Translating Evidence into Practice: Primary Cutaneous Melanoma Guidelines

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Disclosure: Myriad Consultation
Guidelines of care: Management of Primary Cutaneous Melanoma

- AJCC melanoma staging, 7th ed (2010)
- AAD Guidelines of Care (2011)
- Introduction to AJCC, 8th ed (2018)
- Updates in molecular testing
FROM THE ACADEMY

Guidelines of care for the management of primary cutaneous melanoma

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Ann Arbor, Michigan; New York, New York; Norfolk, Virginia; Miami, Florida; Palo Alto, Los Angeles, Palm Springs, San Francisco, and Fairfield, California; Boston, Massachusetts; Chicago and Schaumburg, Illinois; Houston, Texas; and Vancouver, British Columbia, Canada.
AJCC 7th ed Melanoma Staging Update:

• 2009 American Joint Commission on Cancer guidelines
• 17 major global medical cancer centers
• Database contains clinical and pathologic data regarding 38,000 patients with cutaneous melanoma
AJCC 7th ed Melanoma Staging Update:

For patients with localized (stage I or II) melanoma the most powerful prognostic parameters include:

1. Tumor thickness
2. Ulceration
3. Mitotic index
AJCC 7th ed Melanoma Staging Update:

For patients with localized (stage I or II) melanoma the most powerful prognostic parameters include:

1. Tumor thickness
2. Ulceration
3. Mitotic index
Breslow Depth Measurement
10 year survival and Breslow depth

- 96%
- 89%
- 80%
- 65%
- 57%
- 54%
- 42%

Survival rates for different Breslow depth categories:

- 0.01-0.5 mm
- 0.51-1.0 mm
- 1.01-2.0 mm
- 2.01-2 mm
- 3.01-4 mm
- 4.01-6 mm
- >6 mm

Survival rates decrease as Breslow depth increases.
AJCC 7th ed Melanoma Staging Update:

For patients with localized (stage I or II) melanoma the most powerful prognostic parameters include:

1. Tumor thickness
2. Ulceration
3. Mitotic index
Epidermal ulceration
Epidermal ulceration

- Full thickness epidermal defect (absent stratum corneum and basement membrane)
- Evidence of reactive changes
- Epidermal thinning, effacement
- Absent trauma or biopsy site changes
Epidermal ulceration

Fibrinopurulent exudate directly overlying the neoplastic melanocytes
| T1  | ≤ 1.00 | a: Without ulceration and mitosis < 1/mm²  
b: With ulceration or mitoses ≥ 1/mm² |
|-----|--------|-------------------------------------------|
| T2  | 1.01-2.00 | a: Without ulceration  
b: With ulceration |
| T3  | 2.01-4.00 | a: Without ulceration  
b: With ulceration |
| T4  | > 4.00 | a: Without ulceration  
b: With ulceration |
AJCC 7th ed Melanoma Staging Update:

For patients with localized (stage I or II) melanoma the most powerful prognostic parameters include:

1. Tumor thickness
2. Ulceration
3. Mitotic index
Mitotic rate is an important independent adverse predictor of survival.

In T1 melanomas, a mitotic rate of at least 1 mitosis/mm² replaces Clark’s level of invasion as a primary criterion for defining the subcategory of T1b.
Mitotic index
The ‘Hotspot’ method

• Count mitoses in the hot spot (40x lens)
• The count is then extended to adjacent contiguous fields until an area corresponding to 1 mm² is assessed
• The count is expressed as the number of mitoses/mm²
The ‘Hotspot’ method

- When the dermal component area is <1/mm², it is recommended to designate the presence a mitosis as “at least 1/mm²”
- And the absence of mitotic figures as 0/mm²
Effect of mitotic rate on 10-yr disease-related mortality

<table>
<thead>
<tr>
<th>Melanoma characteristics</th>
<th>10-yr mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ulcerated, no mitotic activity, &lt;1mm Breslow (T1a)</td>
<td>5%</td>
</tr>
<tr>
<td>Non-ulcerated, with mitotic activity, &lt;1mm Breslow (T1b)</td>
<td>12%</td>
</tr>
</tbody>
</table>
### Comparison of Mitotic Rate and Ulceration in Thin Melanomas

<table>
<thead>
<tr>
<th>Melanoma characteristics</th>
<th>10-yr mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ulcerated, mitotic, &lt;1mm Breslow, T1b</td>
<td>12%</td>
</tr>
<tr>
<td>Ulcerated, any mitotic rate, &lt;1mm Breslow, T1b</td>
<td>13%</td>
</tr>
</tbody>
</table>
Table VIII. Definitions of histologic features

