Why should you care about Merkel Cell Carcinoma (MCC)?
2. Clinical presentation & pathology
3. Staging & Prognosis
4. Treatment
5. Summary
6. Annotated References

## **Description**

Merkel cell carcinoma (MCC) is a neuroendocrine carcinoma of the skin with a higher mortality (25% at 3 years) than melanoma and evidence of rapidly increasing incidence. Management of MCC is challenging as therapy is different in nature than for other skin malignancies and controversial within the literature. Proper care requires coordination between dermatologists (often the first to diagnose), surgeons, radiation & and medical oncologists.

## **Learning Objectives**

Following this session, the attendee will be able to:

1. Understand the risk factors, incidence, clinical, pathologic, and prognostic characteristics of Merkel cell carcinoma.
2. Be familiar with the limitations and strengths of the literature on MCC.
3. Understand the issues relating to therapy of MCC including wide versus Mohs excision, sentinel lymph node biopsy, radiation and chemotherapy.

## Part 1: Why should you care about MCC?

### Fatality Rates:

MCC	1 in 4
Melanoma	1 in 5
Sq Cell CA	1 in 50
Basal Cell CA	<1 in 10,000

(Nghiem, et al 2001)

### 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 600-1000 cases/year in US

~600 cases/yr	(Agelli JAAD 2003 based on SEER data)
~950 cases/yr	(Pan Plas & Reconstr Surg 2002, CT Tumor Registry)

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

- Age >65 yr
- Fair skin/ prolonged sun exposure/ PUVA therapy
- Profound immunosuppression (HIV, solid organ transplant, CLL)
  - ~8 fold increase among HIV+ pts
  - ~10 fold increase after solid organ transplantation
- Over-represented in MCC patients at Dana-Farber (11% of 61)

### Controversy & mis-information abounds!

- Lack of balanced information due to no "owner" of MCC
- "Narrow" literatures are field/expertise based:
  - Derm/Mohs, Surg, Med Oncol, Rad Tx
- Few MDs are familiar with this disease or its management

### Many patients are mismanaged

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

## Part 2: Clinical presentation and pathology

### Non-specific clinical presentation of MCC

- Firm, red to purple non-tender papule/nodule
- Rapid growth within prior 1-3 months
- Usually in a sun-exposed location (but not always)
- May rarely ulcerate

### Most common presumptive clinical diagnosis was cyst/acneform lesion

32 of 61 cases stated a presumed diagnosis at biopsy

- Cyst/acneform lesion**      **44%** (14 of 32)
- Non-melanoma skin CA**    **19%** (6 of 32)
- DFSP/fibrosarcoma**        **9%** (3 of 32)

All others had 2 or fewer:

insect bite, lipoma, melanoma, lymphoma, dermatofibroma

### Pathology

Merkel cells are mechanoreceptors (fine touch) within basal epidermis

Three histologic patterns

Intermediate type (most common):

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 CA	+	-	-	-
Sm cell lung CA	-	+	-	-
Lymphoma	-	-	+	-
Melanoma	-	-	-	+

### Pathology Summary:

"Peri-nuclear dot pattern of cytokeratin" is pathognomonic

*{favorite boards question!}*

Prior to CK20/CK7, many MCC cases were misdiagnosed as lymphoma, etc.

If immunohistochemistry is done properly, diagnosis is definitive

## Part 3: Staging & Prognosis

<b>MCC Stages at Diagnosis:</b>		<b>% Pts</b>	<b>3 yr survival*</b>
Stage Ia	Localized disease, primary < 2 cm	~30%	~90%
Stage Ib	Localized disease, primary > 2 cm	~30%	~70%
Stage II	Nodal disease	~30%	~60%
Stage III	Metastatic disease	~10%	<20%

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

### Lymph nodes involved in 36% of cases at time of diagnosis

Results from Dana-Farber in Boston (our unpublished series)

**Palpable lymph nodes present in 13 of 61 pts (21%)**

**SLN bx positive in 10 of 31 pts (32%) who underwent SLNBx**

**Total of 36% of 61 patients had LN involvement at dx**

Much higher LN involvement than melanoma (~5%)

### Scans at diagnosis have poor sensitivity & specificity:

Underwent scans (CT/MR/PET)	75%	46 of 61
True positive scan	9%	4 of 46
True positive identified only by scan*	2%	1 of 46
(*met not found on exam/history)		
False positive scan	31%	14 of 46
False negative scan in nodes*	100%	9 of 9
(*SLNBx pos; scan neg)		

### Scan Summary

14 false positive scans per one unique\* true positive scan

(\*identified by scan only and not by exam/history)

False positives cause:

Worry, subsequent scans, invasive procedures, and delayed therapy.

