Select Dermatopathology Topics for the Practicing Dermatologist

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• I have no conflicts of interest
Overview of Lecture

• Cutaneous Squamous Cell Carcinoma staging update
• Changes to melanoma staging from AJCC7 to AJCC8
• Sentinel lymph node biopsy and complete dissection evidence
• Melanoma prognosis predictors
• Genetics of melanocytic neoplasms including Spitz tumors and melanoma
• Prognostic factors of Spitz tumors
• Problems with interpreting melanocytic neoplasms
• Molecular tests for melanocytic neoplasms
• Re-excision of dysplastic Nevi
Cutaneous Squamous Cell Carcinoma staging update
## ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T Any</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N Any</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T Any</td>
<td>N Any</td>
<td>M1</td>
</tr>
</tbody>
</table>

### ANATOMIC STAGE/PROGNOSTIC GROUPS

Patients with primary cSCC or other cutaneous carcinomas with no evidence (clinical, radiologic, or pathologic) of regional or distant metastases are divided into two stages: Stage I for tumors measuring ≤2 cm in size and Stage II for those that are greater than 2 cm in size. In instances where there is clinical concern for extension of tumor into bone and radiologic evaluation has been performed (and is negative), these data may be included to support the Stage I vs. II designation. Tumors that are ≤2 cm in size can be upstaged to Stage II if they contain two or more high-risk features. Stage III patients are those with (1) clinical, histologic, or radiologic evidence of one solitary node measuring ≤3 cm in size or (2) Tumor extension into bone: maxilla, mandible, orbit, or temporal bone. Stage IV patients are those with (1) tumor with direct or perineural invasion of skull base or axial skeleton, (2) ≥2 lymph nodes or (3) single or multiple lymph nodes measuring >3 cm in size or (4) distant metastasis.
AJCC 7th Edition
Cutaneous SCC and Other Cutaneous Carcinomas

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension with less than two high-risk features**</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor greater than 2 cm in greatest dimension or Tumor any size with two or more high-risk features*</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with invasion of maxilla, mandible, orbit, or temporal bone</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base</td>
</tr>
</tbody>
</table>

*Excludes cSCC of the eyelid (see Chap. 48).

**High-risk features for the primary tumor (T) staging**

- Depth/invasion: >2 mm thickness
- Clark level ≥IV
- Perineural invasion
- Anatomic location: Primary site ear
- Primary site non-hair-bearing lip
- Differentiation: Poorly differentiated or undifferentiated

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>N Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node, more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>M Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>
Cutaneous SCC of the Head and Neck

| TX       | Primary tumor cannot be assessed |
| T0       | No evidence of primary tumor     |
| Tis      | Carcinoma in situ               |
| T1       | Tumor < 2 cm in greatest dimension |
| T2       | Tumor ≥ 2 cm and < 4 cm in greatest dimension |
| T3       | Tumor ≥ 4 cm in greatest dimension and/or perineural invasion* and/or deep invasion† and/or minor bone erosion |
| T4a      | Tumor with gross cortical bone/marrow invasion |
| T4b      | Tumor with skull base invasion and/or skull base foramen involvement |

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<table>
<thead>
<tr>
<th>High-risk Feature</th>
<th>Description</th>
<th>Affects T Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size (cm)</td>
<td>≥ 2</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumor thickness (mm)</td>
<td>&gt; 6</td>
<td>Yes</td>
</tr>
<tr>
<td>Level of invasion</td>
<td>Beyond dermis</td>
<td>Yes</td>
</tr>
<tr>
<td>PNI</td>
<td>Large caliber (≥ 0.1 mm diameter)</td>
<td>Yes</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Poor differentiation</td>
<td>No</td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Desmoplastic and spindle cell</td>
<td>No</td>
</tr>
<tr>
<td>LVI</td>
<td>Tumoral cells within vascular spaces</td>
<td>No</td>
</tr>
<tr>
<td>Anatomical location</td>
<td>Hair-bearing (nonglabrous) lip and ear</td>
<td>No</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Organ transplant recipients (heart and lung particularly) at high risk</td>
<td>No</td>
</tr>
</tbody>
</table>

*Perineural invasion of a nerve lying beneath the dermis, or measuring ≥ 0.1 mm in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

†Deep invasion is defined as involvement beyond the subcutaneous fat or > 6 mm.

Minor bone erosion.

AJCC-8 indicates eighth edition of the American Joint Committee on Cancer; cSCC, cutaneous squamous cell carcinoma.

cSCC indicates cutaneous squamous cell carcinoma; LVI, lymphovascular invasion; PNI, perineural invasion.
### AJCC 8th Edition
Cutaneous SCC of the Head and Neck

**Clinical N (cN)**
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE–
- N2: Metastasis in single ipsilateral lymph node, > 3 cm but not > 6 cm in greatest dimension and ENE–; or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE–; or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE–
- N2a: Metastasis in single ipsilateral lymph node, > 3 cm but not > 6 cm in greatest dimension and ENE–
- N2b: Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE–
- N2c: Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE–
- N3: Metastasis in a lymph node > 6 cm in greatest dimension and ENE–
- N3a: Metastasis in any node(s) and clinically overt ENE (ENE +)
- N3b: Metastasis in any node(s) and clinically overt ENE (ENE +)

**Pathologic N (pN)**
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE–; or > 3 cm but not > 6 cm in greatest dimension and ENE–; or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE–; or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE–
- N2: Metastasis in single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE +; or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE–; or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE–
- N2a: Metastasis in single ipsilateral lymph node, > 3 cm but not > 6 cm in greatest dimension and ENE +
- N2b: Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE +
- N3: Metastasis in a lymph node > 6 cm in greatest dimension and ENE +
- N3a: Metastasis in any node(s) and clinically overt ENE (ENE +)
- N3b: Metastasis in any node(s) and clinically overt ENE (ENE +)

**M Category**

<table>
<thead>
<tr>
<th>M Category</th>
<th>M Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

AJCC-8 indicates eighth edition of the American Joint Committee on Cancer; cSCC, cutaneous squamous cell carcinoma; ENE, extranodal extension.
**AJCC7 vs AJCC8**

<table>
<thead>
<tr>
<th>Primary Tumor (T)*</th>
<th>Differences:</th>
</tr>
</thead>
<tbody>
<tr>
<td>TXPrimary tumor cannot be assessed TX</td>
<td>T category changes with T1-2 based on purely on size, and T3 based on size and high risk features</td>
</tr>
<tr>
<td>T0No evidence of primary tumor</td>
<td>High risk feature: depth of invasion changed to beyond the SC fat or &gt;6mm.</td>
</tr>
<tr>
<td>TisCarcinoma in situ</td>
<td>Differentiation, and anatomic location no longer are high risk features.</td>
</tr>
<tr>
<td>T1Tumor 2 cm or less in greatest dimension with less than two high-risk features**</td>
<td></td>
</tr>
<tr>
<td>T2Tumor greater than 2 cm in greatest dimension or Tumor any size with two or more high-risk features*</td>
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<tr>
<td>T3Tumor with invasion of maxilla, mandible, orbit, or temporal bone</td>
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</tr>
</tbody>
</table>

*Excludes cSCC of the eyelid (see Chap. 48).

