Management of Head and Neck Melanomas

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Cutaneous Melanoma - A Rapid Rise

- Leading cause of death from skin cancer
- Death rate has doubled in the last 35 yrs – One American dying / hour
- Lifetime risk of developing melanoma:
  - 1935 - 1:1500
  - 1980 - 1:250
  - 2000 - 1:75
  - 2010 - 1:50
- Increased detection – 68,130 in 2010
- Increased exposure to UV-B
Lifetime Risk
Invasive MM

Rigel et al, NYU Melanoma Cooperative Group, 2001
# Risk Factors for Melanoma

<table>
<thead>
<tr>
<th>Greatly Elevated Risk</th>
<th>Moderately Elevated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>changing mole</td>
<td>one family member with melanoma</td>
</tr>
<tr>
<td>dysplastic nevi in familial melanoma</td>
<td>history of prior melanoma</td>
</tr>
<tr>
<td>&gt; 50 nevi ≥ 2 mm</td>
<td>sporadic dysplastic nevi</td>
</tr>
<tr>
<td></td>
<td>congenital nevus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slightly Elevated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>immunosuppression</td>
</tr>
<tr>
<td>sun sensitivity</td>
</tr>
<tr>
<td>severe sunburns / sun exposure</td>
</tr>
<tr>
<td>(UVB)</td>
</tr>
</tbody>
</table>
Growth Patterns of Melanoma

- **Superficial Spreading Melanoma:** 70%
  - flat with notched perimeter
  - radial growth → vertical growth

- **Nodular Melanoma:** 15-30%
  - raised, dome shaped
  - more aggressive, early vertical growth
Growth Patterns of Melanoma

- **Lentigo Maligna Melanoma:** 4-10%
  - often long history, large size
  - unlikely to metastasize

- **Desmoplastic Melanoma:** 1%
  - tendency to invade nerves
  - high rate of local recurrence
  - low rate of regional metastases
Biopsy Technique

- Always **full thickness** biopsy (never shave)
- Excisional biopsy for small lesions with narrow margin
- Punch or incisional biopsy for larger lesions at the **thickest** area
Immunohistochemistry

- Essential for poorly dif., amelanotic, spindle cell, or small cell melanomas
- S-100 protein
  - expressed by almost all melanomas
  - also expressed by sarcomas, nerve sheath tumors, some carcinomas
- HMB-45
  - more specific for melanoma
  - may not stain desmoplastic or spindle cell melanoma
- MEL-5, Melan-A, NKI/C3, neuron-specific enolase
## Localized Stage I & II

### T Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Thickness</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>&lt; 1.0 mm</td>
<td>a: without ulceration and mitosis &lt; 1/mm²</td>
</tr>
<tr>
<td>T2</td>
<td>1.01 – 2.0 mm</td>
<td>b: with ulceration or mitosis ≥ 1/mm²</td>
</tr>
<tr>
<td>T3</td>
<td>2.01 – 4.0 mm</td>
<td>mitosis ≥ 1/mm²</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.0 mm</td>
<td>mitosis ≥ 1/mm²</td>
</tr>
</tbody>
</table>

### 2 Prognostic Features of Outcome

1. Tumor Thickness (1.0, 2.0, 4.0 mm)
   - Clark’s level of invasion – no longer used; replaced by mitotic rate for thin T1 tumors
2. Ulceration – Histologic Diagnosis; Upstages patient
3. Mitotic Rate
### Regional Metastatic Stage III

<table>
<thead>
<tr>
<th>Class</th>
<th># Nodes</th>
<th>Tumor Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>1</td>
<td>a: Micromets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macromets</td>
</tr>
<tr>
<td>N2</td>
<td>2 - 3</td>
<td>a: Micromets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macromets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: In transit/satellite(s) without metastatic nodes</td>
</tr>
<tr>
<td>N3</td>
<td>4+ or Matted Nodes or in transit mets/satellites with metastatic nodes</td>
<td></td>
</tr>
</tbody>
</table>

### 4 Major Prognostic Features of Outcome

- Number of Metastatic Nodes
- Ulceration
- Micro vs. Macroscopic Disease
- Intralymphatic Mets
Summary of 2010 AJCC Staging System

1) **Local Stage I/II Disease:**
   - Tumor thickness (*** Clarks level NO LONGER used)
   - Ulceration
   - Mitotic rate (< 1/mm$^2$; ≥ 1/mm$^2$) use for thin T1 melanomas

2) **Regional Stage III Disease:**
   - # of metastatic nodes
   - Tumor burden (micro vs macroscopic disease)
   - Ulceration

3) **Metastatic Stage IV Disease:**
   - Anatomic site
   - LDH
Staging Summary

I:  T1, T2a     N0     M0
II: T2b, T3-4   N0     M0
III: Any T      N2-3   M0
IV: Any T       Any N  M1
What is an Adequate Surgical Margin?

