Sentinel Lymph Node Biopsy for Head and Neck Cutaneous Melanoma

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Grand Rounds Presentation
November 28, 2012
1. Which of the following is not a stain used to identify melanoma?
   hematoxylin and eosin
   a. Mart-1
   b. HMB-45
   c. S-100
   d. Silver stain

2. In the absence of spread beyond the primary site of a melanoma, when is it appropriate to use SLNB?
   a. less than 1mm tumor thickness
   b. 1-4mm tumor thickness
   c. Greater than 4mm tumor thickness
   d. All of the above thickness can justify SLNB

3. What percentage of patients with a primary melanoma of the head/neck and no evidence of regional/distant spread will have occult regional metastases??
   a. 5%
   b. 10%
   c. 20%
   d. 30%
Melanoma

### Primary Classification

<table>
<thead>
<tr>
<th>TX</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>Tis</td>
<td>Melanoma <em>in situ</em>.</td>
</tr>
<tr>
<td>T1</td>
<td>Melanomas ≤1.0 mm in thickness.</td>
</tr>
<tr>
<td>T2</td>
<td>Melanomas 1.01–2.0 mm.</td>
</tr>
<tr>
<td>T3</td>
<td>Melanomas 2.01–4.0 mm.</td>
</tr>
<tr>
<td>T4</td>
<td>Melanomas &gt;4.0 mm.</td>
</tr>
</tbody>
</table>

*Note:* a and b subcategories of T are assigned based on ulceration and number of mitoses per mm² as shown below:

<table>
<thead>
<tr>
<th>T classification</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>≤1.0</td>
<td>a: w/o ulceration and mitosis &lt;1/mm².</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration or mitoses ≥1/mm².</td>
</tr>
<tr>
<td>T2</td>
<td>1.01–2.0</td>
<td>a: w/o ulceration.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration.</td>
</tr>
<tr>
<td>T3</td>
<td>2.01–4.0</td>
<td>a: w/o ulceration.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration.</td>
</tr>
<tr>
<td>T4</td>
<td>&gt;4.0</td>
<td>a: w/o ulceration.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration.</td>
</tr>
</tbody>
</table>
Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason).

No regional metastases detected.

Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases).

**Note:** N1–3 and a–c subcategories assigned as shown below:

<table>
<thead>
<tr>
<th>N Classification</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>1</td>
<td>a: micrometastasis. b: macrometastasis.</td>
</tr>
<tr>
<td>N2</td>
<td>2–3</td>
<td>a: micrometastasis. b: macrometastasis.</td>
</tr>
<tr>
<td>N3</td>
<td>≥4 metastatic nodes, or matted nodes, or in transit met(s)/satellite(s)</td>
<td>with metastatic node(s).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: in transit met(s)/satellite(s) without metastatic nodes.</td>
</tr>
</tbody>
</table>
### Melanoma Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Clinical Staging</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
<td>≥N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Historical Treatment of N0 Melanoma
Watch and Wait

VS

Elective Lymph Node Dissection

http://www.frankmiller.com/blog/wrong-end-binoculars

ELND and Mortality

WHO Trial - Veronesi et al. 1982

Mayo Clinic - Sim et al. 1977

H&N
Loree/Spiro - 1989
- 289 pts
Obrien - 1991
- 998 pt series
Kane - 1997
- 424 pt series
Intergroup Melanoma Surgical Trial

Balch 1996/2000
Why does ELND not decrease mortality in Head and Neck?

Unpredictable Lymphatic Spread of melanoma

Shah 1989

“skip mets”

Obrien Classification

34% discordance with lymphoscintigraphy
Bilateral Nodal Drainage in H&N


10% - Morton 1993
SLNB Technique Described - 1990/1992

Donald Morton
Competing Theories of Melanoma Metastasis

**Incubator Hypothesis**
- SN incubates metastatic clones to become source of systemic metastasis
- Primary melanoma
  - Frequently
  - Immunosuppressive factors released by primary allow growth of melanoma in SN
  - Latent growth in sentinel node
  - Spreads to NSN
  - Blood borne to distant sites
  - Establishes distant metastases

**Marker Hypothesis**
- A Marker for Metastatic Phenotype
- Primary melanoma
  - Simultaneous metastases
  - Sentinel node
  - Blood borne to distant sites
  - Establishes distant metastases

Multi-Disciplinary Sentinel Lymph Node Biopsy Team


Fig. 3. Published experience with four-quadrant injection of a facial melanoma with Technetian 99 radiolabeled colloid.

