Melanoma Update: 8th Edition of AJCC Staging System and More

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

- None relevant to these talks
- Other:
  - Royalties Lippincott Williams Wilkins
    - Lever’s Histopathology of the Skin
Dermatopathology, University of Pennsylvania
Guidelines of care

• Management of Primary Cutaneous Melanoma
  ❖ • AJCC melanoma staging, 8th ed (2018)
  ❖ • AAD Guidelines of Care (2019)
• 7th edition 2010
• 8th edition 2018
AJCC Staging System

• Designed for simplicity and easy use
• Attributes that can be determined by any pathologist
• Does not capture all that is known about melanoma prognosis
AJCC 8th Edition Melanoma

- 10 major global medical cancer centers
  - USA, Europe, Australia
- 43,792 patients with melanoma Stage I-III
- Initial diagnosis 1998
- *Eliminates patients from the pre-SLN era*
AJCC Melanoma Update

- For localized (stage I or II) melanoma, the most powerful prognostic parameters include:
  - 1. Tumor thickness
  - 2. Ulceration
AJCC 8th edition update

- T-category tumor thickness cutoffs maintained
- Except substratification of T1:
  - Melanomas < 0.8 mm in thickness = T1a
  - Melanomas 0.8 mm - 1.0 mm = T1b
Several published reports indicate that survival T1 melanomas is related to thickness with a “breakpoint” around 0.7 – 0.8 mm
T1 Melanoma

- Positive SLNB in <5% of MM <0.8 mm
- Positive SLNB in 5-12% of MM 0.8- 1.0mm
T1 Melanomas

- Definitions of T1a and T1b are revised:
  - T1a, <0.8 mm without ulceration
  - T1b, 0.8 – 1.0 with or without ulceration
  - T1b, <0.8 mm with ulceration

- * Mitotic rate no longer a T category criterion
Tumor Thickness

- Tumor thickness measurements to be recorded to nearest 0.1 mm (not 0.01 mm)
Tumor Thickness Example

T1b, 0.8 – 1.0 with or without ulceration

- 0.75–0.84 mm Breslow thickness tumors are reported as 0.8 mm T1b tumor
Tumor Thickness Example

T1b, 0.8 – 1.0 with or without ulceration

- 0.95 – 1.04 mm Breslow thickness tumors are reported as 1.0 mm T1b tumor
Mitotic Rate

• Tumor mitotic rate was removed as a staging criterion for T1 tumors
• Remains an overall important prognostic factor that should continue to be recorded for all patients with T1-T4 primary cutaneous melanoma
Mitotic Rate

• Refers to rate in the dermal component
• Mitotic rate in epidermis not prognostic

• No longer in the staging for the 8th Edition, but should still be reported
Mitotic Rate: Methods

- Identify highest mitotically active area, “hot spot”
- Count mitoses in 1 mm\(^2\) (about 4.5 HPF)
- Report as # mitoses per mm\(^2\)
- No need to cut deeper levels just to find mitoses
- If no mitoses, report as 0/mm\(^2\)
- If rate is 0-1/mm\(^2\), just report as 1/mm\(^2\)
- PHH3 (phosphohistone 3) may highlight mitoses, but not considered standard for AJCC staging
<table>
<thead>
<tr>
<th>Tis (melanoma <em>in situ</em>)</th>
<th>Not applicable</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>$\leq 1.0 \text{ mm}$</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T1a</td>
<td>$&lt;0.8 \text{ mm}$</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T1b</td>
<td>$&lt;0.8 \text{ mm}$</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>$&gt;1.0–2.0 \text{ mm}$</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T2a</td>
<td>$&gt;1.0–2.0 \text{ mm}$</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T2b</td>
<td>$&gt;1.0–2.0 \text{ mm}$</td>
<td>With ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>$&gt;2.0–4.0 \text{ mm}$</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T3a</td>
<td>$&gt;2.0–4.0 \text{ mm}$</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T3b</td>
<td>$&gt;2.0–4.0 \text{ mm}$</td>
<td>With ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>$&gt;4.0 \text{ mm}$</td>
<td>Unknown or unspecified</td>
</tr>
<tr>
<td>T4a</td>
<td>$&gt;4.0 \text{ mm}$</td>
<td>Without ulceration</td>
</tr>
<tr>
<td>T4b</td>
<td>$&gt;4.0 \text{ mm}$</td>
<td>With ulceration</td>
</tr>
</tbody>
</table>
Epidermal ulceration

- Defined as full thickness absence of epidermis above any portion of the primary tumor with an associated host reaction (fibrinous and acute inflammatory exudate)
Ulceration
Ulceration

• Associated host response (fibrin, crust, inflammation, epidermal hyperplasia) helps to distinguish from sectioning artifact
• Ulceration from prior biopsy should not be reported as ulceration
• Pitfalls: sectioning artifact; trauma
Ulceration