**High-risk features for the primary tumor (T) staging

<table>
<thead>
<tr>
<th>Depth/invasion</th>
<th>Anatomic location</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 mm thickness Clark level ≥IV Perineural invasion</td>
<td>Primary site ear Primary site non-hair-bearing lip</td>
<td>Poorly differentiated or undifferentiated</td>
</tr>
</tbody>
</table>

High-risk features defining primary tumor as T3:
* Perineural invasion of a nerve lying beneath the dermis, or measuring ≥0.1 mm in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.
* Deep invasion is defined as involvement beyond the subcutaneous fat or >6 mm.
* Minor bone erosion.

AJCC-8 indicates eighth edition of the American Joint Committee on Cancer; cSCC, cutaneous squamous cell carcinoma.
Evaluation of AJCC Tumor Staging for Cutaneous Squamous Cell Carcinoma and a Proposed Alternative Tumor Staging System

Anokhi Jambusaria-Pahlajani, MD, MSCE; Peter A. Kanetsky, PhD, MPH; Pritesh S. Karia, MPH; Wei-Ting Hwang, PhD; Joel M. Gelfand, MD, MSCE; Faith M. Whalen, MD; Rosalie Elenitsas, MD; Xiaowei Xu, MD, PhD; Chrysalyne D. Schmults, MD, MSCE

Importance: This study proposes an alternative tumor staging system for cutaneous squamous cell carcinoma (CSCC) that more precisely defines the small subset of tumors with a high risk of metastasis and death.

Objective: To identify risk factors for poor outcomes in CSCC and evaluate the 2010 American Joint Committee on Cancer (AJCC) tumor (T) staging system’s ability to stratify occurrence of these outcomes.

Design: Retrospective cohort study.

Setting: A single academic hospital.

Participants: Study participants were identified via a pathology and dermatopathology database search for patients diagnosed as having high-risk CSCC.

Results: Two hundred fifty-six primary high-risk CSCCs were included. Outcomes for AJCC tumor stages T2 to T4 were statistically indistinguishable because only 4 cases (<2% of the cohort) were AJCC stages T3 or T4, which require bone invasion. Subsequently, the bulk of poor outcomes (83% of nodal metastases, 92% of deaths from CSCC) occurred in AJCC stage T2 cases. An alternative tumor staging system was developed with the aim of better stratifying this stage T2 group. Four risk factors were found to be statistically independent prognostic factors for at least 2 outcomes of interest in multivariate modeling. These factors (poor differentiation, perineural invasion, tumor diameter ≥2 cm, invasion beyond subcutaneous fat) were incorporated in the alternative staging with 0 factors indicating T1, 1 factor indicating T2a; 2 to 3 factors, T2b; and 4 factors or bone invasion, T3. Stages T2a and T2b significantly differed in incidences of all 4 end points. Stage T2b tumors comprised only 19% of the cohort but accounted for 72% of nodal metastases and 83% of deaths from CSCC.

Conclusions and Relevance: The proposed alternative tumor staging system offers improved prognostic discrimination via stratification of stage T2 tumors. Validation in other cohorts is needed. Meanwhile, stage T2b tumors are responsible for most poor outcomes and may be a focus of high-risk CSCC study.

Published online January 16, 2013.
doi:10.1001/jamadermatol.2013.2456
Comparison of BWH alternative staging system vs AJCC8

Differences:
• BWH based on number of risk factors including but not limited to size.
• I personally prefer the BWH alternative staging system.

**Table 3. Alternative T Staging System**

<table>
<thead>
<tr>
<th>Alternative T Staging System</th>
<th>Definition</th>
<th>Patients in Study Cohort, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>In situ SCC</td>
<td>Not included</td>
</tr>
<tr>
<td>T1</td>
<td>0 Risk factors</td>
<td>134 (52)</td>
</tr>
<tr>
<td>T2a</td>
<td>1 Risk factor</td>
<td>67 (26)</td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 Risk factors</td>
<td>49 (19)</td>
</tr>
<tr>
<td>T3</td>
<td>4 Risk factors or bone invasion</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
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<tr>
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<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor &lt; 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor ≥ 2 cm and &lt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor ≥ 4 cm in greatest dimension and/or perineural invasion and/or deep invasion and/or minor bone erosion</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor with gross cortical bone/marrow invasion</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor with skull base invasion and/or skull base foramen involvement</td>
</tr>
</tbody>
</table>

High-risk features defining primary tumor as T3:
* Perineural invasion of a nerve lying beneath the dermis, or measuring ≥ 0.1 mm in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.
  † Deep invasion is defined as involvement beyond the subcutaneous fat or > 6 mm.
  ‡ Minor bone erosion.

AJCC-8 indicates eighth edition of the American Joint Committee on Cancer; cSCC, cutaneous squamous cell carcinoma.

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**Notes:**
- Risk factors include tumor diameter 2 cm or greater, poorly differentiated histologic characteristics, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone invasion, which automatically upgrades tumor to alternative stage T3).
A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high risk groups with implications for management

Christian L. Baum, MS, MD,1 Adam C. Wright, MD,2 Juan-Carlos Martinez, MD,3 Christopher J. Arpey, MD,4 Jerry D. Brewer, MD,5 Randall K. Roenigk, MD,5 and Clark C. Otley, MD6
Rochester, Minnesota; Jacksonville, Florida; and Knoxville, Tennessee

Most primary cutaneous squamous cell carcinomas are cured with surgery. A subset, however, may develop local and nodal metastasis that may eventually cause disease-specific death. This subset has been variably termed high-risk. Herein, we review an emerging body of data on the risks of these outcomes and propose an evidence-based risk stratification for low-, intermediate-, and high-risk tumors that takes into account both tumor and patient characteristics. Finally, we discuss a framework for management of these tumors on the basis of data, when available, and our recommendations when data are sparse. (J Am Acad Dermatol. 2017 Sep 13. pii: S0190-9622(17)32160-6. doi: 10.1016/j.jaad.2017.07.031. [Epub ahead of print] Review. PubMed PMID: 28917382.)

Keywords: cutaneous squamous cell carcinoma; immunosuppression; management; radiotherapy; risk stratification; sentinel lymph node biopsy; staging.