- 1988 – Veronesi – WHO Trial - 612 pts
- < 2 mm (trunk/extremity)
- Randomized to 1 cm vs. 3 cm resection margin
- No differences: disease free survival (81.6% vs 84.4%) overall survival regional nodal metastases distant metastases

**What is an Adequate Surgical Margin?**

1. **1993 - Balch – Intergroup Trial – 486 pts**
2. **1-4 mm thick (trunk/extremity)**
3. **Randomized to 2 cm vs. 4 cm resection margin**
4. **No differences:**

<table>
<thead>
<tr>
<th></th>
<th>2 cm</th>
<th>4 cm</th>
</tr>
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<tbody>
<tr>
<td>Local Recurrence</td>
<td>0.8%</td>
<td>1.7%</td>
</tr>
<tr>
<td>5-yr Overall Survival</td>
<td>79.5%</td>
<td>83.7%</td>
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## Summary - Margins for Excision

Margins of excision of H&N melanoma limited:

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1-4 mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>&gt; 4 mm</td>
<td>&gt; 2 cm</td>
</tr>
</tbody>
</table>

- Cosmetic / functional considerations
- Intraoperative frozen sections vs. delayed closure after rush final pathology
Nodal Dissection Enhances Survival for Pts with Microscopic Mets

Sentinel Lymph Node - Principles

1. SLN is the first node in a lymphatic basin into which the primary melanoma drains.

2. SLN reflects the presence or absence of metastases in the remainder of the nodal basin.

3. Patients with microscopic metastases in the SLN may benefit from complete nodal dissection.*
SLNB for Intermediate Thickness

![Bar graph showing risk of regional node metastases and distant metastases based on melanoma thickness.

- For melanoma thickness <0.76 mm (THIN), the risk is 2%-3%.
- For melanoma thickness 0.76-1.50 mm, the risk is 8%.
- For melanoma thickness 1.51-4.00 mm, the risk is 15%.
- For melanoma thickness >4.00 mm (THICK), the risk of distant metastases is 72%.

Note: The risk of regional node metastases is not shown in the graph.]}
Does SLNB and selective node dissection offer a survival benefit?
MSLT-1: Results

1,269 patients, 1.2 - 3.5 mm

Wide excision only

- Nodal Recurrence
  - No: Observation
  - Yes: Delayed TLND
    - 52.4% 5-yr survival

Wide excision plus SLNB

- SLN positive
  - Immediate TLND
    - 72.3% 5-yr survival

- SLN negative
  - Observation
    - 90.2% 5-yr survival

86.6% OS vs. 87.1% OS (NS)

Nodal Recurrence: p=0.004

Hazard ratio for death is 2.48 for positive vs. negative sentinel nodes
"Staging of intermediate thickness (1.2 to 3.5 mm) primary melanomas according to the results of sentinel node biopsy provides important prognostic information & identifies pts with nodal metastases whose survival can be prolonged by immediate lymphadenectomy."

Morton DL et al. NEJM 355:1307, 2006
## SLN Biopsy in the Head and Neck

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% Pts SLN Found</th>
<th>% Pts SLN Positive</th>
<th>% False Negative SLN</th>
<th>Mean F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel* 2002</td>
<td>56</td>
<td>93%</td>
<td>8%</td>
<td>2%</td>
<td>20 mo</td>
</tr>
<tr>
<td>Eicher 2002</td>
<td>43</td>
<td>98%</td>
<td>21%</td>
<td>0%</td>
<td>Immed. ND</td>
</tr>
<tr>
<td>Wagner 2000</td>
<td>70</td>
<td>99%</td>
<td>17%</td>
<td>2%</td>
<td>11 mo</td>
</tr>
<tr>
<td>Bostick 1997</td>
<td>117</td>
<td>92-96%</td>
<td>13%</td>
<td>0%</td>
<td>46 mo</td>
</tr>
</tbody>
</table>

