Head & Neck Melanoma and Cutaneous Malignancies

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Goals
- Epidemiology
- AJCC Staging – highlight recent changes
- Melanoma work-up & treatment – 2012 NCCN guidelines
- 7 Reasons to perform SLN mapping and biopsy
- SLN Mapping Technique
- Current SLN controversies
- Adjuvant treatment
- Other high risk malignancies

Epidemiology – Incidence – on the rise
- 68,130 new cases in 2010
- Men: incidence increasing faster than any other cancer
- Women: incidence increasing faster than any other cancer except lung cancer
- In 2010, 1 in 39 lifetime risk of being diagnosed with melanoma

Epidemiology
- Median age at diagnosis: 59 yrs.
- Currently 1 of 4 new cases pt < 40
- Most common cancer in women 25 – 29
- 2nd most common cancer in women 30 – 34

Epidemiology

Melanoma mortality remains on the rise
- 8,700 deaths from melanoma in 2010
  - 8,650 2009
  - 8,420 2008
  - 8,110 2007
- 1 American dying every hour
- 1.8% increase mortality rate/year
- Second to adult leukemia in lost potential life years

Cutaneous Head & Neck Melanoma

- 25 – 30 % melanomas
- Second most common site overall
- Common anatomic locations
  - Face (40 – 60%)
  - Scalp (14 – 49%)
  - Neck (20 – 29%)
  - Ear (8 – 11%)


2010 AJCC Melanoma Staging (7th Ed.)

Final Version of 2009 AJCC Melanoma Staging and Classification

2010 TNM Staging System for Cutaneous Melanoma…and Beyond

Expanded melanoma database: 60,000 pts (17 institutions)
Effective January 2010

2010 AJCC Melanoma Staging

Localized Stage I & II

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

2 Prognostic Features of Outcome

Tumor Thickness

Ulceration
**T1 Tumors: Mitotic Rate**

- Indicator of tumor proliferation (# mitosis/mm$^2$)
- Associated with decreased survival, esp. for thin melanomas
- Independent predictor of positive sentinel lymph node (Paek Cancer 2007; Sondak Ann Surg Oncol 2004)
- 2nd most powerful predictor of survival in stage III (SLN+ pts) after # of +SLN (Balch, J Clin Oncol 2010)
- Should be included in your biopsy report (American Academy of Dermatology Task Force)

**2010 AJCC Melanoma Staging**

**Localized Stage I & II**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1a N0 M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b N0 M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b N0 M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3a N0 M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T3b N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T4a N0 M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b N0 M0</td>
</tr>
</tbody>
</table>

**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>Micromets</td>
</tr>
<tr>
<td>N2</td>
<td>2 - 3</td>
<td>Micromets</td>
</tr>
<tr>
<td>N3</td>
<td>4+ or Matted Nodes</td>
<td>Micromets or in-transit/metastatic nodes</td>
</tr>
</tbody>
</table>

**4 Major Prognostic Features of Outcome**

- Number of Metastatic Nodes
- Ulceration
- Micro vs. Macroscopic Disease
- Intralymphatic Mets

**Stage III - 5 Year Survival**

- IIA 67%
  - No ulceration
  - Micromets
- IIB 53%
  - Ulcerated w/micromets
  - Non-ulcerated; macromets
- IIC 26%
  - Ulcerated w/ macromets
**2010 AJCC Melanoma Staging**

**Distant Metastatic Disease: Stage IV**

<table>
<thead>
<tr>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a Distant Skin, subcutaneous,</td>
<td>Normal</td>
</tr>
<tr>
<td>or nodal metastasis</td>
<td></td>
</tr>
<tr>
<td>M1b Lung metastasis</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c All visceral metastasis</td>
<td>Normal</td>
</tr>
<tr>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

![Graph showing LDH levels over time](image)

**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

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**Summary of 2010 AJCC Staging System**

1. **Local Stage III Disease:**
   - Tumor thickness (**Clarks level NO LONGER used**)
   - Ulceration
   - Mitotic rate (< 1/mm²; ≥ 1/mm²) 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

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**Additional 2010 AJCC Changes**

1. Melanoma diagnosis can be made on H&E staining or with melanoma specific immunohistochemistry

2. Nodal tumor deposit of any size indicates N+ disease (previous tumor volume ≥ 0.2mm³ required)

3. Unknown primary arising in lymph node or subcutaneous tissue represents stage III disease
**Melanoma Work-Up**

- American Cancer Society ABCD's
  - A – Asymmetry
  - B – Border irregularity
  - C – Color variation
  - D – Diameter > 6mm
  - E – Evolution of change**

- History
  - Signs: recent change in size, color, shape
  - Symptoms: Pruritis, crusting, bleeding, tenderness


