Updates on Melanoma: Are You Following the Latest Guidelines of Care?

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Update on Melanoma
Are You Following the Latest Guidelines of Care?

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Disclosure Statement

I, Jerry D. Brewer, MD, do not have any relevant financial interest or other relationships with a commercial entity producing health-care related product and or services.

Objectives

• Describe the latest NCCN and AAD guidelines for melanoma
• Identify how the new staging criteria and guidelines may affect patient care and clinical practice

Keystone Habits

• “It’s not that family meal or tidy bed causes better grades or less frivolous spending, but somehow those initial shifts start chain reactions that help other good habits take hold…[Keystone habits] establish cultures where change becomes contagious.”

Charles Duhigg

Objectives

• Gain a deeper understanding of the latest NCCN and AAD guidelines for melanoma
• Understand how the new staging criteria and guidelines may affect patient care and clinical practice

Guidelines of care for the management of primary cutaneous melanoma

Disclaimer

- Adherence
  - Will not ensure successful treatment
- Not interpreted
  - Setting a standard of care
- Ultimate judgment
  - Physician and patient
- Does reflect
  - Best available data at time of publication


Scope

- Primary cutaneous melanoma
- Not melanoma of mucous membranes
- Adjuvant therapies for high risk melanoma (Stage ≥ IIIB)
  - Interferon
  - Radiation therapy
  - Outside the scope of guideline

Method

- Work group of melanoma experts
- PubMed search
  - 2000 through 2010
  - 1960 through 2010 – new clinical questions
- Strength of Recommendation Taxonomy
  - Rating the strength of evidence


Method

- Evidence graded with 3 point scale
  I. Good-quality that matters to patients
  II. Limited-quality
  III. Other including consensus guidelines, opinion, case studies, disease-oriented evidence


Method

- Clinical recommendations
  A. Based on consistent and good quality evidence
  B. Based on inconsistent or limited-quality evidence
  C. Based on consensus, opinion, case studies, or disease-oriented evidence

Outline
- Biopsy
- Pathology Report
- Staging Work Up
- Follow Up
- Surgical Management
- Nonsurgical Treatments
- SLNB

Biopsy
- Lesions clinically suspicious for melanoma
- Narrow excisional biopsy
  - Encompasses the entire breadth and depth of the lesion
  - 1 to 3 mm margins suggested
- Punch excisions
- Shave excisions
- Scalpel excision

Biopsy
- Incisional biopsy
  - Of the clinically or dermatoscopically most atypical portion
  - Facial or acral location
  - Very large lesion
  - Repeat biopsy may be needed

Biopsy
- Nail lesion (melanonychia, diffuse pigmentation, amelanotic changes)
  - Nail matrix should be sampled

Table: 1. Strength of recommendations for management of primary cutaneous melanoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Score</th>
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<tbody>
<tr>
<td>Pathology report</td>
<td>Strong</td>
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<td>100</td>
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<tr>
<td>Tumor (Breslow) thickness</td>
<td>Strong</td>
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<tr>
<td>Ulceration</td>
<td>Strong</td>
<td>1</td>
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<tr>
<td>Mitotic rate</td>
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<tr>
<td>Level of invasion (Clark)</td>
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<tr>
<td>Ulceration</td>
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<td>Treatment management</td>
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<tr>
<td>Intensity of treatment</td>
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<td>1.01-2.0 mm thickness</td>
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<td>2.01-4.0 mm thickness</td>
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<tr>
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<td>&gt;10.0 mm thickness</td>
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<tr>
<td>Sentinel lymph node biopsy</td>
<td>Strong</td>
<td>1</td>
<td>100</td>
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</table>
Pathology Report

Should be provided to the pathologist
- Age
- Gender
- Anatomic location

Optional but desirable additional information for the pathologist
- ABCDE criteria
- Dermatoscopic features
- Clinical photograph
- Presence or absence of macroscopic satellitosis

Pathology report - Essential
- Breslow thickness
- Microsatellitosis
- Commented on separately
- Ulceration
  - Tumor induced full-thickness loss of epidermis
  - Subjacent dermal tumor
  - Reactive dermal changes
- Mitotic rate
  - Number of dermal mitoses per mm²
  - 1 mm² = 4.5 high-power (x40) microscopic fields starting in the field with the most

Prognosis

Mitotic rate
- Multivariate analysis
  - Best prognostic indicator 2nd to Breslow depth
  - 0 mitoses = >95% 10 year survival
  - 1-4 mitoses = 80% 10 year survival
  - 5-10 mitoses = 70% 10 year survival
  - >10 mitoses = 60% 10 year survival
- Part of new (2010) AJCC criteria
Mitotic rate
- Regardless of Clark level
- Dermal mitotic rate of $\geq 1$ mitosis/mm$^2$
- Independently associated with worse disease specific survival