Specific issues of SNB in Head & Neck

1. Blue dye not very useful
2. Multiple nodes
3. Parotid nodes / technical issues
4. Role of completion neck dissection
Sentinel Lymph Node Biopsy (SLNB)

- Minimally invasive procedure to identify patients harboring occult nodal disease
  - Identifies patients who warrant therapeutic neck dissection & adjuvant therapy
  - Spares 80% of patients without regional disease the morbidity of a neck dissection and parotidectomy
Importance of SLNB:

Survival benefit for Stage III pts diagnosed with occult nodal metastasis compared to palpable nodal metastasis.

Importance of SLNB:

WHO considers SLNB standard of care.  
*(Oncology. 1999; 13: 288.)*

Sentinel Lymph Node Mapping

• **Positive** SLN biopsy
  – Therapeutic Neck Dissection
  – Superficial Parotidectomy
    • Temple; forehead; cheek; anterior scalp
  – Counseling for adjuvant interferon α-2b & radiation

• **Negative** SLN biopsy
  – Followed clinically

NCCN V.4.2011
Standard of Care
Survival Estimates by SLN Status

- SLN
+ SLN
Conclusions

• Sentinel lymph node biopsy is a safe and effective tool to characterize the regional nodal basin in patients with cutaneous melanoma of the head and neck.

• Status of the sentinel lymph node is highly predictive of overall and disease-free survival.

• Patients with a negative sentinel lymph node must be watched closely for recurrent disease.
Adjuvant hypofractionated radiotherapy improves regional control

N=152 non-randomised node positive patients
Irradiated: 67%
- had > 1 +ve node, 48%
- had ECS
Non-irradiated: 43%
- had > 1 +ve node, 19%
- had ECS
(Head and Neck 1997)
Adjuvant Therapy For Regional Disease: Radiation Therapy

**Adjuvant Tx**: for intermediate thickness lesions
- Multiple positive nodes
- ECS

**Primary Tx**:  
- Elderly, non-surgical candidate
- Large LMM lesions

Note that melanomas are radioresistant
Failure of Systemic Therapy

• Dacarbazine - alkylating agent
  – Response: 10-20%
  – N/V, neutropenia, thrombocytopenia

• Carmustine, Cisplatin, Taxol not better

• Combination therapy is not better

• High dose IL-2

• No survival benefit
Interferon-α\textsubscript{2}b

- 1996 – Kirkwood - ECOG 1684 trial - 280 pts
- thick (> 4 mm) or regionally metastatic (N1)
- IFN-α\textsubscript{2}b vs. observation
  - 20 MU/m\textsuperscript{2}/d IV for 5d/wk x 4 wks
  - 10 MU/m\textsuperscript{2} SC for 3x/wk x 12 mo
- median overall survival prolonged (3.8 vs 2.8 yrs)
- 5-yr RFS survival increased (37% vs 26%)

Kirkwood JM, J Clin Oncol., 14:7-17,1996
Interferon-$\alpha$2b: Controversy

- **Significant Toxicities**
  - Fevers, chills, flu-like symptoms, fatigue, myelosuppression, hepatic & neurotoxicity
  - 78% had grade 3 or worse toxicity
  - 50% required treatment delay or dose ↓
  - 23% of pts discontinued treatment

- **2000 - Kirkwood - ECOG 1690 trial - 642 pts**
  - No benefit of low dose interferon
  - RFS improved for high dose, but not overall survival
MSKCC Active Clinical Trials

- Ph II: Temozolamide + IFN-\(\alpha\)2b
- Ph II: IL-12 + IFN-\(\alpha\)2b
- Ph I/II: Temozolomide + Thalidamide
- Ph I/II: High Dose Tylenol + Carmustine
- Ph I: Dendritic Cell therapy
- Ph I: Gp75 DNA Vaccine
- Ipilimumab (MSK)
Mucusoal Melanoma
MSKCC Patients

- 1978 - 1998
- Complete clinical data on 59 patients
- Sinonasal melanomas = 35
- Oral melanomas = 24
Sinonasal Melanoma
Cause-specific Survival

46% Survival

Median 40.2 months
Oral Melanoma
Cause-specific Survival

- Specific Survival: 38.6%
- Median Survival: 36 months
A good physician treats the disease; a great physician treats the patient who has the disease.