• If doubt remains if ulcer is traumatic or iatrogenic, then report as *ulceration present*
Microsatellites, 8\textsuperscript{th} Edition

- Microscopic metastasis completely discontinuous from primary melanoma with unaffected stroma between them
- No minimum size threshold
- No minimum distance from the primary tumor
Attributes not addressed by AJCC tumor staging
Sex

• Women do better than men
Anatomic Location

- Extremity melanoma better than:
  - Trunk
  - Head
  - Palms/soles
Age

• Younger patients do better
Pathology: Growth Phase

- Radial (MIS and early level II)
- Vertical
Regression

• Inconsistent definitions in literature
• Worse prognosis in most studies
• Not a factor in AJCC staging
Regression comments, 8th Edition

- If regression is present, measure to the deepest tumor cell, not to the base of the regression.
- If all invasive component is regressed, report as Tis (melanoma in situ).
Angiolympathic Invasion

• Associated with poor survival
• Many studies, not an INDEPENDENT variable
Angiolympathic Invasion

- Tumor within vascular spaces, vessels and lymphatics
- Immunoperoxidase stains (CD34, CD31, D2-40) may assist in identification of vascular invasion, but not standard of care.
LVI was associated with poor survival as an independent variable

Double staining for S100/D2-40 utilized

MART1 (red) with D2-40 (brown) double stain
T0, Tis, Tx

- T0 = No evidence of tumor/ completely regressed or unknown primary tumor
- Tis = melanoma in situ
- Tx = tumor thickness cannot be determined/diagnosis by curettage
The N Category

• Documents metastatic disease both in regional lymph nodes and in non-nodal locoregional sites (microsatellites, satellites, and in-transit metastases)
Regional LN metastases

• Number of LN involved remains the primary determinant of N stage
  ❖ N1 = 1
    ▪ Includes negative nodes + microsatellites/in-transits
  ❖ N2 = 2-3
  ❖ N3 = 4 or more metastatic nodes
Metastatic Disease

• “microscopic” = “clinically occult”
  - nodal metastasis determined at SLN Bx and without clinical or radiographic node metastasis

• “macroscopic” = “clinically apparent”
  - regional LN mets identified by clinical, radiographic or US examination
Guidelines of care for the management of primary cutaneous melanoma

Work Group: Susan M. Swetter, MD (Chair), a,b Hensin Tsao, MD, PhD (Co-Chair), c,d Christopher K. Bichakjian, MD, e,f Clara Curiel-Lewandrowski, MD, g,h David E. Elder, MBChB, i,j Jeffrey E. Gershenson, MD, k,l Valerie Guild, MS, MBA, m Jane M. Grant-Kels, MD, n,o,p Allan C. Halpern, MD, q Timothy M. Johnson, MD, c,f Arthur J. Sober, MD, c John A. Thompson, MD, r,s Oliver J. Wisco, DO, t Samantha Wyatt, MD, u Shasa Hu, MD, v and Toyin Lamina, PhD w

Stanford and Palo Alto, California; Boston, Massachusetts; Ann Arbor, Michigan; Tucson, Arizona; Philadelphia, Pennsylvania; Houston and Plano, Texas; Farmington, Connecticut; New York, New York; Seattle, Washington; Portland, Oregon; Decatur, Alabama; Miami, Florida; and Rosemont, Illinois

## Table VI. Recommended clinical information to be provided to the 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 intent (excisional/complete vs partial/incomplete) and technique (elliptical, punch shave/saucerization)</td>
<td>Clinical description/level of suspicion for melanoma/prior change or biopsy (if applicable)</td>
</tr>
<tr>
<td>Sex</td>
<td>Size of lesion</td>
<td>Dermoscopic features (with or without photograph)</td>
</tr>
<tr>
<td>Anatomic location (including laterality)</td>
<td>Clinical impression/differential diagnosis</td>
<td>Macroscopic satellites  Clinical photograph  (if possible)</td>
</tr>
</tbody>
</table>

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### Table VII. Recommended histologic features of primary cutaneous melanoma for inclusion in the pathology report

<table>
<thead>
<tr>
<th>Essential</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of specimen</td>
<td>Gross description of lesion</td>
</tr>
<tr>
<td>Tumor thickness (Breslow), nearest 0.1 mm</td>
<td>Angiolymphatic invasion/lymphovascular invasion</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Histologic subtype</td>
</tr>
<tr>
<td>Dermal mitotic rate; “hotspot” method; No. of mitoses/mm²</td>
<td>Neurotropism/perineural invasion</td>
</tr>
<tr>
<td>Peripheral and deep margin status (negative/positive [broad vs focal transection at deep margin])</td>
<td>Regression</td>
</tr>
<tr>
<td>Microsatellitosis</td>
<td>Tumor category for staging</td>
</tr>
<tr>
<td></td>
<td>Tumor-infiltrating lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Anatomic level of invasion (Clark level)</td>
</tr>
<tr>
<td></td>
<td>Vertical growth phase</td>
</tr>
</tbody>
</table>
Essential information for Pathology Report

