DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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So17 Translating Evidence into Practice:
Primary Cutaneous Melanoma Guidelines

DISCLOSURES

I do not have any relevant relationships with industry.
Learning Objectives

• Review recommended techniques for biopsy of suspected melanoma
  – Risk for metastasis
  – Risk of mis-diagnosis
  – Accurate assessment of histologic prognostic parameters

• Review guidelines for surgical management of the primary site
Does incisional biopsy increase the risk of metastasis?
Incisional Biopsy and Risk of Metastasis

• Sunbelt Melanoma Trial
  – 1,782 patients, primary lesion ≥ 1.0 mm Breslow depth
    • 1,139 (64%) excisional biopsy
    • 282 (16%) incisional biopsy
    • 355 (20%) shave biopsy
  – All patients underwent WLE and SLNB
  – Mean follow up time of 28 months

Incisional Biopsy and Risk of Metastasis

Biopsy technique did not affect rate of sentinel node positivity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Excisional (%)</th>
<th>Incisional (%)</th>
<th>Shave (%)</th>
<th>Total (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive SLN total</td>
<td>220 (19.5)</td>
<td>58 (20.6)</td>
<td>67 (18.9)</td>
<td>345 (19.5)</td>
<td>.9</td>
</tr>
<tr>
<td>Positive by IHC only</td>
<td>38 (3.3)</td>
<td>10 (3.5)</td>
<td>11 (3.1)</td>
<td>59 (3.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive by H&amp;E</td>
<td>182 (16.0)</td>
<td>48 (16.9)</td>
<td>56 (15.7)</td>
<td>286 (16.0)</td>
<td>.9</td>
</tr>
</tbody>
</table>

Biopsy technique did not affect rate of recurrence

<table>
<thead>
<tr>
<th>Site</th>
<th>Excisional (%)</th>
<th>Incisional (%)</th>
<th>Shave (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>36 (3)</td>
<td>14 (5)</td>
<td>12 (3)</td>
<td>63 (4)</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>35 (3)</td>
<td>7 (2)</td>
<td>10 (3)</td>
<td>52 (4)</td>
</tr>
<tr>
<td>Recurrence in regional lymph node mapped</td>
<td>24 (2)</td>
<td>4 (1)</td>
<td>11 (3)</td>
<td>39 (2)</td>
</tr>
<tr>
<td>Recurrence in unmapped nodal basin</td>
<td>11 (1)</td>
<td>1 (0.4)</td>
<td>3 (1)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Recurrence in regional nodal basin following lymphadenectomy</td>
<td>11 (1)</td>
<td>5 (1)</td>
<td>4 (1)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Distant</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Biopsy type does not impact the risk of metastasis

What is the optimal biopsy technique for diagnosis?
Does Biopsy Type Impact Diagnosis?

• 2,470 cases: 2,127 excisional, 163 punch, 180 shave
  – False-negative misdiagnosis
  – False-positive misdiagnosis
  – Adverse outcomes due to misdiagnosis
    • Persistence or progression of primary disease
    • Development of nodal or distant metastasis

Does Biopsy Type Impact Diagnosis?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Excisional</th>
<th>Punch</th>
<th>Shave</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-negative misdiagnosis overall</td>
<td>37 (1.7)</td>
<td>38 (23.3)</td>
<td>8 (4.5)</td>
<td>83 (3.4)</td>
</tr>
<tr>
<td>False-negative misdiagnosis with an adverse outcome</td>
<td>15 (0.7)</td>
<td>19 (11.6)</td>
<td>3 (1.7)</td>
<td>37 (1.5)</td>
</tr>
<tr>
<td>False-positive misdiagnosis</td>
<td>123 (5.8)</td>
<td>3 (1.8)</td>
<td>9 (5.0)</td>
<td>135 (5.5)</td>
</tr>
<tr>
<td>Correct diagnosis</td>
<td>1967 (92.5)</td>
<td>122 (74.8)</td>
<td>163 (90.5)</td>
<td>2252 (91.2)</td>
</tr>
<tr>
<td>Total</td>
<td>2127</td>
<td>163</td>
<td>180</td>
<td>2470</td>
</tr>
</tbody>
</table>

Does Biopsy Type Impact Diagnosis?

**Punch and shave biopsy associated with false-negative misdiagnosis**

**Punch biopsy associated with false-negative misdiagnosis with an adverse outcome**

What is the optimal biopsy technique for accurate staging of a lesion?
Does Partial Biopsy Impact Accuracy of Staging?