Gershenwald JE. Ross MI. Sentinel-Lymph-Node Biopsy for Cutaneous Melanoma. n engl j med 364;18
Blue Dye

Gamma Probe -- 10% rule

Fig. 3. Use of a handheld gamma probe to aid in detection of a sentinel node in the popliteal fossa.
Melanoma Stains

H&E

S-100

HMB-45

MART-1

**Permanent Section**
Landmark SLNB Studies

MSLT I
(Morton)

Sunbelt trial
(McMasters)
- analyzed by Chao for H&N

SLN Working Group
(Leong)

Erman/Bradford et al 2012

**MSLT-1**

**Bx-Proven Melanoma**

Randomized

- **60%**
  - WEX + SNB
  - SN(+) → Immediate CLND
  - SN(-) → Observation

- **40%**
  - WEX + Observation
  - Nodal Recurrence → Delayed CLND
  - No Nodal Recurrence → Observation

**Trial began – Jan. 1994 – March 2002**

**Median follow-up:**
- Living – 8.2 years
- Dead – 3.6 years
3000 Patients Melanoma ≥ 1.0 mm Thickness
SLN Biopsy (PCR for all Pts)

SLN Histologically Negative

- PCR Negative
  - Observation

- PCR Positive
  - Protocol B
    - LN Dissection Only
    - Observation

SLN Histologically Positive

- Protocol A
  - LN Dissection
    - 1 Pos SLN Only
      - Observation
    - > 1 Pos Node Extracapsular Extension
      - Observation
  - Observation
    - Intron A
    - Intron A
    - Intron A

LN Dissection
### Table 3A. Surgical Morbidity (Within 30 d) Related to Wide Excision of the Primary Site in Patients Assigned to the 2 Treatment Arms of MSLT-I

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No.</th>
<th>Wound Separation</th>
<th>Seroma/Hematoma</th>
<th>Infection</th>
<th>Skin Graft Failure</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEO</td>
<td>798</td>
<td>28 (3.5%)</td>
<td>22 (2.8%)</td>
<td>67 (8.4%)</td>
<td>14 (1.8%)</td>
<td>13.9%</td>
</tr>
<tr>
<td>WE + LM/SNB</td>
<td>937</td>
<td>31 (3.3%)</td>
<td>41 (4.4%)</td>
<td>78 (8.3%)</td>
<td>21 (2.2%)</td>
<td>13.8%</td>
</tr>
</tbody>
</table>

*At least 1 complication at the WE site. WEO, wide excision only; LM/SNB, lymphatic mapping and sentinel node biopsy.

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### Table 3B. Surgical Morbidity (Within 30 d) Related to the Regional Nodal Basin in Patients Undergoing Wide Excision With or Without Nodal Dissection

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No.</th>
<th>Wound Separation</th>
<th>Seroma/Hematoma</th>
<th>Infection</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM/SNB</td>
<td>937</td>
<td>11 (1.2%)</td>
<td>52 (5.5%)</td>
<td>43 (4.6%)</td>
<td>95 (10.1%)</td>
</tr>
<tr>
<td>LM/SNB + CLND</td>
<td>234</td>
<td>7 (3.0%)</td>
<td>54 (23.1%)</td>
<td>37 (15.8%)</td>
<td>87 (37.2%)</td>
</tr>
</tbody>
</table>

(Morton 2005)
SLNB Morbidity/Complications

Sunbelt Complication rate

- 4.5% in SLNB vs 23.2% for LND

- 1 transient facial nerve palsy, 2 spinal accessory nerve injuries during neck dissection

<table>
<thead>
<tr>
<th>Complication</th>
<th>H&amp;N n (%)</th>
<th>Trunk n (%)</th>
<th>Extremity n (%)</th>
<th>P value χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound separation</td>
<td>2 (0.6)</td>
<td>23 (2.0)</td>
<td>18 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Wound infection</td>
<td>2 (0.6)</td>
<td>33 (2.9)</td>
<td>52 (4.5)</td>
<td>P≤.01</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>0 (0)</td>
<td>22 (1.9)</td>
<td>67 (5.8)</td>
<td>P≤.001</td>
</tr>
<tr>
<td>Hematoma/seroma</td>
<td>4 (1.2)</td>
<td>48 (4.2)</td>
<td>53 (4.6)</td>
<td>P≤.037</td>
</tr>
<tr>
<td>Sensory nerve</td>
<td>2 (0.6)</td>
<td>7 (0.6)</td>
<td>10 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Motor nerve</td>
<td>5 (1.6)</td>
<td>3 (2.6)</td>
<td>0 (0)</td>
<td>P≤.001</td>
</tr>
</tbody>
</table>

H&N, head & neck; NS, not significant.
Early vs delayed LND - MSLT-1 4th Interim analysis - Morton 2010
- 225 pts had early nodal dissection, 143 underwent delayed LND
- lymphedema higher in delayed LND (20.4% vs 12.4% P=0.04)

Neck
- immediate: 18
- delayed: 14

- hospital stay
  - 7.3 vs 9.9 (P=0.02)