- Specimen size
- Tumor thickness
- Ulceration
- Dermal mitotic rate (# per mm$^2$)
- Margin assessment
- Microsatellites
Optional information for Pathology Report

- Gross description of lesion
- Histologic subtype
- Lymphovascular invasion
- Clark level
- Vertical growth phase
- Regression
- Tumor infiltrating lymphocytes
- Perineural invasion
- Tumor stage
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>B</td>
<td>II</td>
<td>13-30</td>
</tr>
<tr>
<td>• Excision biopsy with 1- to 3-mm clinically negative margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Partial biopsy in select circumstances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Follow-up excision biopsy to partial biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical information provided to the pathologist</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Pathology report</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical information</td>
<td>C</td>
<td>III</td>
<td>31</td>
</tr>
<tr>
<td>Tumor (Breslow) thickness</td>
<td>A</td>
<td>I/II</td>
<td>9,32-42</td>
</tr>
<tr>
<td>Ulceration</td>
<td>A</td>
<td>I/II</td>
<td>9,32-43</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>A</td>
<td>I/II</td>
<td>9,32-42,44,45</td>
</tr>
<tr>
<td>Level of invasion (Clark level)</td>
<td>B</td>
<td>II</td>
<td>36,38,39,46</td>
</tr>
<tr>
<td>Microsatellitosis</td>
<td>B</td>
<td>II</td>
<td>45,49-51</td>
</tr>
<tr>
<td>Angiolymphatic invasion</td>
<td>B</td>
<td>II</td>
<td>45,48,52-54</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>B</td>
<td>II</td>
<td>36,48,54,56</td>
</tr>
<tr>
<td>Neurotropism/perineural invasion</td>
<td>C</td>
<td>III</td>
<td>57,58</td>
</tr>
<tr>
<td>Regression</td>
<td>B</td>
<td>I/II</td>
<td>42,59-63</td>
</tr>
<tr>
<td>Tumor-infiltrating lymphocytes</td>
<td>B</td>
<td>II</td>
<td>42,64,65</td>
</tr>
<tr>
<td>Use of ancillary molecular diagnostic techniques for equivocal</td>
<td>C</td>
<td>III</td>
<td>66-73</td>
</tr>
<tr>
<td>melanocytic neoplasms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Against testing for oncogenic mutations in the absence of</td>
<td>C</td>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td>metastatic melanoma or outside of a clinical study</td>
<td></td>
<td></td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
The working group discouraged reporting a measurement (mm) of distance between the tumor and surgical margin:

- Recommended by CAP
- Treatment recommendations are based on clinical margin measurement, not by pathology
- Routine reporting could lead to unnecessary surgery
- Reporting with a measurement may be necessary if the clear margin is very narrow
Table VIII. Recommendations for diagnostic, prognostic, and therapeutic molecular testing

Ancillary diagnostic molecular techniques (eg, CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms. Routine molecular testing, including GEP, for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management (eg, sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial. Testing of the primary CM for oncogenic mutations (eg, BRAF, NRAS) is not recommended in the absence of metastatic disease.

*BRAF, B-Raf proto-oncogene, serine/threonine kinase gene; CGH, comparative genomic hybridization; CM, cutaneous melanoma; FISH, fluorescence in situ hybridization; GEP, gene expression profiling; NRAS, NRAS proto-oncogene, GTPase gene.*

Synoptic Reporting

• Recommended by CAP (and TJC)
• Recommended in AAD Guidelines
CAP August 2019

• Protocols for
  ❖ Melanoma Biopsy
  ❖ Melanoma Excision
**Surgical Pathology Cancer Case Summary**

Protocol posting date: August 2019

**MELANOMA OF THE SKIN: Excision, Re-Excision**

Select a single response unless otherwise indicated.

**Procedure (select all that apply) (Note A)**
- Excision
- Re-excision
- Sentinel node(s) biopsy
- Lymphadenectomy, regional nodes (specify): ____________
- Other (specify): ____________
  - Not specified

**Tumor Sitz (Note B): ____________

**Macroscopic Satellite Nodule(s) (applicable to invasive tumor only)**
- Not identified
- Present
- Cannot be determined

**Histologic Type (Note C)**
- No residual melanoma identified

**Invasive Melanoma**
- Superficial spreading melanoma (low-cumulative sun damage (CSD) melanoma)
- Lentigo maligna melanoma
- Desmoplastic melanoma
  - Pure desmoplastic melanoma
  - Mixed desmoplastic melanoma
- Acral melanoma
- Melanoma arising in a blue nevus (blue nevus-like melanoma)
- Spitz melanoma (malignant Spitz tumor)
- Nodular melanoma
- Nevus melanoma
- Melanoma, not otherwise classified
- Other histologic type not listed (specify): ____________