Cutaneous squamous cell carcinoma (cSCC) has an incidence of 180,000 to 220,000 tumors per year in the United States1,2 and a metastasis rate of 2% to 5%.3 The prevalence of nodal metastasis (NM) from cSCC in the United States is estimated at 58% to 12.57% cases per year,4 whereas the number of deaths is estimated at 3932 to 8791, with the upper limit of this range representing the number of melanoma-related deaths per year.5 The progression of cSCC often appears to be surpised from local recurrence (LR) to regional or metastatic disease.
New stratification system with management recommendations

### Risk Stratification

<table>
<thead>
<tr>
<th>Risk category and risk factors</th>
<th>Absolute risk for LR</th>
<th>Absolute risk for NM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk cSCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BWH T1</td>
<td>0.6%</td>
<td>0.1%</td>
</tr>
<tr>
<td>BWH T2a</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Intermediate risk cSCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BWH T2a with diameter &gt;2 cm</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>BWH T2a with depth beyond SC fat</td>
<td>14%</td>
<td>—</td>
</tr>
<tr>
<td>High-risk cSCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BWH T2b/T3</td>
<td>21%</td>
<td>67%</td>
</tr>
<tr>
<td>BWH T2a with depth beyond SC fat</td>
<td>—</td>
<td>22%</td>
</tr>
<tr>
<td>BWH T2a AND CLL with Rai stage III or IV</td>
<td>25%</td>
<td>37%</td>
</tr>
</tbody>
</table>

*BRWH, Brigham and Women's Hospital; CLL, chronic lymphocytic leukemia; cSCC, cutaneous squamous cell carcinoma; LR, local recurrence; NM, nodal metastasis; SC, subcutaneous.*

### Follow up recommendations

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Follow-up frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk cSCC</td>
<td>Annually</td>
</tr>
<tr>
<td>Intermediate-risk cSCC</td>
<td>6-12 mo for 2 y, then annually</td>
</tr>
<tr>
<td>High-risk cSCC</td>
<td>2-4 mo for 2 y, then annually; consider repeating imaging yearly for 2 y</td>
</tr>
</tbody>
</table>

*CSHC, Cutaneous squamous cell carcinoma.*
New stratification system with management recommendations  
Staging options and adjuvant therapy recommendations

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<table>
<thead>
<tr>
<th>BWH stage</th>
<th>Disease-specific death rate, %</th>
<th>Local recurrence rate, %</th>
<th>Adjuvant therapy for local recurrence: &quot;safety margin,&quot; immunostains, radiotherapy</th>
<th>Nodal metastasis rate, %</th>
<th>Positive SLNB rate, %</th>
<th>Adjuvant therapy for nodal metastasis: SLNB, imaging, and radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0</td>
<td>0.6</td>
<td>None</td>
<td>0.1</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>T2a</td>
<td>1</td>
<td>5</td>
<td>Consider &quot;safety margin&quot; and/or immunostains if PNI or poor tumor differentiation</td>
<td>3</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>T2b</td>
<td>10</td>
<td>21</td>
<td>Encourage &quot;safety margin&quot; and/or immunostains; consider radiotherapy to primary site especially if PNI or poor tumor differentiation</td>
<td>21</td>
<td>29</td>
<td>Consider imaging; consider SLNB or radiotherapy to nodal basin</td>
</tr>
<tr>
<td>T3</td>
<td>100</td>
<td>67</td>
<td>Encourage &quot;safety margin&quot; excision, immunostaining, and radiotherapy</td>
<td>67</td>
<td>50</td>
<td>Recommend imaging; encourage SLNB or radiotherapy to nodal basin</td>
</tr>
</tbody>
</table>

Data derived from Karia et al,16 Thompson et al,18 and Schmitt et al.26

*BWH*, Brigham and Women's Hospital; *HRcSCC*, high-risk cutaneous squamous cell carcinoma; *PNI*, perineural invasion; *SLNB*, sentinel lymph node biopsy.

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Changes to melanoma staging from AJCC7 to AJCC8
# AJCC 7th Edition
Melanoma of the Skin

## Anatomic Stage/Prognostic Groups

<table>
<thead>
<tr>
<th>Clinical Staging*</th>
<th>Pathologic Staging**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 Tis N0 M0</td>
<td>0 Tis N0 M0</td>
</tr>
<tr>
<td>Stage IA T1a N0 M0</td>
<td>1A T1a N0 M0</td>
</tr>
<tr>
<td>Stage IB T1b N0 M0</td>
<td>1B T1b N0 M0</td>
</tr>
<tr>
<td>Stage IIa T2a N0 M0</td>
<td>IIa T2a N0 M0</td>
</tr>
<tr>
<td>Stage IIa T2b N0 M0</td>
<td>IIa T2b N0 M0</td>
</tr>
<tr>
<td>Stage IIb T3a N0 M0</td>
<td>IIb T3a N0 M0</td>
</tr>
<tr>
<td>Stage IIb T3b N0 M0</td>
<td>IIb T3b N0 M0</td>
</tr>
<tr>
<td>Stage IIc T4a N0 M0</td>
<td>IIc T4a N0 M0</td>
</tr>
<tr>
<td>Stage IIc T4b N0 M0</td>
<td>IIc T4b N0 M0</td>
</tr>
<tr>
<td>Stage III Any T Any N2 N1 M0</td>
<td>III A T1 – 4a N1a M0</td>
</tr>
<tr>
<td></td>
<td>III A T1 – 4a N2a M0</td>
</tr>
<tr>
<td></td>
<td>III B T1 – 4b N1a M0</td>
</tr>
<tr>
<td></td>
<td>III B T1 – 4b N2a M0</td>
</tr>
<tr>
<td></td>
<td>III C T1 – 4b N1b M0</td>
</tr>
<tr>
<td></td>
<td>III C T1 – 4b N2b M0</td>
</tr>
<tr>
<td></td>
<td>Any T N3 M0</td>
</tr>
<tr>
<td>Stage IV Any T Any N M1</td>
<td>IV Any T Any N M1</td>
</tr>
</tbody>
</table>

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

**Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.
AJCC 7th Edition
Melanoma of the Skin

Primary Tumor (T)
- TX: Primary tumor cannot be assessed (e.g., curtagged or severely regressed melanoma)
- T0: No evidence of primary tumor
- Tis: Melanoma in situ
- T1: Melanomas 1.0 mm or less in thickness
- T2: Melanomas 1.01–2.0 mm
- T3: Melanomas 2.01–4.0 mm
- T4: Melanomas more than 4.0 mm

Regional Lymph Nodes (N)
- NX: Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)
- N0: No regional metastases detected
- N1–3: Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1–3 and a–c subcategories assigned as shown below:

