Merkel Cell Carcinoma

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See www.merkelcell.org for more info or for a pdf of this handout.
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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 (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 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 3
Melanoma	1 in 6
Sq Cell CA	1 in 50
Basal Cell CA	<1 in 10,000

(Nghiem et al, 2001) (Agelli et al, 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 600-1000 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 immune suppression (HIV, solid organ transplant, CLL)
  - 13.4-fold increase among HIV+ pts.
  - ~10 fold increase after solid organ transplantation
    - (Engels, et al 2002)
    - (Miller, et al 1999 SEER)
  - 9% of MCC pts had HIV, CLL, Organ Solid Transplant among 141 in our series

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

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. (Manuscript in preparation)

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

Pathology Summary:

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

Part 3: Staging & Prognosis

MCC Stages at Diagnosis per AJCC 6th Edition*:		% 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%

*Currently being updated for 7th Ed. of AJCC staging manual

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

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. Arch Dermatol. 2006)

CT Scans for NODAL DISEASE

(Gupta. Arch Dermatol 2006); CT scans in 34 cases; PET scan in 1 case; Gold Standard for presence of disease: pathologic dx within 6 months of CT Scan

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

No need to scan 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 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:

		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 over 3-fold with the addition of XRT (39% to 12%) (Lewis et al., 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 minimal:

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

Risk of SCCs in those with life expectancy > 20 years

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)

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. 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 adjuvant chemotherapy:

- Mortality: 4-7% deaths due to adjuvant chemo in MCC (Tai, 2000; Voog, 1999)
- Morbidity: neutropenia (60% of pts) fever and sepsis (40%) (Poulsen, 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 with	**MCC-specific survival**
No adjuvant Chemo (n=53)	60%
Adjuvant Chemo (n=23)	40%

(Allen, et al 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

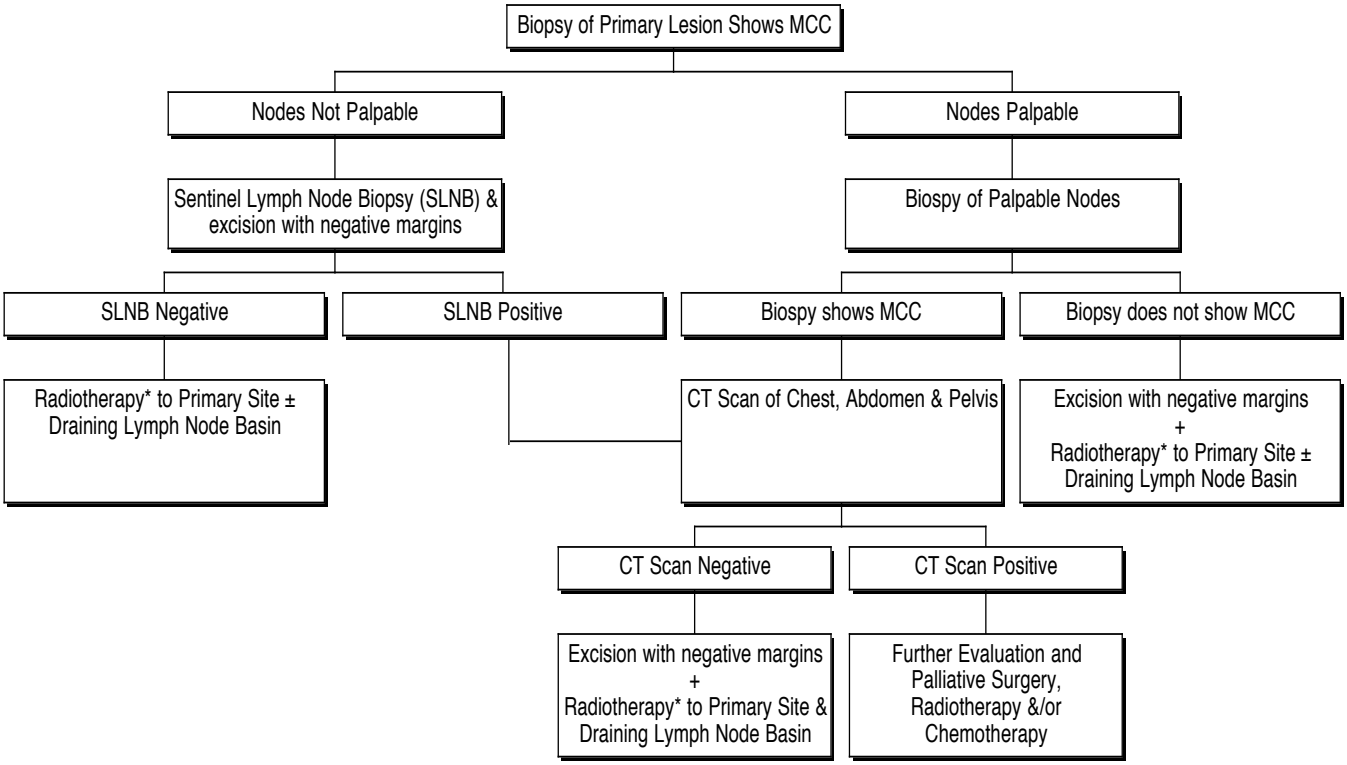
Underuse:

- Sentinel lymph node biopsy
- Radiation therapy

Overuse:

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

***Schematic of our recommended management:**



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* **Recommended Radiation Therapy dose** (based on 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...hit #2 of 240,000 for 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 2003;49:832-41.

- ***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 2005:23 (10); 2300-9.

- ***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. 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. Arch Dermatol 2006; 142: 771-4.

- ***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.***

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 showed excellent success (zero recurrences) in patients treated with radiation therapy alone (9 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.***

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

- ***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.***

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.***

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 across the US.***