**Melanoma in situ (anatomic level)**
- Melanoma in situ, superficial spreading type (low-cumulative sun damage (CSD) melanoma in situ)
- Melanoma in situ, lentigo maligna type
- Melanoma in situ
- Melanoma in situ arising in a giant congenital nevus
- Melanoma in situ, not otherwise classified
- Other histologic type not listed (specify): ____________

*Note: For melanoma in situ, elements that assess the invasive component are not applicable and should not be reported.*

**Maximum Tumor (Breslow) Thickness (applicable to invasive tumor only) (Note D)**
- Specify (millimeters): ___ mm
- Or
  - At least (millimeters): ___ mm (explain): ____________
  - Cannot be determined (explain): ____________

**Ulceration (required for invasive tumor only) (Note E)**
- Not identified
- Present
- Extent of ulceration (millimeters): ___ mm
  - Cannot be determined

**Microsatellite(s) (applicable to invasive tumor only) (Note F)**
- Not identified
- Present
- Cannot be determined

**Margins (Note G)**

**Peripheral Margins**
- Negative for invasive melanoma
  - Distance of invasive melanoma from closest peripheral margin (millimeters):
    - Specify ___ mm
    - Less than ___ mm
    - Greater than ___ mm
    - Cannot be determined (explain): ____________
  - Specify location(s), if possible:

- Invasive melanoma present at margin
  - Specify location(s), if possible:

- Negative for melanoma in situ
  - Distance of melanoma in situ from closest peripheral margin (millimeters):
    - Specify ___ mm
    - Less than ___ mm
    - Greater than ___ mm
    - Cannot be determined (explain): ____________
  - Specify location(s), if possible:

- Melanoma in situ present at margin
  - Specify location(s), if possible:
  - Cannot be assessed

**Deep Margin**
- Negative for invasive melanoma
  - Distance of invasive melanoma from deep margin (millimeters):
    - Specify ___ mm
    - Less than ___ mm
    - Greater than ___ mm
    - Cannot be determined (explain): ____________
  - Specify location(s), if possible:

- Invasive melanoma present at margin
- Negative for melanoma in situ
  - Melanoma in situ present at margin
  - Cannot be assessed

*Note: Margin involvement by melanoma in situ should be recorded if in situ disease is present in the specimen, and if margins are involved by invasive melanoma.*

*Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.*
Excision

Malignant Rate (applicable to invasive tumor only) (Note: H)

- None identified
- Specified (malignant)
- Cannot be determined

Anatomic (Clark’s) Level (applicable to invasive tumor only) (Note D)

- At level
  - (explain)
  - II (malignant present in but does not fill and expand papillary dermis)
  - III (malignant fills and expands papillary dermis)
  - IV (malignant invades reticular dermis)
  - V (malignant invades subcutis)
- Cannot be determined

Lymphovascular Invasion (applicable to invasive tumor only) (Note I)

- Not identified
- Present
- Cannot be determined

Neurotropism (applicable to invasive tumor only) (Note J)

- Not identified
- Present
- Cannot be determined

Tumor-Infiltrating Lymphocytes (applicable to invasive tumor only) (Note K)

- Not identified
- Present, brisk
- Cannot be determined

Tumor Regression (Note L)

- Not identified
- Present, involving less than 75% of lesion
- Present, involving 75% or more of lesion
- Cannot be determined

Regional Lymph Nodes (applicable to invasive tumor only) (Note M)

Note: If nodes from more than one nodal basin are included, each nodal basin should be reported separately.

- No lymph nodes submitted or found
- Uninvolved by tumor cells

Total Number of Lymph Nodes Examined:

Number of Sentinel Nodes Examined (if applicable):

Total Number of Sentinel Nodes Involved (required only if sentinel nodes examined and involved):

- Location (specify)

Note: Locations may include subcapsular, interstitial, and other locations.

Number of Sentinel Nodes Involved in Sentinel Lymph Node:

- Cannot be determined (explain):

Note: Relevant only if larger than sentinel lymph node metastatic deposits.