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>1 node</td>
<td>a: micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: macrometastasis**</td>
</tr>
<tr>
<td>N2</td>
<td>2–3 nodes</td>
<td>a: micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: macrometastasis**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: in transit met(s)/ satellite(s) without metastatic nodes</td>
</tr>
<tr>
<td>N3</td>
<td>4 or more metastatic nodes, or matted nodes, or in transit met(s)/ satellite(s) with metastatic node(s)</td>
<td></td>
</tr>
</tbody>
</table>

Note: *Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy if performed.*

**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.**

Distant Metastasis (M)
- M0: No detectable evidence of distant metastases
- M1a: Metastases to skin, subcutaneous, or distant lymph nodes
- M1b: Metastases to lung
- M1c: Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

<table>
<thead>
<tr>
<th>M Classification</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal mets</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
Important Changes in Melanoma Staging
AJCC8 vs AJCC7

• Measurement to the nearest 0.1mm (from .01mm).
• Mitoses are no longer part of the T1 category for thin Melanoma <1mm.
• T1 category uses 0.8 mm as a threshold with T1b category defined as 0.8 – 1 mm with or without ulceration.
• “Microscopic” and “macroscopic” detection of tumor in lymph nodes is now referred to as “clinically occult” and “clinically detected.”
• New N1c, N2c, and N3c categories that take into consideration the presence of microsatellites, satellite metastases, and in-transit metastases.
• New M1d for distant metastasis to CNS.
AJCC8
T Category

• pTX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage) (explain):
• pT0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)
• pTis: Melanoma in situ (ie, not an invasive tumor: anatomic level I)
• pT1: Melanoma 1.0 mm or less in thickness, ulceration status unknown or unspecified
  • pT1a: Melanoma <0.8 mm in thickness, no ulceration
  • pT1b: Melanoma <0.8 mm in thickness with ulceration, or melanoma 0.8 to 1.0 mm in thickness with or without ulceration
• pT2: Melanoma >1.0 to 2.0 mm in thickness, ulceration status unknown or unspecified
  • pT2a: Melanoma >1.0 to 2.0 mm in thickness, no ulceration
  • pT2b: Melanoma >1.0 to 2.0 mm in thickness, with ulceration
• pT3: Melanoma >2.0 to 4.0 mm in thickness, ulceration status unknown or unspecified
  • pT3a: Melanoma >2.0 to 4.0 mm in thickness, no ulceration
  • pT3b: Melanoma >2.0 to 4.0 mm in thickness, with ulceration
• pT4: Melanoma >4.0 mm in thickness, ulceration status unknown or unspecified
  • pT4a: Melanoma >4.0 mm in thickness, no ulceration
  • pT4b: Melanoma >4.0 mm in thickness, with ulceration
AJCC8
Changes to pT1 category

• pT1: Melanoma 1.0 mm or less in thickness
• pT1a: Melanoma less than 0.8 mm in thickness, no ulceration
• pT1b: Melanoma less than 0.8 mm in thickness with ulceration or Melanoma 0.8 to 1.0 mm in thickness with or without ulceration
• Difference: Mitoses no longer used for subcategory b. Subcategory b changed to Breslow depth of 0.8mm (0.75-0.84). Ulceration remains unchanged.
How could this affect your practice?

• Based on AJCC7 criteria any invasive melanoma <1mm with a single mitosis merited consideration of discussing a SLNB with a patient.
• This is no longer the case.
• The National Comprehensive Cancer Network (NCCN) advises the following concerning a thin melanoma and SLNB.
• In general, SLNB is not recommended for primary melanomas ≤ 0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging.
• For melanomas 0.76 to 1.0 mm thick, 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 lymphovascular invasion (LVI), are very uncommon in melanomas ≤0.75 mm thick. When present, SLNB may be considered on an individual basis.
AJCC8
N Category

- pN0: No regional lymph node metastasis detected
- pN1: One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
- pN1a: One clinically occult tumor-involved node (ie, detected by sentinel node biopsy) with no in-transit, satellite and/or microsatellite metastases
- pN1b: One clinically detected tumor-involved node with no in-transit, satellite and/or microsatellite metastases
- pN1c: Presence of in-transit, satellite and/or microsatellite metastases with no regional lymph node disease
- pN2: Metastasis in two to three regional nodes or in-transit, satellite, and/or microsatellite with one tumor-involved node
- pN2a: Two to three clinically occult tumor-involved node (ie, detected by sentinel node biopsy) with no in-transit, satellite and/or microsatellite metastases
- pN2b: Two to three tumor-involved nodes at least one of which was clinically detected with no in-transit, satellite and/or microsatellite metastases
- pN2c: One clinically occult or clinically apparent tumor-involved node with presence of in-transit, satellite and/or microsatellite metastases
- pN3: 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 matted nodes without or with in-transit, satellite or microsatellite metastases
- pN3a: Four or more clinically occult tumor-involved nodes (ie, detected by sentinel node biopsy) with no in-transit, satellite and/or microsatellite metastases
- pN3b: Four or more tumor-involved nodes, at least one of which was clinically detected, with no in-transit, satellite and/or microsatellite metastases
- pN3c: Two or more clinically occult or clinically detected tumor-involved nodes with in-transit, satellite and/or microsatellite metastases and/or any number of matted nodes with in-transit, satellite and/or microsatellite metastases
AJCC8
M Category

• pM1: Distant metastasis
• pM1a: Distant metastasis in skin, subcutaneous tissues, soft tissues including muscle and/or nonregional lymph nodes
• pM1b: Distant metastasis to lung with or without M1a sites of disease
• pM1c: Distant metastasis to non-CNS visceral 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
Sentinel Lymph Node Biopsy

• What is the evidence?
Thought process/theory of performing SLNB and if positive complete lymph node dissection

• 1. When melanoma normally progresses/metastasizes it first drains to the regional lymph nodes.
• 2. Pt’s with clinically palpable lymph nodes have a worse prognosis.
• 3. Micrometastasis and SLNB is a strong predictor of the surrounding regional nodes.
• 4. Therefore, by performing a SLNB and if positive complete lymph node dissection tumor burden is reduced which will lead to a better outcome (ie. melanoma specific survival).
• But is point number 4 true?
So what is the evidence in the literature?
Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1)

- Randomized controlled study with 2,001 patients were studied with intermediate depth melanoma (1.2mm to 3.5mm) and deep melanoma (>3.5mm).
- The primary end point to determine the melanoma specific survival in patients that underwent SLNB (and if positive complete dissection) versus patients that did not undergo SLNB with observation of lymph nodes.
- There was a 10 year follow up period. 1,667 were included in the final results.

Conclusion: No improvement in melanoma specific survival (MSS).
- secondary end points including relapse-free survival (RFS) and melanoma-specific survival for the subset of node-positive patients showed improvement (these conclusions are controversial).

