NCCN Melanoma Guidelines 2013: What Dermatologists and Dermatopathologists Need to Know

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No conflicts of interest to disclose
How is the evidence assessed?

- **National Comprehensive Cancer Network (NCCN)**
  - Rotating group of interdisciplinary melanoma specialists
  - 25 academic institutions nationwide

- Extensive review of existing evidence to establish clinical practice guidelines:
  - Category 1: high-level evidence, uniform NCCN consensus
  - Category 2A: lower level evidence, uniform NCCN consensus that intervention is appropriate (at least 85% agreement)
  - Category 2B: lower level evidence, less uniform NCCN consensus (at least 50% agreement)
  - Category 3: any level of evidence, reflects major disagreement
  - If <50% agreement, doesn’t go into the guidelines

- All recommendations category 2A unless noted

AAD Guidelines of Care

- Expert Work Group utilized Strength of Recommendation Taxonomy (SORT) – only studies rated as level I-III
  - Addresses quality, quantity, consistency of evidence
  - Emphasizes use of patient-oriented outcomes

- **A-level recommendation**
  - consistent and good-quality patient-oriented evidence

- **B-level**
  - inconsistent or limited quality patient-oriented evidence

- **C-level**
  - consensus, opinion, case studies, or disease-oriented evidence

Principles of Biopsy

- **Excisional biopsy** (elliptical, punch, or saucerization) with 1-3 mm margins preferred.
- **Avoid wider margins** to permit accurate subsequent lymphatic mapping.
- Orientation of Bx should be planned with definitive WLE in mind:
  - parallel to underlying lymphatics
- Full thickness incisional or punch biopsy of clinically thickest portion of lesion acceptable, in certain anatomic locations.
- Shave biopsy may compromise pathologic diagnosis and complete assessment of Breslow thickness
  - Exception: Broad shave biopsy may be best for lentigo maligna

Recommended clinical information to be provided to the pathologist

- **Essential:**
  - Age of patient
  - Gender
  - Anatomic location
- **Strongly recommended:**
  - Biopsy technique (excisional or incisional)
  - Size of lesion
- **Optional:**
  - Clinical description and level of clinical suspicion
  - Dermatoscopic features
  - Photograph
  - Macroscopic satellites

What Pathologists Need to Report  
(NCCN/AAD Guidelines)

- **Minimal elements to be reported** should include:
  - Breslow thickness (mm)
  - histologic ulceration (present or absent)
  - dermal mitotic rate per mm2
  - Clark level (encouraged for lesions ≤1mm, optional for lesions >1mm)
  - peripheral and deep margin status of biopsy (present or absent), i.e. **NO HISTOLOGIC MARGIN MEASUREMENT**

- **Mitotic rate is an independent risk factor for survival and SHOULD BE ASSESSED by pathologists** (hot spot technique, #/mm2)

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Primary Melanoma Mitotic Rate  
2008 AJCC Melanoma Staging Database

11,664 Stage I/II patients

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Number of Mitoses/ mm²</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year</td>
<td>10-year</td>
<td></td>
</tr>
<tr>
<td>0-0.99</td>
<td>673</td>
<td>70%</td>
</tr>
<tr>
<td>1.0 - 1.9</td>
<td>2049</td>
<td>78%</td>
</tr>
<tr>
<td>2.0 – 4.9</td>
<td>3254</td>
<td>87%</td>
</tr>
<tr>
<td>5.0 – 10.9</td>
<td>2117</td>
<td>92%</td>
</tr>
<tr>
<td>11.0 – 19.9</td>
<td>3312</td>
<td>97%</td>
</tr>
<tr>
<td>≥ 20</td>
<td>259</td>
<td>59%</td>
</tr>
</tbody>
</table>

How Should Mitotic Rate be Measured?

- Locate dermal “hot spot” containing most mitotic figures
- Extend count to adjacent fields until assess area = 1 mm²
  - Corresponds to ~ 4 high power fields at 400x magnification
- If no “hot spot” found and mitoses sparse/scattered:
  - Choose representative mitoses and extend to 1 mm² area
  - Problem is that a single dermal mitosis can make the rate = 1/mm²
- Record mitoses as # per mm²
  - If mitotic figures not present, recommendation is to list as zero rather than <1 / mm²
- Excellent interobserver reproducibility reported


ME-A: Pathology Reporting of Melanoma

- Microsatellitosis (present or absent)
- ENCOURAGE consistent reporting of additional factors (c/w AAD guidelines):
  - Location
  - Regression
  - Tumor infiltrating lymphocytes
  - Vertical Growth Phase
  - Angiolymphatic invasion
  - Neurotropism
  - Histologic subtype (key for lentigo maligna)
  - Pure desmoplasia, if present or specify pure vs. mixed desmoplastic with spindle cell and/or epithelioid cells
  - Consider CGH or FISH for histologically equivocal lesions
ME-1: Pathology Report Changes

● Pathology Report:
  – Both Ulceration and Microsatellitosis should be listed as either “present or absent”

● Why?
  – “Microsatellitosis, when present in the initial biopsy specimen or wide excision specimen, defines at least N2C and at least Stage IIIB disease.”