- Size of Largest Metastatic Deposit in Sentinel Lymph Node:

- Extracapsular Extension

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CAP Approved

Skin + Melanoma

Excision

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note N)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting. Definitions that are not included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

Classification assigned in this report includes information from a prior procedure (explain):

TNM Descriptors (required only if applicable) (select all that apply)

- m (multiple)
- r (recurrence or retreatment)
- y (posttherapy or post-neoadjuvant therapy)

Primary Tumor (pT)

- pTX: Primary tumor thickness cannot be assessed (e.g., diagnosed by curettage) (explain)
- pT0: No evidence of primary tumor (e.g., unknown primary or completely regressed melanoma) (explain)
- pT1a: Melanoma in situ (i.e., not an invasive tumor; anatomic level) (explain)
- pT1b: Melanoma 1.0 mm or less in thickness, ulceration status unknown or unspecified (see Note D)
- pT1c: Melanoma >1.0 mm in thickness, no ulceration
- pT1d: Melanoma >1.0 mm in thickness with ulceration or melanoma 0.8 to 1.0 mm in thickness with or without ulceration
- pT2a: Melanoma >1.0 to 2.0 mm in thickness, ulceration status unknown or unspecified
- pT2b: Melanoma >2.0 to 4.0 mm in thickness with ulceration
- pT2c: Melanoma >2.0 to 4.0 mm in thickness, ulceration status unknown or unspecified
- pT2d: Melanoma >4.0 to 5.0 mm in thickness, ulceration status unknown or unspecified
- pT2e: Melanoma >5.0 to 6.0 mm in thickness, ulceration status unknown or unspecified
- pT2f: Melanoma >6.0 to 7.0 mm in thickness, ulceration status unknown or unspecified
- pT2g: Melanoma >7.0 to 9.0 mm in thickness, ulceration status unknown or unspecified
- pT2h: Melanoma >9.0 to 10.0 mm in thickness, ulceration status unknown or unspecified

Regional Lymph Nodes (pN) (applicable to invasive tumor only)

- pNX: Regional lymph nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason)

Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
CAP Approved

Skin + Melanoma 4.1.0.0

Excision

MN1: No regional lymph node metastasis detected

MN1: One tumor-involved node or in-transit, satellite, and microsatellite metastases with no tumor-involved nodes

MN2: One clinically occult tumor-involved node (e.g., detected by sentinel node biopsy) with no in-transit, satellite, and microsatellite metastases

MN1: One clinically detected tumor-involved node with no in-transit, satellite, and microsatellite metastases

MN1: Presence of in-transit, satellite, and microsatellite metastases with no regional lymph node disease

MN2: Metastasis in two to three regional nodes or in-transit, satellite, and microsatellite with one tumor-involved node

MN2: Two to three clinically occult tumor-involved nodes (e.g., detected by sentinel node biopsy) with no in-transit, satellite, and microsatellite metastases

MN2: Two to three tumor-involved nodes at least one of which was clinically detected with no in-transit, satellite, and microsatellite metastases

MN2: One clinically occult or clinically apparent tumor-involved node with presence of in-transit, satellite, and microsatellite metastases

MN3: Metastasis in four or more regional lymph nodes, or in-transit, satellite, or microsatellite metastases with two or more tumor-involved nodes or any number of metastatic nodes without or with in-transit, satellite, or microsatellite metastases

MN3: Four or more clinically occult tumor-involved nodes (e.g., detected by sentinel node biopsy) with no in-transit, satellite, and microsatellite metastases

MN3: Four or more tumor-involved nodes, at least one of which was clinically detected with no in-transit, satellite, and microsatellite metastases

MN3: Two or more clinically occult or clinically detected tumor-involved nodes with in-transit, satellite, and microsatellite metastases and/or any number of metastatic nodes with in-transit, satellite, and microsatellite metastases

* Note: phases 1, 2, and 3b subcategories are dependent on clinical information that may be unavailable to the pathologist. If this information is not available, the parent category (MN1, MN2, or MN3) should be selected.

Distant Metastasis (pM) (required only if confirmed pathologically in this case)

Note: AJCC TNM category suffixes “a” and “b”, which denote LDH level of elevation, are NOT included in the surgical pathology report. LDH levels, as well as other clinical parameters, may be included in the final classification by clinicians with access to this data.

pM1: Distant metastasis documented in this specimen

pM1a: Distant metastasis in skin, subcutaneous tissues, soft tissues including muscle and nonregional lymph nodes

pM1b: Distant metastasis to lung with or without M1a sites of disease

pM1c: Distant metastasis to non-CNS vascular sites with or without M1a or M1b sites of disease

pM1d: Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease

Specify site(s), if known.

* Additional Pathologic Findings (select all that apply)
  * Associated nerves (specify type)
  * Other (specify)

* Ancillary Studies

Note: For molecular genetic reporting, the CAP Melanoma Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