“The importance lies in the identification of patients with distant micrometastatic disease that would be candidates for adjuvant therapies.”

MELANOMA
MSLT-1—SNB Is a biomarker, not a therapeutic intervention

Alexander C. J. van Akkooi and Alexander M. M. Eggermont

The final analysis of the MSLT-1 trial confirms that sentinel lymph node biopsy (SNLB) does not improve survival in patients with melanoma >1 mm thickness. Subgroup analyses remain inconclusive. SNLB provides prognostic information for adjuvant therapy decisions, as recent data indicate that adjuvant therapies are effective in patients with positive sentinel nodes with an ulcerated primary.

Changes in the management of cutaneous melanoma, the malignancy with the fastest rising incidence in the world, are occurring at all stages of the disease. The most important prognostic biomarkers for patients with primary stage I or stage II melanoma are Breslow thickness, ulceration, mitotic index and microscopic nodal status, which is detected by sentinel lymph node biopsy (SLNB). The prognosis of patients with microscopic sentinel node involvement is very heterogeneous and correlates closely with tumour load in the sentinel nodes. Depending on tumour load, the prognosis ranges from negative sentinel nodes to palpable macroscopic disease. Sentinel node positivity is considered a biomarker for the likelihood of systemic micrometastatic disease, and can thus provide clinical guidance for adjuvant therapy decisions. The management of sentinel

SLNB status is a biomarker with all the caveats that come with a biomarker

The final 10-year results of the Multicentre Selective Lymphadenectomy Trial-1 (MSLT-1) have been published, shortly after the demise of the much respected and beloved Donald Morton, the principal investigator and pioneer of SLNB. The question addressed in this trial is whether SLNB—and, in the instance of sentinel node positivity, a completion lymph node dissection (CLND)—can improve survival in the patient population with primary melanomas >1 mm thickness, in particular in patients with melanomas of intermediate thickness (1.2–3.5 mm).

The MSLT-1 trial was well designed with a rigorous and elegant melanoma-specific re-calculation for power analysis. Patients were randomly assigned in a 60:40 fashion to SLNB or nodal observation, resulting in 770 patients undergoing SLNB and 500 patients undergoing nodal observation. Both intention-to-treat and per-protocol analyses were conducted, but did not show any differences to each other. The respective 10-year melanoma-specific survival rates were 81.4% in the SLNB group compared with 78.3% in the observation group (HR 0.84, 95% CI 0.64–1.09, P = 0.18). Therefore, we must conclude that SNLB-based management does not improve survival in melanoma. For melanomas >4 mm, any hint of an impact on survival was completely absent (HR 1.12, 95% CI 0.76–1.67, P = 0.56).

Multiple subgroup analyses were performed to identify a beneficial effect for SLNB. The subgroup analysis of patients with a positive sentinel node (10-year MSS 62.1%) in the intervention arm compared with patients with palpable positive lymph-nodes in the observation arm (10-year MSS 41.5%) indicate a significant benefit for those patients staged by SLNB (HR 0.56, P = 0.006). The authors justify this subgroup analysis on the grounds of the obvious rationale to compare those two node-positive groups. However, the biological rationale would be to include the false-negative sentinel node patients who develop a nodal recurrence in this analysis. This analysis showed a reduced effect of SLNB on survival (56.4% versus 41.5%; HR 0.67, 95% CI 0.46–0.97, P = 0.04). Inclusion of prognostically false-positive SNLB cases will further reduce any survival differences.
What about thin Melanoma (<1mm)?
Where did the NCCN recommendation for SLNB come from?

- Small retrospective study of thin melanoma, 6.4% showed a positive SLNB.
- All nodal metastases were found in the group with a Breslow thickness of 0.76-1.0 mm, resulting in 12.8% of positive SNBs in this subgroup ($X(2)$ p = 0.02).
- In AJCC stage 1a, 4.3% had a positive SLNB, in AJCC stage 1b the SLNB positive proportion was 9.4% ($X(2)$ p = 0.38).
- Disease free survival in the node positive group was 100%.
- Breslow thickness only appears to be a practical tool in predicting lymph node involvement.
- Recommendation: SLNB can be omitted in melanoma patients with a Breslow thickness $\leq 0.75$ mm.

SLNB for thin Melanoma Considerations

- SLNB for melanoma 0.75-0.99mm should be considered in patients age ≤45, Breslow depth ≥0.85 mm, mitotic rate >1mm², and/or with ulceration.

- Thin melanoma <0.85mm without high-risk features may be treated with WLE alone.

SLNB for thin Melanoma Considerations

Is age a factor?

It appears so, but maybe not what you would have guessed

- Patients younger than 40 years with category T1b tumors 0.50 to 0.75 mm, who would generally not be recommended for SLNB, had an LN positivity rate of 5.6% (95%CI, 3.3%-8.6%).

- Patients 65 years or older with T1b tumors 0.76 mm or larger, who would generally be recommended for SLNB, had an LN positivity rate of only 3.9% (95%CI, 2.7%-5.3%).
If the SLNB is positive does complete dissection improve survival? No

- Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information.
- Did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases.
Melanoma Prognosis Predictors
• Criteria based on
  • Primary or metastatic
  • Age of patient
  • Location
  • Breslow depth
  • Ulcerated vs non-ulcerated

• Estimates 1, 2, 5, and 10 year survival dates
Prognostic factors beyond TNM staging and positive SLNB

• Gene Expression Profile
What about Gene Expression Profile (GEP)?

• Original poster presentation at 2013 Summer AAD
• A 31-gene expression profile signature was created to help accurately predict metastatic risk in Stage I and II cutaneous melanoma primary tumors that are negative for SLNB.
• Showed improved prognostic accuracy compared to SLNB for overall survival.
• Small study: N=268.
• Test divides melanoma into two categories
  • Class 1 (Low risk)
  • Class 2 (High risk)
Gene Expression Profile

Castle Biosciences’ Non-Invasive Gene Expression Profile Test Shown to Identify Sentinel Lymph Node Negative Melanoma Patients at High Risk of Metastasis Presented at the 72nd Annual Meeting of the American Academy of Dermatology
• In all, 43 (21%) cases had discordant GEP and AJCC classification (using 79% cutoff).

• Eleven of 13 (85%) deaths in that group were predicted as high risk by GEP but low risk by AJCC.

