# Merkel cell carcinoma of the skin

BC Cancer Surgery Network Fall Update
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# Outline

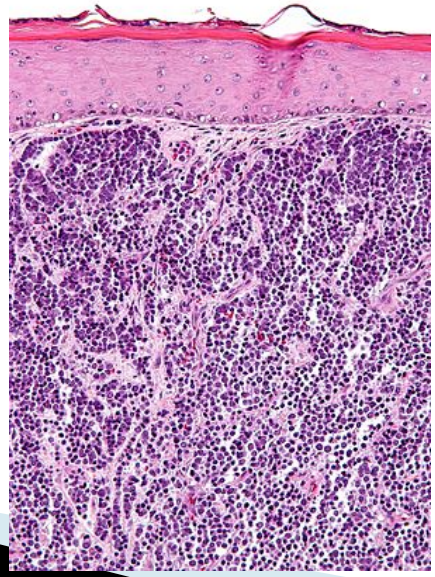
- What it is
- Clinical Features and Staging
- What to do with localized/nodal disease
  - Site of primary
    - Surgery – surgical margins?  How aggressive?
    - Radiotherapy – After surgery?  For gross disease?
  - Nodal drainage sites
    - Surgery – sentinel node biopsy? Nodal dissection?
    - Radiotherapy – Adjuvant with/without SNB? For gross disease
- Treatment outcomes

# What is Merkel cell CA?

- Small blue cell tumor of the skin
- Neuroectodermal origin – from Merkel cell?
- Etiology
  - Sunlight (>90% patients of European origin)
  - Immunosuppression
  - Merkel cell polyomavirus
- Used to be rare, but 3x incidence 1986→2001

# Diagnosis/Clinical Features

| A | Asymptomatic |
|---|---|
| E | Expanding quickly (over 3 – 4 months) |
| I | Immunosuppressed individuals |
| O | Older (male > female) |
| U | UV exposed skin |



# Pathological DDX

**Immunocytochemical differential diagnosis of Merkel cell carcinoma**

| Tumour | CK20 | CK7 | NSE | NFP | S100 | LCA | CD99 | TTF1 |
|---|---|---|---|---|---|---|---|---|
| Merkel cell carcinoma | + | - | + | + | - | - | Rarely + (cytoplasmic) | _ |
| Small cell carcinoma | - | + | + | +/- | - | - | Rarely + (cytoplasmic) | + |
| Lymphoma | - | - | - | - | - | + | - | - |
| Primitive neuroectodermal tumour | - | - | + | Rarely + | - | - | + (membranous) | - |
| Small-cell melanoma | - | - | + | - | + | - | - | - |

CK20: cytokeratin 20; CK7: cytokeratin 7; NSE: neuron-specific enolase; NFP: neurofilament protein; S100: S100 protein; LCA: leucocyte common antigen; CD99: cluster-of-differentiation antigen 99; TTF1: thyroid transcription factor 1; +: positive stain; -: negative stain.

# Staging

- TNM and AJCC Stages I – IV
- *Stage I*: Primary $\leq$ 2 cm, node negative
- *Stage II*: Primary $>$ 2cm, node negative
- *Stage III*: Node positive
- *Stage IV*: distant metastases
- At presentation: Localized disease ~ 66%, Nodal disease ~ 25%, metastatic disease ~10%

# Prognosis

- BC Cancer series* (1979 – 2007, N =179)
  Median age 75, median tumor size 1.5cm

- MGH series** (1980 –2010, N = 161)
  Median age 72, median tumor size 2.3cm)

| Cause specific Survival 5 yrs | Stage I | Stage II | Stage III |
|---|---|---|---|
| BC Cancer | 88% | 70% | 64% |
| MGH | 87% | 63% | 42% |

* Harrington C: Ann Sug Oncol (2016) 23: 573–578
** Santamaria-Barria JA: Ann Surg Oncol (2013) 20: 1365–1373

# Management

- At the local disease site

# Wide local excision

- How wide?
  - NCCN: 1 – 2 cm margins to investing fascia or pericranium when feasible
  - "… that any reconstruction involving extensive undermining … be delayed until negative histologic margins are verified and SLNB is performed if indicated"
- Why do you need the 1 – 2 cm margin?
  - Early retrospective review suggested better overall survival*
  - Modern series with adjuvant radiation cast doubts on the need for wide excision
- BC Results:
  - If margin < 1cm, No RT local recurrence 25% Vs 5% with RT
  - If margin > 1cm, local recurrence 7% with/without RT

* Tai PT et el: Merkel cell carcinoma of the skin. J Cutan Med Surg. 2000; 4(4):186

# Wide excision not possible or cosmetically very undesirable …

- Radiation likely can provide as good local control …

- BC series*: 57 patients underwent primary radiotherapy in the presence of gross disease
  - 58% had clinical nodal disease (Stage III)
  - 5 year local relapse free = 90%
- Fred Hutchinson series**: 28 patients
  - All had nodal disease without nodal dissection
  - 2 year regional relapse free = 100% (microscopic disease) & 78% (palpable disease)

*Harrington C: Ann Surg Oncol (2014) 21: 3401-3405
**Fang LC: Cancer (2010) 116(7) : 1783-1790

# Radiation alone for Merkel cell

- Australian systemic review
  - Outcomes of treatment with “definitive” radiotherapy
  - 332 sites of MCC radiated (Primary Vs regional ~50% each)
  - Findings:
    - In field control 75 – 85%
    - 5 year overall survival 40 – 60%

*Gunaratne DA: J Am Acad Dermatol (2017) 77 No. 1: 142-148

# *Summary slide: local disease*

- Excise with 1cm margin minimum if possible
- If achieving the margin requires extensive disfiguring surgery, consider sending patient to oncologist
- Radiation to local site indicated if margin $< 1$cm
- Definitive radiation to local site in the setting of gross disease results in good local control up to 90%

# Management

- At the nodal drainage basin

# Clinically node negative

- BC results* (N = 137) nodal relapse rate

| | Observation | Elective RT |
|---|---|---|
| Nodal relapse rate | 23% | 11% |

Retrospective data exist showing patients given adj radiation have better OS⁂.