Prognostic Value of Microsatellites

● Intralymphatic metastasis can manifest as satellites, microsatellites, on in-transit disease
  – Defined as N2c melanoma
  – 2008 AJCC database reports 69% 5-year survival

● Microsatellites have comparable survival outcome to clinically detectable satellites

● Highly predictive of locoregional recurrence and lower disease-free survival (even if lymph nodes negative)

● Microsatellite definition:
  – Any discontinuous nest of intralymphatic metastatic cells >0.05 mm in diameter
  – Clearly separated by normal dermis from main invasive melanoma component by at least 0.3 mm

ME-1: Clinical Stage, Workup, Treatment

- Stratification of Stage IA and IB patients revised according to **risk for SLN metastasis**, rather than AJCC stage:
  - Stage IA (≤0.75mm, no ulceration, MR <1/mm²)
  - Stage IB (≤0.75 mm, + ulceration and/or MR ≥1/mm²)
  - Stage IA (0.76-1.0 mm, no ulceration, MR <1/mm²)
  - Stage IB (0.76-1.0 mm with ulceration or MR ≥1/mm² or >1mm, any characteristic)

- Why?
  - Thickness is the only consistent predictor of SLN positivity in thin melanoma, NOT mitotic rate
Key Change in SLNB Recommendations for T1 Melanoma – Footnote “e”

- “In general, SLNB is NOT RECOMMENDED for primary melanomas ≤0.75 mm, unless there is significant uncertainty about the adequacy of microstaging.
- For melanomas 0.76-1.0 mm, SLNB MAY BE CONSIDERED in the appropriate clinical context.
- In patients with thin melanomas (≤1.0 mm), apart from primary tumor thickness, there is little consensus as to what should be considered ‘high-risk features’ for a positive SLN.
- Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and LVI, are very uncommon in melanomas <0.75 mm; when present, SLNB may be considered on an individual basis.”

How Does this Correlate with +SLNB?

- Thickness >0.75 mm, risk of + SLNB is ~5%
- Thickness ≤0.75 mm, risk is 2-2.5%
- Need to define “high-risk” T1 melanoma, and thickness appears to be the most reproducible risk factor across multiple series
- AAD 2011 Guidelines: Risk of + SLNs should be 10% or more before recommending SLNB
  - True for tumors 0.76 mm-1.0mm with MR ≥1/mm2
  - SLNB NOT RECOMMENDED for T1a melanoma (≤1mm with no ulceration and MR of zero or <1/mm2)
What Does this Mean for Dermatologists?

- Don’t recommend SLNB in patients with melanoma ≤0.75 mm, unless there are true high-risk features:
  - Strong patient preference
  - Partial biopsy – particularly with deep transection of the tumor (i.e. inadequate microstaging)
  - Nonrepresentative biopsy (large clinical residual lesion)
  - Lymphovascular invasion, ulceration - rare
  - Clark level IV/V – only when MR can’t be assessed
  - (Very) high mitotic rate

Lymphatic Invasion

Lymphatic invasion confirmed with D2-40 Mab immunostain (podoplanin)

Differentiated from microsatellite

Doeden K et al. J Cutan Pathol. 2009;36:772-80
Importance of Lymphovascular Invasion (LVI)

- Also called angiolymphatic or lymphatic invasion
  - LI can be differentiated from vascular invasion (CD 31 immunostain) – less common than LI
  - LI/LVI correlates with greater Breslow depth

- Lymphovascular invasion is a key predictor of SLN metastasis in thin (T1) melanoma:
  - 432 patients with T1 melanoma, SLNB+ in 6.7%
  - No SLN positivity in 37 pts with tumors ≤0.5 mm
  - Breslow thickness and LVI only factors associated with + SLNB
  - SLNB should be considered if there is lymphatic invasion!


Melanoma Work-Up

- Careful Hx and PE detect metastasis, NOT baseline or surveillance studies
- Labs almost never sole indicator of metastatic disease; CXR rarely
- LDH- staging value only for stage IV melanoma – AT TIME OF DIAGNOSIS
- Extensive radiologic scans (CT/ MRI/ PET/ skeletal survey) generally not of value in asymptomatic pts
- Presymptomatic detection of stage IV melanoma does not affect survival – will this change with new drugs?

### ME-3,4,7: Baseline and Surveillance Studies

- **For All Stage I and II Melanoma (including T4 lesions) at Baseline:**
  - Routine imaging/lab tests not recommended
  - Imaging (CT scan, PET/CT, MRI) at baseline only to evaluate specific signs or symptoms

- **Same true for Surveillance:**
  - Routine blood tests are not recommended
  - Radiologic imaging (CT, PET/CT, MRI) is indicated to investigate specific signs or symptoms
    - Not recommended to screen for asymptomatic recurrent/metastatic disease; optional for Stage IIB-IV
    - No tests for asymptomatic pts of ANY STAGE after 5 years!