Additional GEP studies

Conclusions

- Results achieved in this independent multi-center performance study confirm the prognostic accuracy of the 31-gene expression profile test.
- GEP offers prognostic information that is independent from and adds to conventional staging.
- A Class 1 result in combination with a negative SLNB leads to 5-year RFS, DMFS and MSS rates of 92%, 94% and 99%, respectively.
- A Class 2 result identified 67% and 83% of the SLN-negative cases that experienced recurrence or death, respectively.
- Given the increased risk for metastasis in Class 2 patients, closer surveillance is warranted per follow-up guidelines, and the GEP offers the opportunity for improved clinical trial design to advance adjuvant treatment in SLN-negative patients.
Additional GEP studies

**CONCLUSION**

- GEP classification is significantly associated with early recurrence in cutaneous melanoma.
- GEP results should be considered in adjuvant treatment trials for early stages of melanoma.
Additional GEP studies

• GEP outcome was a more significant and better predictor of each end point in univariate and multivariate regression analysis, compared with SLNB.

• In combination with SLNB, GEP improved prognostication. For patients with a GEP high-risk outcome and a negative SLNB result, Kaplan-Meier 5-year disease-free, distant metastasis-free, and overall survivals were 35%, 49%, and 54%, respectively.
Are there any helpful serum studies?

- LDH positivity with metastatic melanoma has a worse prognosis.
- Elevated S100-Beta Protein correlates to tumor burden, disease progression and poor outcomes (Stage III and IV). Some have suggested it should replace LDH in AJCC staging criteria.
- Melanoma Inhibitory Activity (MIA).
- Elevated C-Reactive Protein correlates to tumor burden (Stage III and IV).
- Elevated plasma IL-12p40 (common subunit of inflammation- and tumor growth-controlling cytokines IL-12 and IL-23) was associated with melanoma recurrence, a poorer melanoma specific survival and overall survival (Stage I and II only).
Genetics of Melanocytic Neoplasms
Genetics of Melanocytic Nevi

- Acquired melanocytic nevi: vast majority (>80%) show activating hotspot mutations leading to an amino acid exchange at codon 600 of BRAF (BRAFV600E/K)
- Congenital melanocytic nevi: often activating NRAS hotspot mutations (~75%), most commonly affecting codon 61
- Blue nevi: most show activating mutations of GNAQ or GNA11, commonly affecting codon 209

Genetics of Spitzoid Melanocytic Neoplasms

• **BAP1** inactivation occurs in ~5% of Spitz tumors and is predominantly intradermal with enlarged epithelioid nuclei. Spitz tumors with BAP1 loss are associated with a hereditary tumor predisposition syndrome

• **HRAS** mutations occur in ~15% of spitzoid lesions, are often associated with desmoplasia, and are commonly designated as desmoplastic Spitz nevi

• Genomic rearrangements (translocations, kinase fusions) ~50 of various receptor tyrosine kinases, including **ALK, ROS1, NTRK1, RET, and MET, or the serine-threonine kinase BRAF.** The most characteristic features of ALK+ spitz tumors are plexiform, intersecting fascicles of predominantly fusiform melanocytes in the dermis

Genetics of Melanoma

• ~50% characterised by BRAF V600E mutations (BRAF subtype) (intermittently sun-exposed skin)

• Activating mutations in RAS genes account for approximately 25% of melanoma (RAS subtype), and subsume cases with NRAS mutations (~24%), as well as HRAS and KRAS hot-spot mutations (<1%)

• ~10% have NF1 aberrations affecting genes that mildly activate the MAPK/ERK pathway. Occur more frequently in desmoplastic melanoma and in melanoma of chronically sun-exposed skin

• Melanomas lacking BRAF, N/H/KRAS, or NF1 mutations comprise the heterogeneous group of ‘triple wild-type subtype’, which includes KIT mutations (more frequently found in acral and mucosal melanoma), GNAQ/GNA11 mutations (uveal melanoma14,15), or genomic rearrangements involving BRAF or RAF1

Genetics of Melanocytic Neoplasms

Spitzoid Neoplasms

• The spectrum of melanocytic neoplasms with enlarged epithelioid and or spindle cells
• Spitz Nevus (benign)
• Atypical Spitz Tumor (indeterminate behavior and capable of regional lymph node metastasis, but rare systemic spread and normally displays indolent behavior)
• Spitzoid Melanoma (malignant)
The problem: lack of consensus based on histopathology

17 of 30 Spitzoid lesions yielded no clear consensus as to diagnosis; in only one case did six or more pathologists agree on a single category, regardless of clinical outcome.

These results illustrate (1) substantial diagnostic difficulties posed by many Spitz tumors, especially those with atypical features, even among experts, and (2) the lack of objective criteria for their distinction from melanoma and for gauging their malignant potential.

The problem: lack of consensus based on histopathology

- The results support the assertion that there is a lack of consensus in the assessment of atypical Spitz tumors by expert dermatopathologists.

- Importantly, many features used to distinguish conventional melanoma from nevi were not useful in predicting the behavior of atypical Spitz tumors.
Poor histopathologic prognostic factors for AST

- Factors most correlated with adverse behavior:
  - frequent mitotic activity
  - deep mitoses
  - lack of symmetry
  - high-grade cytologic atypia
  - ulceration

What about IHC?  

p16

Not helpful

P16 aberrations more likely in AST and Spitzoid melanoma

Expression of p16 alone does not differentiate between Spitz nevi and Spitzoid melanoma

Background: Spitz nevi and Spitzoid melanomas show overlapping histopathologic features, making the diagnosis challenging. The p16 protein functions as a tumor suppressor, and loss of its expression may be seen in some melanomas.

Methods: We evaluated 18 Spitz nevi and 19 Spitzoid melanomas from the Yale Spindle Neoplasm Repository for p16 expression. A staining intensity score (0-5) was calculated by multiplying a score for the percentage of stained cells (0-3) by a score for staining intensity (0-3).

Results: Staining with p16 was positive in 15/18 (83%) Spitz nevi and 14/19 (74%) Spitzoid melanomas. p16 was similar in 8/14 (57%) Spitz nevi and Spitzoid melanomas. However, 8/14 (57%) Spitz nevi and 11/19 (58%) Spitzoid melanomas had a score of 0-3, all 19 patients with Spitzoid melanomas had a score of 0-3, and 15/19 (79%) patients with Spitzoid melanomas had p16 expression. All 18 patients with Spitz nevi and Spitzoid melanomas had a score of 0-3, and 15/18 (83%) patients with Spitz nevi and Spitzoid melanomas had a score of 0-3.

Conclusions: We found no significant difference in p16 staining in Spitz nevi and Spitzoid melanomas. We conclude that p16 does not appear to be a useful immunohistochemical marker in distinguishing between Spitz nevi and Spitzoid melanomas.