- In the era of SLNB, we know why
  - MSKCC series**, 122 Stage I patients
  - SLNB yielded positive nodes in ~30%

- In the absence of SLNB, we recommend adjuvant radiation to regional nodes


* Harrington C: Ann Sug Oncol 2016; 23: 573-578
** Gupta SG: Arch Dermatol 2006; 142: 685-690
⁂Mojica P: J Clin Oncol 2007; 25:1043-1047
⁂Bhatia S: J NCI 2016; 108(9) Epub 2016 May 31

# Clinically N0 in the era of SLNB

- Dana Farber series:
  - If SLN –ve, no difference between control of those who received adjuvant therapy
  - If SLN+, much better RFS if adjuvant therapy is given

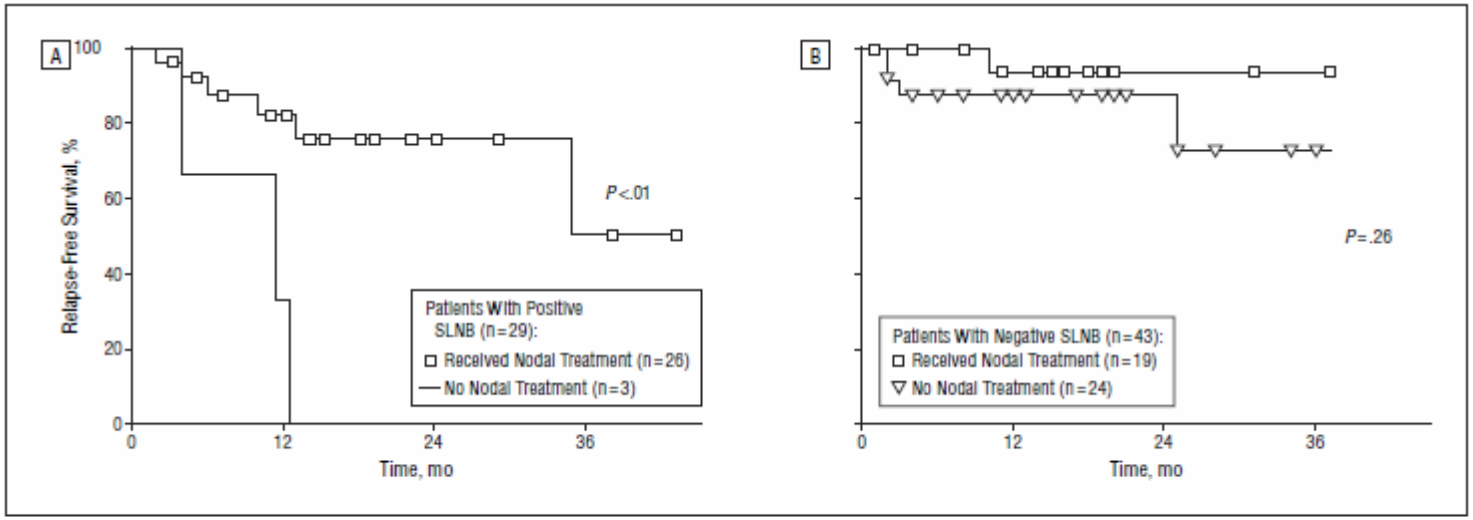



**Figure 3.** Influence of adjuvant lymph node therapy on relapse-free survival in patients with a positive sentinel lymph node biopsy (SLNB) and those with a negative SLNB. A, Patients with a positive SLNB who did not receive adjuvant therapy had a 0% 3-year relapse-free survival rate vs 51% for those who received therapy ($P<.01$). Data are from 29 patients who had a positive SLNB and for whom follow-up was reported. B, Patients with a negative SLNB who did not receive adjuvant therapy had a 70% 3-year relapse-free survival rate vs 90% for those who received therapy ($P=.26$). Data are from 43 patients who had a negative SLNB and for whom follow-up was reported.

** Gupta SG: Arch Dermatol 2006; 142: 685-690

# *Summary slide*
# *Clinically Node Negative*

- If no SLNB is done or if SLNB fails, adjuvant radiation is indicated

- If SLNB is negative, no adjuvant radiation
- If SLNB is positive, adjuvant radiation indicated

# Clinically node positive

- NCCN guidelines:
  - Multidisciplinary tumor board or
  - Node dissection +/- radiation therapy or
  - Clinical Trial

- Depends on the bulk of disease
  - BC results (N = 42)

| | Surgery alone (N=3) | Definitive RT (N=33) | Surgery + Adj RT (N=2) |
|---|---|---|---|
| Nodal relapse rate | 33% | 21% | 33% |

# Clinically node positive Adjuvant chemotherapy?

- *No evidence it helps*

- TROG 96-07 Phase II*
  - 40 patients treated with chemoRT (Etoposide & Platinum)
  - No improvement compared to historical patients (Queensland) treated without chemo
- MSKCC review, retrospective**
  - Patients who got adj chemo had poorer survival

*Poulson M: J Clin Oncol 2003; 21: 4371-4376
**Allen PJ: J Clin Oncol 2005; 23: 2300-2309

Friedrich Sigmund Merkel
1845 – 1919
German anatomist, pathologist