**NCCN 2.2013 Guidelines**

**Melanoma Work-Up**

**Biopsy Suspicious Lesions**

- Excisional with narrow (1-3mm) margins
- Full thickness incisional or punch biopsy of thickest portion for larger lesions
- Never shave biopsy pigmented lesion
- Repeat non-diagnostic biopsies

**Biopsy Read by Dermatopathologist**

- Tumor Depth; Ulceration; Regression; Mitotic Rate; Satellitosis; Vertical Growth Pattern; Tumor infiltrating lymphocytes (TIL)

**NCCN 2.2013 Guidelines**

**Melanoma Work-Up**

- Stage 0 (in situ)
  - H & P

- Stage IA (<1mm; mitosis<1)
  - H & P

- Stage IB to II (1 – 4 mm)
  - H & P

- Stage III (N0;>4mm)
  - H & P
  - Recommend baseline imaging (CT, PET/CT, MRI)

- Stage III (N+; in transit)
  - H & P, FNA
  - Recommend baseline imaging

- Stage IV (distant mets)
  - H & P, LDH
  - Recommend CT abx/pelvis vs CT/PET, MRI brain

**NCCN 2.2013 Guidelines**

**Treatment: Wide Local Excision**

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>≤ 1.0 mm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td>1.01 – 2.0 mm</td>
<td>1.2 cm</td>
</tr>
<tr>
<td>2.01 – 4.0 mm</td>
<td>2.0 cm</td>
</tr>
<tr>
<td>&gt; 4.0 mm</td>
<td>2.0 cm</td>
</tr>
</tbody>
</table>

**Margins modified to accommodate anatomic/cosmetic considerations**
Therapeutic Neck Dissection

- **STAGE III** – Standard of Care
  - Neck Dissection (selective vs. modified) preserving:
    - Sternocleidomastoid Muscle
    - Internal Jugular Vein
    - Spinal Accessory Nerve
  - Superficial Parotidectomy for areas that drain to the parotid basin:
    - Temple
    - Forehead
    - Cheek
- **STAGE IV** – Consider for locoregional control

Adjuvant Therapy For Regional Disease

Interferon α-2b

**Indications**
- Depth > 4 mm
- Node positive
- Only FDA approved adjuvant therapy for stage III disease
- Modest improvement in DFS

**Treatment Course**
- IV 5 days/wk for 4 wks
- SC TIW for 48 wks

**Side Effects**
- Neutropenia/thrombocytopenia
- Fatigue, myalgia, HA, fever, N/V
- Elevated SGOT
- Depression & suicidal behavior

Radiation Therapy

**Adjuvant Tx:**
- Multiple positive nodes
- Macroscopic extranodal extension

*Adjuvant RT for high risk stage III disease to reduce the likelihood of regional recurrence is supported by 2 randomized controlled trials: Burmeister B et al. Lancet Onc 2012, Crespián ET et al. Cancer 1978.

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

Note that melanomas are radioresistant

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:

1) Pathologic status of SLN is the most important prognostic factor for recurrence and survival.

<table>
<thead>
<tr>
<th>612 Stage I/II Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Thickness</td>
<td>HR = 1.23</td>
</tr>
<tr>
<td>Clark Level &gt; III</td>
<td>HR = 2.32</td>
</tr>
<tr>
<td>SLN Status</td>
<td>HR = 6.53</td>
</tr>
</tbody>
</table>


Importance of SLNB:

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


Importance of SLNB:

3) AJCC incorporated SLNB into 2002 and subsequent melanoma staging.

4) SLNB is the most sensitive and specific modality for regional staging.

5) SLNB now incorporated into NCCN practice guidelines

Importance of SLNB:

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

Indications for SLNB

• Localized Stage Only!
• Breslow depth $\geq$ 1 mm
• Breslow depth 0.75-1 mm (T1) if adverse prognostic variables:
  - Tumor extension to deep margin
  - Ulceration
  - Lymphovascular invasion
  - Extensive regression to 1.0 mm
  - Young age
  - High mitotic rate ($\geq$ 1 mm)
  - Clark level IV or V (reticular dermis or deeper)

Case Study 1: Scalp Melanoma

Sentinel Lymph Node Mapping

- WLE primary melanoma
- SLN identification
  - Gamma probe
  - Blue dye
- SLN individually dissected from surrounding tissue
- FN monitoring for parotid bed
- Permanent histologic evaluation