<table>
<thead>
<tr>
<th>Clark levels</th>
<th>Tumor confined to epidermis</th>
<th>Tumor present in papillary dermis</th>
<th>Tumor fills papillary dermis</th>
<th>Tumor present in reticular dermis</th>
<th>Tumor present in subcutis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level II</td>
<td></td>
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<tr>
<td>Level III</td>
<td></td>
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<tr>
<td>Level IV</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Level V</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
AJCC melanoma staging update:

- Clark level of invasion was replaced by mitotic index for patients with thin melanomas

- Included when mitotic rate cannot be assessed in thin tumors (≤1mm)
Tumor infiltrating lymphocytes
Regional LN metastases

Number of LN involved remains the primary determinant of N stage

N1 = 1
N2 = 2-3
N3 = 4 or more metastatic nodes
• Micrometastases can be defined by H&E or immunohistochemical staining
• There is no longer a minimum “tumor burden” in evaluation of lymph nodes
Identification of LN metastasis with immunohistochemical stains

- S-100 (sensitive, but lacks specificity)
- Melan-A/ Mart-1
- HMB-45
- Sox10
SOX10: Distinguishing melanophages and nodal dendritic cells from melanocytic metastases in lymph nodes

Immunohistochemical staining in SLN

• There is no lower threshold of tumor burden used to define the presence of regional nodal metastasis
• Nodal tumor deposits of any size are included in staging nodal disease
• Starts Jan 1, 2018
• All newly diagnosed cases through Dec 31, 2017 should be staged with the 7th edition
AJCC 8\textsuperscript{th} ed

Definition of Primary Tumor (T)

- T-category tumor thickness cutoffs maintained
- Except substratification of T\textsubscript{1}:

Melanomas <0.8 mm in thickness = \textit{T1a}
Melanomas 0.8 mm - 1.0 mm = \textit{T1b}
AJCC 8th ed

Definition of Primary Tumor (T)

- Tumor thickness recorded to the nearest 0.1 mm
- Melanomas measured to be in the range of 0.75 to 0.84 mm are reported as 0.8 mm in thickness; hence T1b
AJCC 8th ed
Definition of Primary Tumor (T)

- **T1b** melanomas now are defined:
  - 0.8 to 1.0 mm in thickness regardless of ulceration
  - Ulcerated melanomas <0.8 mm in thickness
Definition of Primary Tumor (T)

• Tumor mitotic rate was removed as a staging criterion for \textbf{T1} tumors

• Remains an overall important prognostic factor that should continue to be recorded for all patients with T1-T4 primary cutaneous melanoma
# AJCC 8th ed Melanoma Staging

<table>
<thead>
<tr>
<th>T category</th>
<th>Thickness</th>
<th>Ulceration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis (in situ)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>T1</td>
<td>≤ 1.0 mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T1a</td>
<td>≤ 0.8 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T1b</td>
<td>≤ 0.8 mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td></td>
<td>0.8–1.0 mm</td>
<td>With or without ulceration</td>
</tr>
<tr>
<td>T2</td>
<td>&gt; 1.0–2.0 mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T2a</td>
<td>&gt; 1.0–2.0 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T2b</td>
<td>&gt; 1.0–2.0 mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 2.0–6.0 mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T3a</td>
<td>&gt; 2.0–6.0 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T3b</td>
<td>&gt; 2.0–6.0 mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.0 mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T4a</td>
<td>&gt; 4.0 mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T4b</td>
<td>&gt; 4.0 mm</td>
<td>With ulceration</td>
</tr>
</tbody>
</table>
AJCC 8th ed Melanoma Staging

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Mitotic Rate</th>
<th>Ulceration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>T1</td>
<td>( \leq 1.0 ) mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T1a</td>
<td>( \leq 0.8 ) mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T1b</td>
<td>( \leq 0.8 ) mm, 0.8-1.0 mm</td>
<td>With ulceration, With or without ulceration</td>
</tr>
<tr>
<td>T2</td>
<td>( &gt;1.0-2.0 ) mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T2a</td>
<td>( &gt;1.0-2.0 ) mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T2b</td>
<td>( &gt;1.0-2.0 ) mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>( &gt;2.0-4.0 ) mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T3a</td>
<td>( &gt;2.0-4.0 ) mm</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T3b</td>
<td>( &gt;2.0-4.0 ) mm</td>
<td>With ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>( &gt;4.0 ) mm</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T4a</td>
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<td>Without ulceration</td>
</tr>
<tr>
<td>T4b</td>
<td>( &gt;4.0 ) mm</td>
<td>With ulceration</td>
</tr>
</tbody>
</table>