Spitz Tumor
Molecular abnormalities

• Molecular abnormalities identified
  • Gain of 11p (and rarely 7q)
  • Deletion of 6q23 and 3p21
  • Gain of 6p25 and 11q13 (poorer prognosis)
  • Heterozygous deletions of 9p21 (poor prognosis)
  • +BRAF mutation and loss of BAP1 expression
  • HRAS mutation
  • Gene fusions involving receptor tyrosine kinases ALK, ROS1, NTRK1, and RET or the serine threonine kinase BRAF (seen in lesions without HRAS mutation or loss of BAP1)
Poor prognostic indicators

FISH

- Gains in 6p25 or 11q13 associated with aggressive clinical behavior.
- Homozygous 9p21 deletion was highly associated with clinically aggressive behavior (extension beyond the SLN) and death due to disease.
Poor prognostic indicators

**TERT Promoter mutations**

- *TERT*-p mutations identified all 4 (of 56) patients that developed hematogenous metastasis.
- Negative in tumors from patients who had favorable outcomes.

Poor prognostic indicators

Imaging Mass Spectrometry

- Uses a proteomic signature
- Predicted clinical outcome better than histopathology.
- Diagnosis of Spitzoid melanoma by was strongly associated with aggressive clinical behavior.

Is SLN bx a helpful prognostic factor?  
No

- “Our results suggest that having a positive sentinel lymph node biopsy does not seem to be predictive of a poorer outcome for patients. We therefore suggest that no prognostic benefit can be gained from doing a sentinel lymph node biopsy in patients with atypical Spitz tumours.”

- “Our results show that 99% of patients with atypical Spitz tumours and positive sentinel lymph node biopsy did not have disease progression beyond the regional draining lymph nodes over 5 years.”

Problems with interpreting melanocytic neoplasms

• “In brief, morphological diagnosis, whether of birds, fish, plants, or pathological processes in human beings, is 100% subjective.”
  • A. Bernard Ackerman
Subjectivity

• The good news is most dermatopathologist using standard criteria for melanocytic proliferations tend to agree on the same “subjective” diagnosis

• What happens when dermatopathologists using similar criteria come to differing conclusions about whether a melanocytic proliferation is benign or malignant?
Discordance Studies in Melanocytic Proliferations


Discordance Studies in Melanocytic Proliferations

• “Changes in diagnosis occurred in 168 of 478 cases (35%), more frequently when the original diagnostician was a general pathologist.”

• “Patient treatment is affected in more than 10% of cases.”

• “A second opinion from an expert pathologist on problem-prone melanocytic lesions improves patient care, in our series in 27% of cases.”

• “The discordance rate of melanomas and nevi between the referring centers and UCSF was 14.3%.”

• “Thirty-eight percent had two or more discordant interpretations.”

• “However, a high level of disagreement was found in 25% of the cases.”

• “Evaluation of 17 Spitzoid lesions yielded no clear consensus as to diagnosis; in only one case did six or more pathologists agree on a single category, regardless of clinical outcome.”
Best Subjectivity Study to Date

- Intraobserver reproducibility: class I 76.7%, class V 82.6%. Class II 35.2%, class III 59.5%, and class IV 63.2%.

- Interobserver concordance rates of experienced pathologists: Class I 92%, Class II 25%, Class III 40%, Class IV 43%, Class V, 72%.

- It is estimated that at a population level, 82.8% of melanocytic skin biopsy diagnoses would have their diagnosis verified if reviewed by a consensus reference panel of experienced pathologists 8.0% of cases overinterpreted by the initial pathologist and 9.2% underinterpreted.
Discordance Studies in Melanocytic Proliferations

• What do the studies tell us?

• Even among expert dermatopathologists there is a disagreement on the interpretation of a subset of melanocytic lesions as to whether they are benign or malignant.
Tools to aid in a more definitive diagnosis
(less subjective, more interobserver agreement)

• Immunohistochemistry
  • Ki-67/Mart1 dual stain
  • pHH3/Mart1 dual stain
  • HMB-45
  • p16

• Molecular studies
  • FISH
  • CGH
  • GEP
  • NGS
  • TERT-p
  • Imaging mass spectrometry
The Molecular Study
(of melanocytic lesions)

• Comparative genomic hybridization (CGH)
  • Extract DNA from tissue
  • Hybridize to gene chip containing human genome
  • Tests entire genome
  • Analyze for copy number variants

• Comparative genomic hybridization (CGH) was performed on 186 melanocytic tumors (132 melanomas and 54 benign nevi) to determined DNA copy number changes in using.

• Significant differences found between melanomas and nevi.

• 127 (96.2%) of the melanomas had some form of chromosomal aberration, only 7 (13.0%) of the benign nevi cases had aberrations.

• Melanoma
  • gains in chromosomes 6p, 1q, 7p, 7q, 8q, 17q, 11q, and 20q
  • losses in 9p, 9q, 10q, 10p, and 6q.

• All seven cases with aberrations were Spitz nevi, in six of which the aberration was an isolated gain involving the entire short arm of chromosome 11.

• Increases in chromosome 11 was not observed in any of the 132 melanomas.

Florescent *In situ* hybridization (FISH)

- Disease-related mutations are detected as abnormal numbers of copies of genes
- Uses chromogen or fluorescent-labeled DNA probes that are visualized microscopically
- Semi-quantitative measure of the abnormal gene copies in a tissue section
- Standard 4-probe FISH assay targets
  - 6p25 (RREB1)
  - 6q23 (MYB)
  - Cep6 (centromere 6)
  - 11q13 (CCND1)
- Original sensitivity of 86.7% and specificity of 95.4%.
- Additional probes that are helpful
  - 9p21
  - 8q24
  - Up to 94% sensitive and 98% specific

FISH compared to CGH

• The overall concordance in aberrations detected using the two methods was 90%.

• Most discrepancies were due to a minor abnormal clone identified via FISH that was below analytical sensitivity of the aCGH test.

Gene Expression Profile (GEP)

• Unique, clinically validated molecular test that uses qRT-PCR methodology to measure 23 genes.

• Detects expression of genes involved in cell differentiation of tumor cells (PRAME), cell signaling (S100A9 group), as well as the immune response within the tumor microenvironment (multiple genes).

• 91.5% sensitivity and a specificity of 92.5%.

Next Generation Sequencing Panel

• Analyzes millions of DNA segments in parallel, thus allowing to sequence multiple cancer-driving genes in a single assay, with improved sensitivity in mutation detection.

• Provide similar information to aCGH with additional sequence information (ie, TERT promoter mutation).

• Well accepted for detecting single molecular alterations to predict drug sensitivity (ie, BRAF mutation or ALK fusion).

• More studies are needed to determine how the results of this complex testing correspond with clinical outcomes and response to therapy.

Re-excision of Dysplastic Nevi

• Controversial with newer literature suggesting re-excision for only moderate to high grade (moderate to severe atypia) and high grade lesions (severe atypia) and observation for low grade and moderate grade lesions (mild and moderate atypia).

• Standard of care not rigorously defined in literature or by AAD.
What is the evidence?