1 mCi TC Sulfur Colloid
Case Study 2: Parotid SLN

Scalp Melanoma s/p WLE

Images courtesy of Cecelia Schmalbach, MD

Parotid SLN Mapping

Gamma Probe Right Parotid SLN

Images courtesy of Cecelia Schmalbach, MD

CT SPECT for Parotid SLN

SPECT/CT for SLN Mapping


- Patients (n=38) staged with lymphoscintigraphy followed by hybrid SPECT/CT
- SPECT/CT detected an additional 2.6 node/patient
- SPECT/CT led to adjustment of surgical approach in 11 pts (55%).
  - Provides better anatomic information
SLN Histologic Evaluation

- Permanent Histologic Evaluation
  - 10% False Neg. Rate on Frozen Section
- Serial sectioning (5-microns)
- H&E Staining
- S-100 & Melan-A (MART-1) IHCS


IHCS Sensitivity: 97% S-100
96% Melan-A (MART-1)
75% HMB-45 (does not add)

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

Is H&N SLNB Safe and Reliable?

- Complexity of cervical lymphatics
- Damage to vital H&N structures
  - Carotid Artery
  - Internal Jugular Vein
  - Facial Nerve
  - Spinal Accessory Nerve

Largest Single Institutional H&N SLN Study

*University of Michigan Melanoma Database:*
April 1997 - December 2007

- 353 Evaluable patients
  - Median age 54 years (range 2 to 84 years)
  - Mean follow-up 48 months, (min. 12 mon)
  - Longest follow-up to date
- No major complications
- 6 patients required superficial parotidectomy

Recurrence

Only 4.24% recurred in regional nodal basin

Significance

• Negative predictive value of a negative sentinel lymph node: NPV = 95.8%*
  – *this is the important number!
• Patients with local control and a negative SLN failed in the regional basin in 4.2% of cases

Disease-Free Survival by SLN Status

Best Multivariate Model for Overall Survival

Table 4. ‘Best’ multivariate model for overall survival.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulceration (present vs. absent)</td>
<td>3.05 (1.22 – 7.45)</td>
<td>0.0097</td>
</tr>
<tr>
<td>Age at diagnosis (1 year increase)</td>
<td>1.08 (1.02 – 1.15)</td>
<td>0.0001</td>
</tr>
<tr>
<td>SLN</td>
<td>1.33 (1.22 – 4.02)</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

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.

Collaborative Effort

• Surgeon
• Dermatologists
• Nuclear Medicine Staff
• Pathologists

Multicenter Selective Lymphadenectomy Trial

Primary cutaneous melanoma
Breslow thickness ≥ 1.0 mm or Clark IV

Wide excision only
  Nodal Recurrence
    No
    Yes
      Observation
      Delayed TLND

Wide excision plus SLNB
  SLN positive
    Immediate TLND
  SLN negative
    Observation

Observation

? Survival Benefit of SLNB: MSLT-I

Interim Analysis of MSLT-I

• Mortality Rate for SLNB = 0
• Complication rate of SLNB (10%) significantly lower than TLND (37%)
• Learning curve increased to 50 cases
  – False omission rate = 10.3% for first 25 cases
  – False omission rate = 5.1% for next 25 cases
**MSLT-1: Results**

- **WLE + SLNB:** 16.0% ≥ 1 positive SLN
- **WLE only:** 15.6% regional nodal relapse
- 7.4% (56/755) with a negative SLNB failed in the regional lymph node basin
- SLNB can accurately identify occult nodal dz that will lead to advanced palpable nodal disease if left *in situ*.
- Mean # of tumor-involved nodes was 1.4 in the SLN group vs. 3.3 in the observation group (p <0.001), indicating disease progression during observation.

*Morton DL, et al. NEJM 355;1307, 2006*

**High Risk Cutaneous Malignancies**

- **Merkel Cell Cancer**
  - Behaves like melanoma but is sensitive to radiation
- **High-risk Cutaneous SCCA**
  - > 2cm
  - Recurrence
  - Immunocompromised host
  - Perineural, lymphovascular invasion
  - Ear, lip location

Consider SLN Biopsy to stage regional basin in all vs. elective dissection/radiation

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**For Intermediate Thickness Melanomas**

1,269 patients, 1.2 and 3.5 mm

- **Wide excision only**
  - Nodal Recurrence only
  - Immediate TLND
  - 73.1% DFS
  - 52.4% 5-yr melanoma specific survival
  - No
  - p=0.004

- **Wide excision plus SLNB**
  - Nodal Recurrence
  - Delayed TLND
  - Observation
  - 76.3% DFS
  - 72.3% 5-yr melanoma specific survival
  - Yes

- **SLN positive**

- **SLN negative**

- **p=0.009**

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**MSLT-1: SLN Take Home Point**

“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*
Questions

National Comprehensive Cancer Network
www.nccn.org

AJCC Cancer Staging Manual
www.cancerstaging.net

National Cancer Institute
Current Melanoma Clinical Trials:
www.cancer.gov

cbradfor@med.umich.edu

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