- 250 patients with ≥ 50% of the clinical lesion remaining after partial biopsy
  - 53 (21%) had upstaging of their melanoma
  - 26 (10%) became candidates for SLNB

Consensus Recommendation - Biopsy

- Narrow excisional biopsy with 1-3 mm clinical margin
- Depth of biopsy must be sufficient to ensure lesion is not transected
  - Saucerization
  - Punch excision
  - Elliptical excision

Consensus Recommendation – Elliptical Excisional Biopsy

- If performed, elliptical excision should be oriented longitudinally on an extremity
  - Optimizes subsequent WLE
  - Minimizes disruption to underlying lymphatics
    - Important if sentinel lymph node biopsy is indicated

Biopsy Technique – Large Lesions

Broad shave biopsy extending into the deep papillary or superficial reticular dermis may allow for better evaluation than multiple partial biopsies

Biopsy Technique – Large Lesions

• Hemostasis
  – Topical hemostatic agents preferred to use of electrocautery or electrofulguration
  – If ferric subsulfate solution is used, indicate on pathology requisition
    • may lead to deposition of brown ferric pigment in the dermis

Biopsy Technique – Nail Lesions

• Subungual lesions
  – Adequate biopsy requires sufficient removal of the nail plate to allow for either excisional or incisional biopsy of the lesion

• Suspicious Nail Lesions
  – Melanonychia striata, diffuse pigmentation, or amelanotic changes
  – Nail matrix biopsy should be performed

Partial biopsy is acceptable in select clinical circumstances
  - Facial or acral location, low clinical suspicion, very large lesion

Repeat biopsy
  - If initial biopsy specimen is inadequate for diagnosis
  - Prior to definitive treatment if there is significant clinical residual remaining

Biopsy Site Photography
Avoiding Wrong Site Surgery

• Study evaluating the value of preoperative biopsy site photography within a Mohs practice
• 271 surgical sites evaluated, all with photograph at the time of biopsy
  – At surgical visit, patients were asked to identify site in the mirror without help
  – Physician then asked to identify site with only anatomic location and a diagram
  – Identified sites were then compared to photo from the day of biopsy
• Patients were incorrect 16.6% of the time
• Physicians were incorrect 5.9% of the time
• Both patient and physician incorrectly identified the site 4.4% of the time

Tips for Biopsy Site Photography

- Circle the site with marker
- Consider two photos of each site
  - Distance to help with anatomic landmarks
  - Close up to compare to nearby landmarks
- Ruler within the photo to measure from nearby landmark

Recommendations for surgical margins
Surgical Margins for the Primary Site

• What margin is necessary?
  – Prior to the 1970’s recommendation was 5 cm margin
    • general anesthesia, more complex repairs or grafts

• Goals of surgical resection
  – Durable local disease control
  – Cure for patients with localized primary melanoma
### TABLE 1. Completed Prospective Randomized Trials Addressing Surgical Excision Margins for Primary Cutaneous Melanomas

<table>
<thead>
<tr>
<th>Surgical trial group</th>
<th>No. of patients</th>
<th>Primary tumor thickness (mm)</th>
<th>Surgical margin treatment arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>French Cooperative Study</td>
<td>362</td>
<td>≤ 2</td>
<td>2 cm vs 5 cm</td>
</tr>
<tr>
<td>Swedish Melanoma Study Group 1</td>
<td>989</td>
<td>≤ 2</td>
<td>2 cm vs 5 cm</td>
</tr>
<tr>
<td>World Health Organization (WHO) Melanoma Program</td>
<td>612</td>
<td>≤ 2</td>
<td>1 cm vs 3 cm</td>
</tr>
<tr>
<td>Intergroup Melanoma Surgical Trial</td>
<td>486</td>
<td>1–4</td>
<td>2 cm vs 4 cm</td>
</tr>
<tr>
<td>UK Melanoma Study Group</td>
<td>900</td>
<td>≥ 2</td>
<td>1 cm vs 3 cm</td>
</tr>
<tr>
<td>Swedish Melanoma Study Group 2</td>
<td>936</td>
<td>&gt; 2</td>
<td>2 cm vs 4 cm</td>
</tr>
</tbody>
</table>

Due to higher rates of local recurrence with 1 cm margin, for lesions 1.01-2.0 mm a slightly wider margin than 1 cm may be preferable.

Intergroup Melanoma Surgical Trial

lesions 1-4 mm, 2 cm vs. 4 cm margin

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor ulceration</td>
<td>6.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Anatomic site:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head/neck</td>
<td>9.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Extremity</td>
<td>3.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Trunk</td>
<td>2.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Tumor thickness (&lt;2.0 mm vs &gt;2 mm)</td>
<td>2.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Surgical margin (2 cm vs 4 cm)</td>
<td>1.0</td>
<td>0.79</td>
</tr>
<tr>
<td>Surgical wound closure (skin graft vs primary closure)</td>
<td>0.9</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Intergroup Melanoma Surgical Trial

Lesions 1-4 mm, 2 cm vs. 4 cm margin

<table>
<thead>
<tr>
<th>Event</th>
<th>Excision margin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 cm</td>
</tr>
<tr>
<td>Local recurrence % (first relapse)</td>
<td>0.9</td>
</tr>
<tr>
<td>Local recurrence (%) (anytime)</td>
<td>2.6</td>
</tr>
<tr>
<td>In-transit metastasis (%) (anytime)</td>
<td>5.2</td>
</tr>
<tr>
<td>10-year survival (%)</td>
<td>77</td>
</tr>
<tr>
<td>Skin graft (%)</td>
<td>46</td>
</tr>
<tr>
<td>Wound complication (%)</td>
<td>10</td>
</tr>
</tbody>
</table>

NS, not significant.