Increased tumor burden?
Prognostic Information Gained by SLNB

Most important independent predictor of recurrence and disease-free survival

- Leong SLNWG 2006

- more predictive than Breslow depth and ulceration

*Confirmed by Erman/Michigan study

Accurately reflects status of the nodal basin

- Morton 1992: 0.06% non-SLN positivity rate when SLN negative
Head and Neck Accuracy/False Negative Rate

Chao et al 2003 H&N Analysis
- SLN identification rate: 97% in h&n
  100% in trunk/extremity

- Higher false negative rate (same basin recurrence)
  - 1.9% in h&n
  - 0.5% in trunk/extremity

- Lower incidence of detecting SLN metastasis
  - h&n: 15%  20%/23% t/e P=0.01

Sunbelt trial (McMasters)
MSLT 2005
- overall 95.3% success rate of identifying SLN
- 85% success rate in the neck

Carlson 2003
- 211 h&n patients
- equivalent nodal recurrence between positive and negative SLNB's
“SLNB for H&N melanoma is less reliable and more technically challenging than for melanomas in other locations”
SLNB more difficult/less accurate in H&N?

- Faster washout
  - 59% h&n nodes stain blue
  - 68% & 74% trunk/ext (P<0.001)

- Smaller lymph nodes

- Complicated/delicate anatomy
  - (25% parotid SLN)

- Shine through

- In-transit mets
  Higher in H&N?
# Accuracy/False Negative Rate

## TABLE 1. Summary of the Results of the Published Studies on SLND for H&N Melanoma

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients</th>
<th>Male to female ratio</th>
<th>Blue dye technique only (%)</th>
<th>Radiotracer technique only (%)</th>
<th>Both technique (%)</th>
<th>Patients with positive SLN (%)</th>
<th>False negative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morton et al. [36]</td>
<td>1993</td>
<td>72</td>
<td>7:1</td>
<td>90</td>
<td>Not used</td>
<td></td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>Wells et al. [37]</td>
<td>1996</td>
<td>58</td>
<td>3:1</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>NA</td>
</tr>
<tr>
<td>Bostick et al. [38]</td>
<td>1997</td>
<td>117 (including upper chest)</td>
<td>7:1</td>
<td>92</td>
<td></td>
<td></td>
<td>11</td>
<td>NA</td>
</tr>
<tr>
<td>Alex et al. [39]</td>
<td>1998</td>
<td>23</td>
<td>2:1</td>
<td>75</td>
<td>96</td>
<td></td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>Wagner et al. [40]</td>
<td>2000</td>
<td>70</td>
<td>3:1</td>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td>2% (regional recurrence rate)</td>
</tr>
<tr>
<td>Carlson et al. [41]</td>
<td>2000</td>
<td>58</td>
<td>4:1</td>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>21.3% (regional recurrence rate)</td>
</tr>
<tr>
<td>Jansen et al. [42]</td>
<td>2000</td>
<td>30</td>
<td>2:1</td>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>2% (regional recurrence rate)</td>
</tr>
<tr>
<td>Medina-Franco et al. [43]</td>
<td>2001</td>
<td>38</td>
<td>4:1</td>
<td>56</td>
<td>92</td>
<td></td>
<td>11</td>
<td>NA</td>
</tr>
<tr>
<td>Eicher et al. [44]</td>
<td>2002</td>
<td>43</td>
<td>4:1</td>
<td></td>
<td></td>
<td></td>
<td>98</td>
<td>0% (regional recurrence rate)</td>
</tr>
<tr>
<td>Patel et al. [45]</td>
<td>2002</td>
<td>56</td>
<td>3:1</td>
<td>73</td>
<td>93</td>
<td></td>
<td>8</td>
<td>2% (regional recurrence rate)</td>
</tr>
<tr>
<td>Schmalback et al. [46]</td>
<td>2003</td>
<td>80</td>
<td>2:1</td>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>4.5% (regional recurrence rate)</td>
</tr>
<tr>
<td>Chao et al. [47]</td>
<td>2003</td>
<td>321</td>
<td>2:1</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>2% (regional recurrence rate)</td>
</tr>
<tr>
<td>Fincher et al. [48]</td>
<td>2004</td>
<td>51</td>
<td>2:1</td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>0% (regional recurrence rate)</td>
</tr>
<tr>
<td>MacNeill et al. [49]</td>
<td>2005</td>
<td>44</td>
<td>1:1</td>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td>0% (regional recurrence rate)</td>
</tr>
<tr>
<td>Leong et al. [50]</td>
<td>2006</td>
<td>614</td>
<td>3:1</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>Regional recurrence was not Specified</td>
</tr>
</tbody>
</table>

*Only cases with identified SLNs were submitted in this multicenter study*

Kloot et al. [51] | 2011 | 65 | 1.6:1 | 100 | | | 23 | 12% (regional recurrence rate) |
Head & Neck Accuracy/False Negative Rate