- 3661 melanomas from Sydney Melanoma Unit
- Mitotic rate 0/mm better survival than 1/mm
- No significant differences for stepwise increases from 1-2, 2-3, 3-4, & 4-5
- Tumor thickness, ulceration & mitotic rate closely correlated
- Cox regression analysis indicated mitotic rate highly significant, second only to tumor thickness

Prognostic factors
- Breslow depth in mm
- Clark level
- Ulceration
- In transit metastases
- Age
- Anatomic location
- Gender
- Tumor volume
- Cross-sectional profile
- Mitoses per mm
- Growth phase (radial vs vertical)
- Association with nevus
- Regression
- Inflammatory response
- Angioplasia
- Vascular invasion
- Histologic type
- Cell type
- Desmoplasia
- Neurotropism
- Cellular atypia
- VEGF
- PTEH

Pathology report

Synoptic melanoma report

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Tumor (Breslow) thickness</th>
<th>Ulceration</th>
<th>Dermal mitotic rate</th>
<th>Perineural involvement</th>
<th>T-stage classification</th>
<th>Tumor infiltrating</th>
<th>Vertical growth phase</th>
<th>Anatomic (Clark) level of invasion</th>
<th>Histologic subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>mm</td>
<td>mm</td>
<td>Absent</td>
<td>Masses per mm² or demal</td>
<td>Present or absent</td>
<td>Tta-Nlo</td>
<td>Not identified, norbrik, or lymphoosphin</td>
<td>Present or absent</td>
<td>Superficial spreading, nodular, lentigo maligna, acral lentiginous, desmoplastic/neurotropic, nevoid, or other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

History of physical

- The cornerstone of the initial diagnostic workup
- Focused ROS – invasive disease
  - Constitutional
  - Neurologic
  - Respiratory
  - Hepatic
  - Gastrointestinal
  - Musculoskeletal
  - Skin
  - Lymphatic signs and symptoms

The physical exam

- Total body skin exam
- Regional and distant lymph node examination

Staging workup

- In asymptomatic patients with melanoma of any thickness
  - Blood tests
  - Imaging studies
  - Generally not recommended
  - Only for suspicious signs and symptoms
Chest X-ray
- Stage IIB-IIC
  - Optional (nccn version 3.2012)

What about stage IV patients
- Currently available interventions
  - Not associated with better outcomes
  - Compared to initiation of treatment when pt becomes symptomatic

Screening blood tests and imaging
- Serum lactate dehydrogenase
  - Insensitive
- Imaging studies
  - Very low yield
  - Relatively high false-positive rate
  - Routine chest x-ray (and CT)
    - Cost-inefficient
    - High false positive rate

Imaging studies
- Can be considered in higher risk of recurrence
  - Stage IIB and above
  - Yield still remains low
  - Not recommended past 5 years
Impact of false positives

- Unnecessary invasive procedures
- Substantial patient anxiety
- Time and energy

Micrometastatic nodal disease

- In micrometastatic disease detected by SLNB
- CT or PET
  - 0.5% to 3.7%
  - Very low yield

Referral to a medical oncologist

- High risk patient
- Relapse
- Disease stage
- Tumor thickness
- Ulceration
- SLN status
- Combination

Follow up of asymptomatic patients

- Primary goal – Early detection
- Resectable recurrent disease
- Additional primary melanomas
- Early detection
  - Distant metastatic disease
  - No effect on overall survival
- At least annual
  - Range of every 3 to 12 months
  - Based in risk factors

Follow-up
Follow up of asymptomatic patients

- Factors that influence follow-up
- Multiple primary melanomas
- Stage
- Atypical nevi
- Family history of melanoma
- Patient anxiety
- Patient awareness


Patient education

- Monthly self-skin exams
- Monthly regional lymph node exams

Surgical Management

Surgical excision

- Primary goals
  - Achieve histologically free margins
  - Prevent local recurrence

Table XII. Surgical margin recommendations for primary cutaneous melanoma

<table>
<thead>
<tr>
<th>Tumor thickness</th>
<th>Clinically measured surgical margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.8 mm</td>
<td>0.5-1.0 cm</td>
</tr>
<tr>
<td>1.0-1.9 mm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td>≥ 2.0 mm</td>
<td>2.0 cm</td>
</tr>
</tbody>
</table>

*Wider margins may be necessary for lentigo maligna subtype.