Margins for Deep Lesions

• United Kingdom Melanoma Study group (1 cm vs. 3 cm for ≥ 2 mm Breslow depth lesion)
  – Higher number of locoregional recurrences with 1 cm
  – Higher number of melanoma specific deaths in 1 cm group, but not statistically significant

• Swedish Melanoma Study Group (2 cm vs. 4 cm for > 2 mm Breslow depth lesion)
  – Preliminary data showed no difference in recurrence or survival

Excision recommendations are based on measured clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist.

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**PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA**

| Tumor Thickness | Recommended Clinical Margins
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ¹</td>
<td>0.5–1.0 cm</td>
</tr>
<tr>
<td>≤1.0 mm</td>
<td>1.0 cm (category 1)</td>
</tr>
<tr>
<td>1.01–2 mm</td>
<td>1–2 cm (category 1)</td>
</tr>
<tr>
<td>2.01–4 mm</td>
<td>2.0 cm (category 1)</td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>2.0 cm (category 1)</td>
</tr>
</tbody>
</table>

* Margins may be modified to accommodate individual anatomic or functional considerations.

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¹ Indicates a lesion less than 1 mm thick
² Indicates a lesion greater than or equal to 1 mm thick
Surgical management of melanoma on a digit
Surgical Management of Melanoma on a Digit

- Requires specialized surgical expertise
- Traditional recommendation was partial amputation
- Digit sparing surgery may be an alternative

Digit Sparing Surgery for Melanoma - Evidence

- Literature is insufficient to make definitive recommendation
  - Prospective, randomized trial data not available
  - Lack of data reporting
    - Breslow depth missing in 82%
  - Treatment bias

- Digit sparing surgery may be an option for melanoma in situ and select thin lesions (≤ 0.8 mm)
  - Further investigation needed

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Table 4. Comparison between Wide Local Excision and Amputation as Treatment for Subungual Melanoma

<table>
<thead>
<tr>
<th></th>
<th>Wide Local Excision</th>
<th>Amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of cases</td>
<td>82</td>
<td>801</td>
</tr>
<tr>
<td>Depth not defined in</td>
<td>17</td>
<td>705</td>
</tr>
<tr>
<td>literature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth clearly defined in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>literature</td>
<td>65</td>
<td>96</td>
</tr>
<tr>
<td>Melanoma in situ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 mm</td>
<td>10/65 (15.3%)</td>
<td>20/96 (20.8%)</td>
</tr>
<tr>
<td>1–2 mm</td>
<td>10/65 (15.3%)</td>
<td>11/93 (11.8%)</td>
</tr>
<tr>
<td>2–4 mm</td>
<td>9/65 (13.8%)</td>
<td>21/96 (21.8%)</td>
</tr>
<tr>
<td>≥4 mm</td>
<td>6/65 (9.2%)</td>
<td>33/96 (34.3%)</td>
</tr>
<tr>
<td>Presented with locally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>recurrent disease</td>
<td>1/82 (1.2%)</td>
<td>30/801 (3.7%)</td>
</tr>
<tr>
<td>Presented with positive regional nodes or distant metastasis</td>
<td>2/82 (2.4%)</td>
<td>91/801 (11.3%)</td>
</tr>
<tr>
<td>Local recurrence after treatment</td>
<td>10/82 (12.2%)</td>
<td>18/801 (2.2%)</td>
</tr>
<tr>
<td>Nodal/metastatic recurrence after treatment</td>
<td>12/82 (14.6%)</td>
<td>107/801 (13.3%)</td>
</tr>
</tbody>
</table>

Conclusions: Biopsy

• Remove entire lesion with 1-3 mm margin to a depth sufficient to avoid transecting the lesion

• Orient elliptical excisions along the longitudinal axis of extremities

• If incisional biopsy necessary:
  – Repeat biopsy if pathology doesn’t fit clinical picture
  – Microstaging excision may be necessary prior to definitive treatment
Conclusions: Surgical Margins

• Surgical margins are based on depth of the lesion
  – Clinical margins, not histologic

• Digit sparing surgery may be an option for select lesions
  – Melanoma in situ
  – Thin melanoma ≤ 0.8 mm without additional adverse features