100% scan false negative rate for SLNBx positive cases:

9 of 10 patients with + SLNBx had scans; all were neg by scan

Scans are useful as baseline

(but must be ready for high false pos rate)

Make sense if + LN involvement or large primary

## 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% recurrence in 41 pts (O'Connor, et al 1997)

### Is Mohs excision sufficient? (no)

Mohs excision +/- "safety margin" of 1 cm:  
16% recurrence in 25 patients (Boyer, et al 2002)

Mohs + XRT:  
0% recurrence in 20 patients (Boyer, et al 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 2003)

### Effect of adding XRT to surgery: (Longo, et al 2003)

	<u>local recurrence</u>	<u>nodal recurrence</u>	<u>distant spread</u>
<b>Surgery only (n=63)</b>	25%	42%	21%
<b>Surg + XRT (n=37)</b>	3%	22%	11%
<i>P value</i>	.005	.045	.27

### 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 minimal:  
mild-moderate fatigue, acute erythema, chronic radiation skin changes

### 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, 2003)

### What is optimal local therapy?

**Pathologic clear margins by surgery (1-2.5 cm, depending on site)**  
**XRT of 50-60 Gray (25-30 treatments over 5-6 wks)**  
**Treat draining node bed with XRT if high risk disease**

### Lymph node surgery beneficial if nodes involved

Lymph node surgery is associated with improved survival  
Was only marker of relapse-free survival in 102 pts in NY (Allen 1999)  
2 year survival after LN excision 100% vs 35%  
(but non-randomized study...Kokoska 1997)

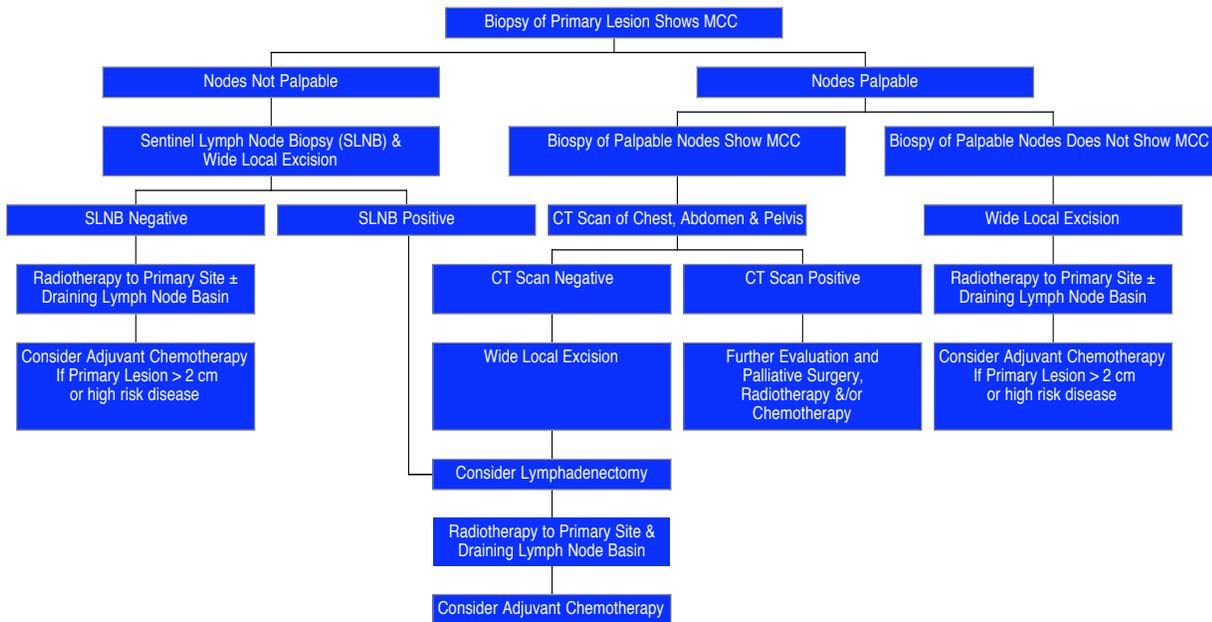
**Chemotherapy**

Effective for shrinking advanced metastatic disease, rarely curative  
 Unclear role in adjuvant setting [no evidence met disease]:  
 53 patients with stage I & II MCC  
 Received carboplatin & etoposide + radiation  
 76% survival at 3 years  
 Similar survival to that expected for patients of these stages  
 Need randomized studies to assess if true benefit or not.  
 Toxicity is significant (Poulson et al 2003)