Mitotic rate not prognostic factor
AJCC 8th ed Melanoma Staging

<table>
<thead>
<tr>
<th>T1s (melanoma in situ)</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>≤1.0 mm</td>
</tr>
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<td>T1a</td>
<td>≤0.8 mm</td>
</tr>
<tr>
<td>T1b</td>
<td>≤0.8 mm</td>
</tr>
<tr>
<td></td>
<td>0.8-1.0 mm</td>
</tr>
<tr>
<td></td>
<td>With ulceration</td>
</tr>
<tr>
<td></td>
<td>With or without ulceration</td>
</tr>
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<tr>
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</tr>
<tr>
<td></td>
<td>With ulceration</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>With ulceration</td>
</tr>
<tr>
<td></td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt;4.0 mm</td>
</tr>
<tr>
<td>T4a</td>
<td>&gt;4.0 mm</td>
</tr>
<tr>
<td>T4b</td>
<td>&gt;4.0 mm</td>
</tr>
<tr>
<td></td>
<td>With ulceration</td>
</tr>
</tbody>
</table>

Substratification of T1 category with cutoff of 0.8 mm
2011 AAD Guidelines
Recommendations

Guidelines of care for the management of primary cutaneous melanoma

J Am Acad Dermatol 2011;65:1032-47
### Table VI. Recommended clinical information to be provided to pathologist

<table>
<thead>
<tr>
<th>Essential</th>
<th>Strongly recommended</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>Biopsy technique (excisional or incisional)</td>
<td>Clinical description and level of clinical suspicion</td>
</tr>
<tr>
<td>Gender</td>
<td>Size of lesion</td>
<td>Dermatoscopic features</td>
</tr>
<tr>
<td>Anatomic location</td>
<td></td>
<td>Photograph</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macroscopic satellitosis</td>
</tr>
</tbody>
</table>

*J Am Acad Dermatol 2011;65:1032-47*
Recommended Histologic Features

Essential
• Breslow thickness
• Ulceration
• Dermal mitotic rate (mitoses/ mm²)
• Margin status
• Clark level*
• Microsatellitosis
Recommended Histologic Features

Optional
• Angiolympathic invasion
• Histologic subtype
• Neurotropism
• Regression
• T stage classification
• Tumor infiltrating lymphocytes
• Vertical growth phase
Molecular Ancillary Tests

• FISH studies
• CGH studies
• Whole exome/ genome sequencing
• Targeted sequencing
Genetic evolution of melanoma
The Genetic Evolution of Melanoma from a Precursor Nevus

- 77% intermediate lesions with TERT mutation
- CDKN2A biallelic mutations in invasive lesions
- PTEN and TP53 mutations found in advanced lesions
• 47-year-old male with no history of cutaneous, mucosal, or eye lesions
• Presented with an enlarging right adrenal mass identified incidentally by imaging
• Prelim Dx
  – primary adrenal adenocarcinoma

Kim J et al. unpub
Dx: Malignant melanoma
Primary adrenal melanoma Vs metastatic of unknown primary
Targeted Next Generation Sequencing
Stanford Solid Tumor Actionable Mutation Panel or “STAMP”
<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation Description</th>
<th>Interpretation</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB1</td>
<td>c.234G&gt;Ap.Trp78Ter</td>
<td>Pathogenic</td>
<td>0.252</td>
</tr>
<tr>
<td>RB1</td>
<td>c.18_19delinsTTp.Arg7Ter</td>
<td>Pathogenic</td>
<td>0.149</td>
</tr>
<tr>
<td>BRAF</td>
<td>c.1799T&gt;Ap.Val600Glu</td>
<td>Pathogenic</td>
<td>0.280</td>
</tr>
<tr>
<td>PTEN</td>
<td>c.491dup p.Val166fs</td>
<td>Pathogenic</td>
<td>0.498</td>
</tr>
<tr>
<td>RB1</td>
<td>c.411A&gt;Tp.Glu137Asp</td>
<td>VUN</td>
<td>0.487</td>
</tr>
</tbody>
</table>
Mutations Point to Metastatic Disease

- **RB1**
  - Nonsense with premature truncation and LOF
  - Missense

- **BRAF**
  - Nonsense mutation with premature truncation and LOF

- **PTEN**
  - Duplication of codon 491 leading to a frameshift mutation on position 166 and premature stop codon formation
Adrenal Metastatic Melanoma of Unknown Primary

• Mutations identified support adrenal metastatic melanoma arising from primary cutaneous melanoma with complete regression

• Potential for targeted therapy using known targets
Summary

• Most important histologic predictive histologic factors (AJCC 7\textsuperscript{th} ed)
  – Breslow thickness
  – Ulceration
  – Mitotic rate

• Dermal mitotic activity is an important prognostic factor in thin (< 1 mm) melanoma
• Synoptic reporting is strongly encouraged
  – Complete information
  – Standardization
• Role of the immune system in cancer
• Molecular tests that provide personalized diagnostic and therapeutic information will transform the care of melanoma patients, particularly those with advanced-stage disease
• Starts Jan 1, 2018
• All newly diagnosed cases through Dec 31, 2017 should be staged with the 7th edition