N=353 H&N melanoma patients
99.7% SLN identification rate

H&N SLNB negative predictive value = 95.8%
- False negative rate 14.8%

Miller et al 2010-Oregon: 98.1%
- 153 pt study (32% false neg rate)

Controversy in Calculating false negative rate
- false neg: false neg/false neg + true pos
- false omission: false neg/false neg + true neg
Accuracy/False Negative Rate

Controversy in Calculating false negative rate
- false neg: false neg/false neg + true pos
- false omission: false neg/false neg + true neg

Michigan false omission rate: 4.2%
- MSLT: 3.4%

SLN positivity rate: 19.7%
- Sunbelt trunk/ext: 21.4%
Accuracy/False Negative Rate

Table 6. Best Multivariate Model for Recurrence-Free Survival

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow depth, 1-mm increase</td>
<td>1.15 (1.04-1.27)</td>
<td>.0049</td>
</tr>
<tr>
<td>Age at diagnosis, 1-year increase</td>
<td>1.03 (1.02-1.04)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PSLNB</td>
<td>4.23 (2.73-6.54)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Table 7. Best Multivariate Model for Overall Survival

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulceration, present vs absent</td>
<td>2.05 (1.22-3.45)</td>
<td>.0069</td>
</tr>
<tr>
<td>Age at diagnosis, 1-year increase</td>
<td>1.03 (1.02-1.05)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PSLNB</td>
<td>3.33 (1.99-5.58)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Comparable to trunk/extremity SLNB
Who should perform H&N SLNB?

H&N Surgeons vs Surg Onc
- "surgical familiarity"

Learning curve
- 30 cases- Morton
- 60 cases- Erman

Multidisciplinary Team- high volume center
- nuclear medicine
- melanoma pathologists
Parotid Nodes

Formal parotidectomy vs excisional lymph node biopsy

Loree 2006: 28 patient case series of H&N melanoma patients with SLN located in the parotid - did not perform formal parotidectomy
- 96% success rate of identifying the SLN
- no permanent facial nerve injuries
- no increased risk of facial nerve injury on completion parotidectomy if parotid SLN was positive

McKean 1985 - cadaveric study performed
- >92% of parotid nodes were lateral to facial nerve or in the tail
SLNB and Survival

MSLT- 3rd interim analysis 2005
- statistically significant increase in disease-free survival
- fewer positive nodes if recurrence occurred (1.9 vs 3.2)
- no statistically significant difference in OVERALL survival

**Final analysis pending**
Who should receive SLNB?

- NCCN recommendation is for patients with stage Ib or stage II (no evidence of spread outside the primary lesion
  - correlates to patients with primary melanomas less than 1 mm thick ulcerated histology or high mitosis rate
  - OR any patient with
- much thinner melanomas have a lower propensity for spread and SLNB may be unnecessary
  - exception- there may be a role for SLNB for thin melanomas that have histologic features that have been associated with early nodal spread and poor outcomes: e.g. ulcerated histology
  - often patients are referred to head/neck surgeons after shave biopsy performed by dermatologists- if the deep margin of the shave is positive, the true depth of invasion cannot be known
- thick melanomas: >4mm have been shown to be associated with early distant metastasis. A SLNB and subsequent regional LND would not address distant mets and would not improve survival (Morton 2003)
Future Areas of Research/Controversy

MSLT-II

RT-PCR - (molecular staging)
  - can detect 1 melanoma cell in 1 million normal cells (mRNA)
  - plasma test for melanoma?

Who should perform SLNB?
Summary/Conclusions

- Elective lymph node dissection in melanoma is not indicated.
- Sentinel lymph node biopsy is an accurate and relatively safe procedure (low-morbidity) for staging.
- Accuracy/false negative rate for SLNB for the head/neck region specifically is currently being debated (complex regional lymphatic drainage).
- Who should perform SLNB in H&N is being debated.
- SLNB has not been shown to increase overall survival in melanoma in a randomized control trial, although it has been shown to increase disease-free survival.
- There continues to be ongoing research and debate in this area:
  - 5th/final analysis from MSLT I
  - MSLT II trial
  - RT-PCR
Post-Test

1. Which of the following is not a stain used to identify melanoma?
   a. hematoxylin and eosin
   b. Mart-1
   c. HMB-45
   d. S-100
   e. Silver stain

2. In the absence of spread beyond the primary site of a melanoma, when is it appropriate to use SLNB?
   a. less than 1mm tumor thickness
   b. 1-4mm tumor thickness
   c. Greater than 4mm tumor thickness
   d. All of the above thickness can justify SLNB

3. What percentage of patients with a primary melanoma of the head/neck and no evidence of
   regional/distant spread will have occult regional metastases?
   a. 5%
   b. 10%
   c. 20%
   d. 30%
Bibliography


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