* Comments

* Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
# Melanoma Template

<table>
<thead>
<tr>
<th><strong>DIAGNOSIS:</strong></th>
<th>MALIGNANT MELANOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type:</td>
<td>Nodular type</td>
</tr>
<tr>
<td>Radial Growth Phase:</td>
<td>Absent</td>
</tr>
<tr>
<td>Vertical Growth Phase:</td>
<td>Present</td>
</tr>
<tr>
<td>Level of Invasion:</td>
<td>Level III</td>
</tr>
<tr>
<td>Greatest Thickness:</td>
<td>0.7mm</td>
</tr>
<tr>
<td>Site:</td>
<td>Left forearm</td>
</tr>
<tr>
<td>Sex:</td>
<td>Male</td>
</tr>
<tr>
<td>Mitotic Count:</td>
<td>1/mm²</td>
</tr>
<tr>
<td>Tumor Infiltrating</td>
<td>Present, brisk</td>
</tr>
<tr>
<td>Lymphocytes:</td>
<td>Absent</td>
</tr>
<tr>
<td>Regression:</td>
<td>Absent</td>
</tr>
<tr>
<td>Precursor Lesion:</td>
<td>Compound dysplastic nevus</td>
</tr>
<tr>
<td>Ulceration:</td>
<td>Absent</td>
</tr>
<tr>
<td>Elastosis Grade:</td>
<td>Moderate</td>
</tr>
<tr>
<td>Predominate Cell Type:</td>
<td>Epithelioid and heavily pigmented</td>
</tr>
<tr>
<td>Satellite Lesions:</td>
<td>Absent</td>
</tr>
<tr>
<td>Lymphovascular Invasion:</td>
<td>Absent</td>
</tr>
<tr>
<td>Perineural Invasion:</td>
<td>Absent</td>
</tr>
<tr>
<td>Tumor Stage:</td>
<td>T1a</td>
</tr>
</tbody>
</table>
Survival of patients with early invasive melanoma down-staged under the new 8th AJCC edition


Survival of patients with early invasive melanoma down-staged under the new 8th AJCC edition

- Queensland, Australia
- Compared the outcomes of patients classified as T1b in AJCC 7th Ed
  - $T \leq 1.0 \text{mm}$ with mitoses
- Reclassified in 8th edition
Total 208 T1b patients (7th)

• Reclass to 8th edition criteria
  ❖ Removal of mitoses as criterion
• 111 (53%) remained T1b
• 97 (47%) became T1a
<table>
<thead>
<tr>
<th>Mitotic Rate</th>
<th>Disease Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1-3 per mm$^2$</td>
<td>• 96%</td>
</tr>
<tr>
<td>• &gt;3 per mm$^2$</td>
<td>• 80%</td>
</tr>
</tbody>
</table>
Survival of patients with early invasive melanoma down-staged under the new 8th AJCC edition

- Reclassified T1b $\rightarrow$ T1a patients
- Mitotic rate $>3$/mm2
  - 80% survival
- *Reinforces the importance of reporting mitotic rate*
Concordance and Reproducibility of Melanoma Staging According to the 7th vs 8th Edition of the AJCC Cancer Staging Manual

Joann G. Elmore, MD, MPH; David E. Elder, MBChB, FRCPA; Raymond L. Barnhill, MD; Stevan R. Knezevich, MD, PhD; Gary M. Longton, MS; Linda J. Titus, MA, PhD; Martin A. Weinstock, MD, PhD; Margaret S. Pepe, PhD; Heidi D. Nelson, MD, MPH; Lisa M. Reisch, PhD; Andrea C. Radick, MS; Michael W. Piepkorn, MD, PhD


- 187 pathologists in the US
- Evaluated 116 invasive melanoma
Concordance and Reproducibility of Melanoma Staging According to the 7th vs 8th Edition of the AJCC Cancer Staging Manual

• **Using AJCC8 in comparison to AJCC7:**

  • Greater concordance with consensus reference
  • Greater interobserver reproducibility
Selected New Literature
Epidermal Genetic Information Retrieval

- Stratum corneum stripping
- DermTech, Inc, “Pigmented Lesion Assay”
- Adhesive patch applied to lesion of concern
- Extracts RNA
Pigmented Lesion Assay

- 2 gene RNA molecular assay
- Gene expression by RT-PCR
  - LIN00518 (long intergenic protein coding RNA518)
  - PRAME (preferentially expressed antigen in melanoma)
Pigmented Lesion Assay

- Tape stripping, instructions on website
- Patients 18 years and older
- Lesion size 5-16mm
- Not for:
  - Palms, soles, nails, mucous membranes (cannot get enough RNA)
  - Bleeding or ulcerated lesions
Epidermal Genetic Information Retrieval

• Largest study: 555 patients, validation sample of 398
  - Sensitivity 91%
  - Specificity 69%

Gerami P et al JAAD 2017;76(1): 114-120
Epidermal Genetic Information Retrieval

• When might it get used?
  ❖ Wound healing issues
    ▪ Diabetes, vascular compromise
  ❖ Patient preference
  ❖ Cosmetically sensitive areas (face)
  ❖ Patients who develop keloids
Dermatologic surgery

Mohs micrographic surgery with melanoma antigen recognized by T cells 1 (MART-1) immunostaining for atypical intraepidermal melanocytic proliferation

Jeremy R. Etzkorn, MD, Olivia S. Jew, BA, Thuzar M. Shin, MD, PhD, Joseph F. Sobanko, MD, Donald E. Neal, BA, and Christopher J. Miller, MD