- Retrospective study
- Excision of biopsy diagnosed mildly or moderately dysplastic nevi is unlikely to result in a clinically significant change in diagnosis, and risk of transformation to melanoma appears very low.
- Moderately-to-severely and severely dysplastic nevi are more often associated with melanoma, and excision may be beneficial for melanoma detection or prevention.

Low rates of clinical recurrence after biopsy of benign to moderately dysplastic melanocytic nevi

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Background: Little is known about the recurrence/persistence rates of dysplastic nevi (DN) after biopsy, and whether incompletely removed DN should be re-excised to prevent recurrence.

Objective: Our purpose was to determine the recurrence rates of previously biopsied DN, and to assess whether biopsy method, margin involvement, congenital features, epidemic location, and degree of dysplasia are associated with recurrence.

Methods: Patients having a history of a “nevus biopsy” at least 2 years earlier were assessed for clinical recurrence. Slides of original lesions were re-reviewed by a dermatopathologist.

Results: A total of 271 nevus biopsy sites were assessed in 115 patients. Of 195 DN with greater than 2 years of follow-up, 7 (3.6%) demonstrated recurrence on clinical examination. In all, 98 DN had a follow-up period of at least 4 years with no clinical recurrence. Of 61 benign nevus biopsy sites examined, clinical recurrence was observed in two (3.3%). For all nevi, recurrence was significantly associated with shave biopsy technique but not with nevus dysplasia or subtype, or the presence of positive margin or congenital features.

Limitations: Most biopsies were performed in a pigmented lesion clinic at a single tertiary referral center. Determinations of nevus recurrence were made on clinical rather than histologic grounds, and follow-up times were limited in some cases.

Conclusion: In this cohort, rates of clinical recurrence after DN and benign nevi were extremely low. Re-excision of nevi, including mildly to moderately DN with a positive margin, may not be necessary.

Key words: biopsy; dysplastic; nevus; recurrence.

What is the evidence?

• Retrospective study
• Rates of clinical recurrence after biopsy of DN (3.6%) and benign nevi (3.3%) were extremely low.
• Re-excision of nevi, including mildly to moderately DN with a positive margin, may not be necessary.
What is the evidence

- Retrospective study
- 3.3% recurrence rate in observation group
- 2.0% of observed group developed melanoma
- 0.6% of reexcised group developed melanoma
- In cases of mild and moderate DN with microscopically positive margins and no concerning clinical residual lesion, observation, rather than reexcision, was a reasonable management option.

What is the evidence?

- Retrospective study
- 765 of 1809 (42.3%) of mildly and moderately DN were reexcised, 495 (64.7%) had positive surgical margins. Melanocytic residuum was present in 18.2% of reexcisional specimens.
- Re-excision resulted in a clinically significant alteration of the diagnosis in only 1 case (0.2%).
- Re-excisioning mildly and moderately DN results in a low histopathological yield and rarely results in a clinically significant change in diagnosis. As such, clinical monitoring of margin-positive lesions may be warranted.
What is the evidence?

- Retrospective study
- During long-term follow no patient developed melanoma at the site of an incompletely or narrowly removed DN
- Routine re-excision of mildly or moderately dysplastic nevi may not be necessary.

What is the evidence?

- Retrospective study
- 134 excisions 34% of DN were excised because of the presence of moderate or severe atypia, personal history of melanoma, or both.
- None of the excised lesions showed evidence of melanoma
- 14% of excised lesions were found to have residual lesions
- 4.4% showed recurrent nevi
What is the evidence?

- Retrospective study
- In 451 patients with SDN, re-excision was performed on 36.6%. 2 melanomas were diagnosed in the re-excision specimens.
- Re-excision of all SDN may not be necessary.

Mildly and moderately DN with clear margins do not need to be reexcised.

Mildly DN biopsied with positive histologic margins without clinical residual pigmentation may be safely observed rather than reexcised.

Observation may be a reasonable option for management of moderately DN with positive histologic margins without clinically apparent residual pigmentation; however, more data is needed to make definitive recommendations in this clinical scenario.
Pigmented Lesion Subcommittee Consensus Statement

• “If a partial or incisional biopsy is performed revealing a DN with positive margins and the remaining clinical pigmentation is not reexcised, the clinician and patient should be aware that the level of histopathologic dysplasia in the remaining lesion may not be identical to that in the biopsy specimen. The biopsy site needs to be monitored for clinical warning signs of melanoma and reexcised if there are unusual clinical changes.”

• “The decision to reexcise DN should be based on both the degree of clinical concern and the histologic findings. If the prebiopsy level of concern for a pigmented lesion is high, one should consider reexcision if the biopsy reveals positive margins, even if the level of histopathologic dysplasia is low. Similarly, if the pathology report reveals severe dysplasia with positive margins, reexcision to achieve a 2- to 5-mm clinical margin is generally recommended.”

• “There may be clinical scenarios in which complete excision or reexcision of a mildly, mildly to moderately, or moderately DN may be warranted, including strong patient preference.”

Re-excison of Dysplastic Nevi

- My opinion (based on my training, experience, and literature) is that some flexibility is necessary due to the inherent subjectivity of melanocytic neoplasms, and the problem that most melanocytic neoplasms are removed by the shave technique and not excisional biopsy (margin of safety).

- “The gray zone of lesions with higher grade that extend to or closely approach a specimen margin is problematic, as one dermatopathologist’s moderately atypical nevus may be another’s melanoma.”

Re-excison of Dysplastic Nevi

• Low grade lesions (mild cytologic atypia)
  • Low risk for recurrence and misdiagnosis of melanoma.
  • No re-excision necessary even with a positive margin.
Re-excison of Dysplastic Nevi

• Moderate grade lesions (moderate cytologic atypia)
  • Low risk for recurrence but an increased risk of misdiagnosis of melanoma.
  • If out in the planes of section examined (shave or punch), and clinically completely removed, likely ok to observe for recurrence.
  • If extends to bx margin and clinically completely removed observation for recurrence is likely ok.
  • If it extends to bx margin and clinically is visible, I would suggest completely removing (shave, punch, ellipse).
  • Will this lead to dermatopathologists upgrading nevi that in the past would be called moderate to now be called moderate to severe to ensure being completely excised?
Re-excison of Dysplastic Nevi

- High grade lesions (severe cytologic atypia)
  - Higher risk for misdiagnosis of Melanoma.
  - Full thickness elliptical excision recommended (with up to 5mm margin of normal skin).
  - If diagnosis is confirmed by FISH, CGH, or GEP I would still do a full thickness elliptical excision.
One other caveat

• I am a big proponent of re-excising any recurrent or changing melanocytic neoplasm regardless of the previous diagnosis.

• You never know when melanoma will arise in a precursor benign or dysplastic nevus (up to 36% of melanomas are a/w a precursor nevus).