### Follow-up of Primary Melanoma: NCCN Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>NCCN Recommended Follow-up</th>
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<tbody>
<tr>
<td>Stage 0 (in situ)</td>
<td>- At least annual skin exam for life (ALL PATIENTS)</td>
</tr>
<tr>
<td></td>
<td>- Educate patient in regular self skin exam (ALL PATIENTS)</td>
</tr>
<tr>
<td>Stage Ia-IIa NED</td>
<td>- H&amp;P (with emphasis on nodes and skin) every 6-12 mo x 5 y, then annually as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>- At least annual skin exam for life</td>
</tr>
<tr>
<td></td>
<td>- Educate patient in regular self skin and LN exam (stage Ia-Iv)</td>
</tr>
<tr>
<td></td>
<td>- Routine blood tests/radiologic imaging to screen for asymptomatic recurrent/metastatic disease not recommended</td>
</tr>
<tr>
<td>Stage Iib-Iv NED</td>
<td>- H&amp;P (emphasis on nodes and skin)</td>
</tr>
<tr>
<td></td>
<td>- Every 3-6 mo for 2 yr, then</td>
</tr>
<tr>
<td></td>
<td>- Every 3-12 mo for 3 yr, then annually as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>- Routine blood tests not recommended</td>
</tr>
<tr>
<td></td>
<td>- Consider CXR, CT and/or PET-CT every 4-12 mos to screen for recurrent/metastatic disease (category 2B)</td>
</tr>
<tr>
<td></td>
<td>- Consider brain MRI annually (category 2B)</td>
</tr>
<tr>
<td></td>
<td>- Routine radiologic imaging not recommended after 5 y</td>
</tr>
</tbody>
</table>
AAD Guidelines 2011

● Baseline:
  – No baseline lab or imaging studies in asymptomatic patients with newly-diagnosed primary melanoma of any thickness

● Surveillance:
  – Surveillance labs/imaging studies have low yield for metastatic detection and high false-positive rates
  – Regular clinical follow-up and interval patient self exam of skin and regional LNs
  – History and PE findings direct need for further studies to detect metastatic disease
  – No clear f/u interval – at least annual history and PE with attention to skin and lymph nodes recommended


Surgical Margin Guidelines (NCCN/AAD)

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Excisional Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma in situ</td>
<td>0.5 – 1 cm</td>
</tr>
<tr>
<td>≤1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01 mm – 2 mm</td>
<td>1 cm – 2 cm</td>
</tr>
<tr>
<td>&gt;2 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

Margins >2 cm do not improve LR, DFS, or OS

**Surgical Margins - KEY POINTS**

- Excision margins based on clinical margins taken at time of surgery and **NOT GROSS OR HISTOLOGIC MARGINS** measured by the pathologist
  - Clinically negative margins do not need to match histologically negative margins!

- For large melanoma in situ, *lentigo maligna* type, **margins >0.5 cm** may be necessary for histologically clear margins
  - Techniques for more exhaustive histologic margin assessment (i.e. MOHS) should be considered
  - For **SELECTED** patients with positive margins after optimal surgery, consider topical imiquimod or RT (category 2B, NCCN)
  - AAD – surgical alternatives include topical imiquimod, RT, cryosurgery, and observation
  - Use of imiquimod remains off-label


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**ME-D: Principles of Radiation Therapy for Melanoma**

- **ADJUVANT TREATMENT FOR PRIMARY DESMOPLASTIC MELANOMA:**
  - Narrow margins
  - Locally recurrent disease
  - Extensive neurotropism

- **REGIONAL NODAL ADJUVANT THERAPY:**
  - Consider based on location, size, and number of involved nodes
  - Only reduces lymph node field recurrence
  - **NO IMPACT on Relapse-free or Overall Survival**
  - Long term skin and regional toxicities
  - Potential reduced quality of life (ASCO 2013)
ME-E: Systemic Therapy Options for Advanced Metastatic Melanoma

● Many changes with advent of newer targeted and immunotherapy agents

● For Dermatologists:
  – Vemurafenib and Dabrafenib have the potential for significant dermatologic complications including cutaneous SCC and extreme photosensitivity.

● REGULAR DERMATOLOGIC EVALUATION with REFERRAL TO A DERMATOLOGIST is recommended

● Key is getting this message out to medical oncologists!

How to Access the NCCN Guidelines

● GO to: NCCN Clinical Practice Guidelines in Oncology – NCCN.org

● For Health Care Professionals:
  – www.nccn.org/professionals/physician_gls/

● Click on “NCCN Guidelines for Treatment of Cancer by Site”

● Then on “MELANOMA”
  – PDF File: “NCCN Guidelines”

● Register with email address and create account - FREE!