Philadelphia, Pennsylvania

J Am Acad Dermatol 2018;79:1109-16.
Atypical Intraepidermal Melanocytic Proliferation

• Proliferation of predominantly single melanocytes in the epidermis without a developed nevus or melanoma

• Other names
  - Atypical junctional melanocytic lesion
  - Proliferation of solitary units of melanocytes
  - Atypical melanocytic hyperplasia
  - Lentiginous junctional melanocytic proliferation
Mohs for AIEMP, Etzkorn et al

- Retrospective review
- Single institution
- 223 such lesions of the head, neck, hand, foot, or pretibial
- Treated with Mohs surgery

- 42 (18.8%) of all lesions upstaged to unequivocal melanoma in situ or invasive melanoma
Melanoma and Melanoma In-Situ Diagnosis after Excision of Atypical Intraepidermal Melanocytic Proliferation (AIMP)

Blank, NR et al
doi.org/10.1016/j.jaad.2019.01.005
Melanoma and Melanoma In-Situ Diagnosis after Excision of Atypical Intraepidermal Melanocytic Proliferation

- Retrospective
- 1127 biopsies reported as AIMP
- subsequently excised
- one academic institution

- Melanoma (in-situ, stage 1A) was diagnosed after excision in 8.2% (92/1127) of AIMP samples
Factors associated with MIS diagnosis

- Age > 60 years
- Head and neck location
- Incomplete sampling

doi.org/10.1016/j.jaad.2019.01.005
Both studies, limitations

- Retrospective
- Single institution
- No evaluation of AIMP that were NOT removed

- Issues
  - Difficulty in defining AIEMP
  - Difficulty in defining MIS
Take home message

- More work needed on AIEMP
  - ?genetics
- Complete excision should be considered if incompletely removed
- A subset represent MIS/MM
PRAME Expression in Melanocytic Tumors

Cecilia Lezcano, MD,* Achim A. Jungbluth, MD,* Kishwer S. Nehal, MD,†
Travis J. Hollmann, MD, PhD,* and Klaus J. Busam, MD*

PRAME

- PRerentially expressed Antigen in Melanoma

- Antigen that was isolated from T cells in patient with metastatic melanoma
PRAME

• Found in:
  - Melanoma, Lung CA, non-small cell, breast CA, renal cell CA, ovarian CA, leukemia, synovial sarcoma, myxoid liposarcoma

• Not in normal tissue except:
  - Testis, ovary, placenta, adrenals, endometrium

• Member of “Cancer Testis Antigens”
PRAME Expression

Immunohistochemistry

- 155 primary MM
- 100 metastatic MM
- 145 nevi
PRAME Expression, Immunohistochemistry

• Diffuse positivity in melanoma
  - 87% of metastatic MM
  - 83% of primary MM
    - Desmoplastic MM lowest at 35%

• Nevi: 13.6% positive
  - 1/145 diffuse + (spitz nevus)
  - 18/145 focal + (< 50% cells)
Normal skin and lentigo

• Rare PRAME expression

• Potentially useful for margin assessment in MIS of chronically sun-damaged skin
PRAME for use in margin evaluation

Nodular MM vs Metastasis
Pathology Report

- Nodular Malignant Melanoma 2.5mm
  - Note: metastatic melanoma cannot be excluded
Primary Nodular vs Epidermotropic Metastasis

Comprehensive histopathological comparison of epidermotropic/dermal metastatic melanoma and primary nodular melanoma

Stephanie L Skala,1 David P Arps,2 Lili Zhao,3 Kelly B Cha,4 Min Wang,1 Paul W Harms,1,4 Aleodor A Andea,1,4 Douglas R Fullen1,4 & May P Chan1,4

1Department of Pathology, University of Michigan, Ann Arbor, MI, 2Consolidated Pathology Consultants, Libertyville, IL, 3Department of Biostatistics, University of Michigan, and 4Department of Dermatology, University of Michigan, Ann Arbor, MI, USA
Primary vs Metastasis

- 75 Primary Nodular Melanomas
- 74 Epidermotropic Metastatic Melanomas
Features associated with Mets

- Diameter <2mm
- Absent TILs
- Absent infiltrating plasma cells
- Monomorphism
- Involvement of adnexal epithelium
Features associated with Primary

- Exophytic
- Prominent TILs
- Prominent Plasma cells
- Diameter >10mm
- Ulceration
- Epidermal collarette

- Hi mitotic count
- Necrosis
- Pleomorphism
- Multiple phenotypes
- Lichenoid inflammation
Multivariate analysis

Features predictive of Primary Tumor

• Large size
• Ulceration
• Prominent infiltrating plasma cells
• Lichenoid inflammation
• Collarette
Risk of Subsequent Cutaneous Melanoma in Moderately Dysplastic Nevi Excisionally Biopsied but With Positive Histologic Margins