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

- Underuse:  
 Sentinel lymph node biopsy  
 Radiation therapy
- Overuse:  
 Over-aggressive/mutilating surgery  
 Scans (CT/MR/PET)  
 Chemotherapy

**Schematic of our recommended management:**



**Refer to [www.merkelcell.org](http://www.merkelcell.org) website:**

Created with Sheela Gupta & Linda Wang using funds donated from patients  
 Comprehensive review of topics discussed here  
 Non-technical language  
 20 page color pdf can be downloaded from the site

## **Part 5: Summary**

- **MCC incidence is rising and it has highest mortality of any skin cancer**
- **SLN bx, surgery and radiation are indicated in almost all cases**
- **Scans (CT/MR/PET) have poor sensitivity and specificity at time of dx**
- **Mutilating surgery and adjuvant chemotherapy have high morbidity and no proven benefits**
- **The [www.merkelcell.org](http://www.merkelcell.org) website is a practical reference for patients & MDs in determining therapy and prognosis.**

(Easy to find as hit #14 of 35,800 for Google search of "Merkel cell carcinoma")

## Part 6: Annotated References

Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *Journal of the American Academy of Dermatology* 2003;49:832-41. ***Largest study (1034 patients) 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, Zhang Z-F, Coit DG. Surgical management of Merkel cell carcinoma. *Annals of Surgery* 1999;229:97-105. ***Study of 102 patients from Memorial Sloan-Kettering Cancer Center that concluded 1) tumor size at presentation was an independent predictor of survival for stage I disease, 2) lymph nodes were the most common site of first recurrence, and 3) elective lymph node dissection decreased the rate of recurrence, but was not associated with improved overall survival.***

Engles EA, Frish M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. *Lancet* 2002;359:497-498. ***National Cancer Institute study that found that immune suppression from HIV increased MCC risk by roughly 8-fold.***

Gupta S, Wang L, Nghiem P. Merkel cell carcinoma: Information for patients and their physicians. [www.merkelcell.org](http://www.merkelcell.org). ***The only website dedicated to providing easily understood information on MCC causes, prognosis and therapy.***

Mortier L, Mirabel X, Fournier C, Piette F, Lartigau E. Radiotherapy alone for primary Merkel cell carcinoma. *Archives of Dermatology* 2003;139:1587-1590. ***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).***

Longo MI, Nghiem P. Merkel cell carcinoma treatment with radiation: a good case despite no prospective studies. *Archives of Dermatology* 2003;139:1641-1643. ***Editorial that accompanied Mortier, et al discussing the importance of adjuvant radiation therapy and a proposed algorithm for MCC treatment.***

Nghiem P, McKee PH, Haynes HA. Merkel cell (cutaneous neuroendocrine) carcinoma, in Sober AJ, Haluska FG (ed): *American Cancer Society Atlas of Clinical Oncology: Skin Cancer*. Hamilton, Ontario, BC Decker Inc, 2001, pp 127-141. ***Comprehensive chapter on MCC in a multiauthored atlas of skin cancer.***

Penn I, First MR. Merkel cell carcinoma in organ recipients: report of 41 cases Transplantation. 1999;68:1717-21. ***University of Cincinnati study that concluded that organ transplant patients, on drugs that suppress the immune system, have a roughly 10-fold higher risk of developing MCC, which proved to be more aggressive.***

Poulsen M, Rischin D, Walpole E, Harvey J, Mackintosh J, Ainslie J, Hamilton C, Keller J, Tripcony L. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a trans-tasman Radiation Oncology Group study TROG 96:07. *Journal of Clinical Oncology* 2003;21:4371-4376. ***Australian phase II study of 53 patients with stage I and II MCC treated with both chemotherapy (carboplatin/etoposide) and radiation therapy. This study showed 76% overall survival at 3 years, which was roughly similar, but perhaps better, than expected from previous studies. This study was not randomized or controlled.***