Surgical excision

- Margins
  - Clinical measurement
  - Not histologically measured tumor-free margins
- Three concepts
  - WLE associated with decreased recurrence
  - No evidence for > 1cm in thin melanomas
  - No evidence for > 2cm in any melanoma
Melanomas thicker than 2.0mm
• 1 cm margin vs 3 cm margin
  • Higher combined local, regional, and nodal recurrence rate
  • No difference
    • True local recurrence
    • Melanoma specific survival
    • Overall survival


Other studies
• 1 cm margin vs 3 cm margin
  • Slightly higher local recurrence rates
  • Melanomas thicker than 1mm


Thick primary melanomas
• No conclusive evidence
  • Surgical margins > 2cm offers benefit


Depth of excision
• Most excised to but not including muscular fascia
  • Extremities (71%)
  • Trunk (66%)
  • Head and neck (62%)
  • Significant variability
  • Even within the same institution


Depth of excision
• Recommendation
  • Whenever possible
    • Excise to the level of the muscular fascia
    • Or at least deep adipose tissue


Melanoma in situ
• No prospective controlled data
  • 0.5 to 1.0 cm margins
  • MMIS, lentigo maligna type
  • Wood lamp
  • Contralateral sampling
  • Careful histologic examination
    • Permanent section total peripheral margin
    • Mohs micrographic surgery

Melanoma in situ, lentigo maligna type

- 6mm margins
- 86% clearance
- 9mm margins
- 98.9% clearance
- Not effected by gender, location, or diameter
- 0.3% recurrence rate


Non-Surgical Management

- For all melanomas
- Surgery
- Standard of care
- Alternatives
  - Considered when surgery not an option
  - Clearly discuss limitations
    - Risk of under treating invasive melanoma
    - Higher recurrence rates


Non-Surgical Management

- Topical imiquimod
  - Off-label use for melanoma in situ
  - Highly variable treatment regimens
  - Lack of long-term follow-up
    - Average 18 months
    - Persistent disease in 25%


Non-Surgical Management

- Topical imiquimod
  - High cost
  - Low threshold for subsequent biopsy
  - Severe inflammatory reaction

Non-Surgical Management
- Primary radiation
  - When surgery not an option
  - Recurrence rates 0% to 14%

Non-Surgical Management
- Cryosurgery
  - Clinical clearance rate
  - 60% or higher
  - Insufficient data

Non-Surgical Management
- Observation
  - None of the non-surgical modalities
  - Superior to observation

Sentinel Lymph Node Biopsy

SLNB
- Described in early 1990’s
- Most sensitive and specific staging test
- Micrometastatic melanoma in regional LN
- Not without controversy!
- SLN status – most important prognostic factor
  - Disease specific survival of MM > 1mm
- Overall impact remains unclear

Early detection
• Lower rate of post-operative complications
  • LND for micrometastatic disease vs
  • Therapeutic LND for clinically palpable disease


MSLT-1
• SLNB vs observation
  • No significant difference in overall survival
  • Higher 5 year survival
  • LND after positive SLNB vs delayed therapeutic LND
  • 26% decrease in recurrence in group with SLNB for at least 10 years
  • Was study powered enough?


SLNB
• Intermediate depth melanoma
  • 15% to 20% positive
  • Decreases significantly in < 1mm thick tumors
  • Around 5-7%
  • Large selection bias


SLNB recommendations
• T1a or T1b with ≤0.75mm tumor thickness
  • Generally not be considered
  • Other parameters
    • Ulceration
    • Increased mitotic rate
    • Angiolymphatic invasion
    • Positive deep margin
    • Young age


SLNB recommendations
• T1b – 0.76 to 1.00mm tumor thickness
  • Occult nodal disease increases to 10%
  • SLNB should be discussed
• NCCN guidelines
  • SLNB offered for T1b
  • Discussed for T1a


A word on mitosis
• 2010 AJCC staging system
  • Overall survival (error in AAD paper)
  • Mitotic rate as a continuous variable
  • Increasing mitotic rate – greater concern
  • Melanoma 0.5 to 0.75mm, 2 or more mitoses/mm²
    • May have sufficient risk for SLNB
    • Especially if other adverse factors
  • Melanoma 0.76 to 1.00mm with 1 mitosis/mm²
    • Relatively low risk

Additional adverse factors

- Outside the AJCC staging system
- Angiolymphatic invasion
- Positive deep margin
- Younger age

Melanoma > 4mm tumor thickness

- SLNB
  - Remains a strong independent predictor of outcome in these patients
  - Distant disease free survival
    - 85.3% vs 47.8%
  - Angiolymphatic invasion, satellitosis, or ulceration
  - Predictors of positive SLNB

Providers vs patients perceptions

- Women with breast cancer
- 50% judged 1 extra day survival
- Sufficient to justify adjuvant chemotherapy
- The dilemma with SLN biopsy
  - Patient perceptions
  - Physician perceptions

SLNB recommendations

- Advisable
  - Discuss with all patients with invasive MM
- If a candidate
  - Value
  - Cost
  - Complications
  - Limitations

How to unlock the puzzle?...

Significant gaps in research

- Interpretation of Mitotic rate
- Treatment of LM
- The use and value of dermatoscopy
- Biomarkers and mutational analysis
- Use of SLNB
Sometimes coming to consensus

Because of research gaps

• Recommendations
  • Many times based on consensus expert opinion
  • Management of primary cutaneous melanoma
    • Should thus always be tailored to meet the individual patient’s needs


Melanoma

Are You Following the Latest Guidelines of Care?

Thank You!