Caroline C. Kim, MD; Elizabeth G. Berry, MD; Michael A. Marchetti, MD; Susan M. Swetter, MD; Geoffrey Lim, MD; Douglas Grossman, MD, PhD; Clara Curiel-Lewandrowski, MD; Emily Y. Chu, MD, PhD; Michael E. Ming, MD, MSCE; Kathleen Zhu, BA; Meera Brahmbhatt, MD; Vijay Balakrishnan, BS; Michael J. Davis, BMus; Zachary Wolner, BA; Nathaniel Fleming, BA; Laura K. Ferris, MD, PhD; John Nguyen, BA; Oleksandr Trofymenko, BA; Yuan Liu, PhD; Suephy C. Chen, MD, MS; for the Pigmented Lesion Subcommittee, Melanoma Prevention Working Group
Moderately Dysplastic Nevi

• 9 academic centers

• Does melanoma develop at the sites of moderately dysplastic nevi with + margins?
Moderately Dysplastic Nevi

- 467 nevi, 438 patients
- No melanomas developed at sites
- 23% developed MM at separate site
Moderately Dysplastic Nevi: Limitations of study

• Number of cases
• Cases that had any concern, clinically or histologically were likely re-excised and therefore eliminated from study
Dysplastic nevi with severe atypia: Long-term outcomes in patients with and without re-excision

Kathleen Engeln, MD, a Kaitlin Peters, MD, c Jonhan Ho, MD, MS, d Jaroslaw Jedrych, MD, d Daniel Winger, MS, b Laura Korb Ferris, MD, PhD, c and Timothy Patton, DO c
San Diego, California and Pittsburgh, Pennsylvania

Conclusion: Re-excision of all SDN may not be necessary. (J Am Acad Dermatol 2017;76:244-9.)
Immunohistochemistry of p16 in nevi of pregnancy and nevoid melanomas

Stephen S. Koh | Brian F. Roehmholdt | David S. Cassarino
Outcomes of surgical re-excision versus observation of severely dysplastic nevi: A single institution retrospective cohort study

- 125 severely dysplastic nevi
  - 40 observed: 1 developed MIS
  - 85 re-excised, 6 upstaged to MM

J Am Acad Dermatol 82(1); 238-240, 2020
P16, melanocytic lesions

- Benign nevi: p16+, close to 100%
- MM p16+ 12-93% (most 40-60%)
- MM vs Spitz
  - Conflicting studies
P16

• Do not use p16 alone to differentiate benign and malignant

• Consider using with panel IHC
  ❖ HMB45
  ❖ Ki67/MART double stain
Methods

• 14 nevi from pregnant/postpartum women
• 20 nevoid melanoma
• % nuclear p16 staining
Results

• 81% of nevi showed >5% +
• 65% of MM showed <5% +

• Maybe helpful in this scenario
• Limitations:
  - Small sample size
  - Long term follow-up
• More studies needed
Follicular involvement is frequent in lentigo maligna: Implications for treatment

Karen L. Connolly, MD, a Cerrene Giordano, MD, a Stephen Dusza, DrPH, a
Klaus J. Busam, MD, b and Kishwer Nehal, MD a
New York, New York

J Am Acad Dermatol 2019;80:532-7
Follicular involvement in lentigo maligna

- 100 surgical excisions of LM
- Follicular involvement in 96% of specimens
- Mean depth of follicular involvement: 0.45mm
  - Thickest 1.1mm
Follicular involvement in lentigo maligna

- Implications:
  - Assume follicular involvement is present
  - Full thickness excision
  - May explain treatment failures with liquid nitrogen or topical therapy
The prognostic significance of tumor-infiltrating lymphocytes for primary melanoma varies by sex

Andrew J. Sinnamon, MD, a, b Cimarron E. Sharon, BS, a Yun Song, MD, a Madalyn G. Neuwirth, MD, a David E. Elder, MBChB, c Xiaowei Xu, MD, PhD, c Emily Y. Chu, MD, PhD, d Michael E. Ming, MD, MSCE, d Douglas L. Fraker, MD, a Phyllis A. Gimotty, PhD, b and Giorgos C. Karakousis, MD a

Philadelphia, Pennsylvania

Journal of the American Academy of Dermatology
Volume 79, Issue 2, August 2018, Pages 245-251
Tumor Infiltrating Lymphocytes

- Not in AJCC staging
  - Not recorded by many labs
- Lymphocytes infiltrating the dermal melanoma cells
- Recording
  - Brisk
  - Non-brisk
  - Absent
The prognostic significance of tumor-infiltrating lymphocytes for primary melanoma varies by sex

- Brisk and nonbrisk TIL in men: associated with lower risk of SLN positivity
- Brisk TIL in men: associated with longer overall survival
- TIL in women: no associated with survival or SLN positivity
Thank you!

University of Pennsylvania, Philadelphia