Malignant Melanoma

Diagnostic Criteria of Malignant Melanoma

2014-02-25
Opportunistic screening strategy for cutaneous melanoma does not change the incidence of nodular and thick lesions nor reduce mortality: a population-based descriptive study in the European region with the highest incidence.

Bordoni A. et al.
Clinical Diagnosis

A= Asymmetry
B= Irregular Border
C= multiple Colors
D= Diameter (over 5mm) and Dynamic
Sentinel Lymph Node Procedure

**Breslow >1mm**

**Breslow >0.75mm & at least one of the following:**

- Clark Level IV-V
- Ulceration
- High mitotic count
- Young Patient
**Biologically Relevant Melanoma Subtypes**

**Skin with intermittent UV exposure**
- Association with nevi (hereditary component)
- Incidence increasing sharply. Histology: often SSM

**Skin with chronic UV exposure**
- Very slowly growing
- Incidence moderately increasing
- Histology: often melanoma in situ (lentigo maligna)

**Acral Melanoma**
- Early genomic instability with gene amplifications (Cyclin D1)
- Histology: often acrolentiginous melanoma

**Mucosal Melanoma**
- Early genomic instability with gene amplifications (CDK4)
- Histology: often lentiginous growth

**Uveal Melanoma**
- Blue nevi
- Melanoma ex blue nevus

*Pigment Cell Melanoma Res 2011; 24: 879-897*
Size > 6mm
Patient Age

Solar Elastosis
Ugly Duckling Sign
Asymmetry of Silhouette
Mitoses and Cellular Pleomorphism
Asymmetry of Epidermal Alteration
Asymmetry in Distribution of Junctional Nests
Asymmetry of Lateral Borders
Asymmetry of Cytological Details
Asymmetry of Pigment Distribution
Asymmetry of Inflammatory Response
Consumption of Epidermis
Epidermal Ulceration
Poor Delimitation
Large Confluent Nests
Expansile Nodules and Solid Growth
Absence of Maturation
Cellular Atypia
Low specificity and sensitivity of many criteria
Conflicting criteria in the same lesion
Vaguely defined criteria

→ Use criteria in groups
→ Criteria must be sufficient in number and weight
→ Start from differential diagnosis of well-defined histologic entities as Spitz nevus and spitzoid melanoma
### Table 3: Distribution of 13 histological features in a series of 72 conventional malignant melanomas and 73 conventional melanocytic naevi (including Clark’s naevi): sensitivity, specificity and P values with Fischer’s exact test

<table>
<thead>
<tr>
<th>Histological features</th>
<th>No. of cases (melanomas)</th>
<th>No. of controls (naevi)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimension &gt; 6 mm</td>
<td>67</td>
<td>14</td>
<td>93.1</td>
<td>80.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>69</td>
<td>26</td>
<td>95.8</td>
<td>64.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Poor circumscription</td>
<td>55</td>
<td>50</td>
<td>76.4</td>
<td>31.5</td>
<td>0.35</td>
</tr>
<tr>
<td>Irregular and confluent nests</td>
<td>46</td>
<td>18</td>
<td>63.9</td>
<td>75.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Single melanocytes</td>
<td>52</td>
<td>40</td>
<td>72.2</td>
<td>45.2</td>
<td>0.038</td>
</tr>
<tr>
<td>Predominating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of maturation</td>
<td>66</td>
<td>0</td>
<td>91.7</td>
<td>100.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Suprabasal melanocytes</td>
<td>60</td>
<td>4</td>
<td>83.3</td>
<td>94.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asymmetrical melanin</td>
<td>36</td>
<td>1</td>
<td>50.0</td>
<td>98.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Melanin in deep cells</td>
<td>26</td>
<td>7</td>
<td>36.1</td>
<td>90.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cytological atypia</td>
<td>72</td>
<td>10</td>
<td>100.0</td>
<td>86.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mitoses</td>
<td>59</td>
<td>0</td>
<td>81.9</td>
<td>100.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Necrosis</td>
<td>11</td>
<td>0</td>
<td>15.3</td>
<td>100.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dermal lymphocytic infiltrate</td>
<td>70</td>
<td>36</td>
<td>97.2</td>
<td>50.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Sensitivity and specificity of histological criteria in the diagnosis of conventional cutaneous melanoma.
Urso, Carmelo; Saieva, Calogero; Borgognoni, Lorenzo; Tinacci, Galliano; Zini, Enzo

Digital Object Identifier: 10.1097/CMR.0b013e3283043cc0
### Table 4: Distribution of 13 histological features in a series of 20 conventional malignant melanomas ≤ 2 mm and 73 conventional melanocytic naevi (including Clark’s naevi): sensitivity, specificity and $P$ values with Fischer’s exact test

<table>
<thead>
<tr>
<th>Histological features</th>
<th>No. of cases (melanomas)</th>
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<tr>
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<td>80.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>20</td>
<td>26</td>
<td>100.0</td>
<td>64.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Poor circumscription</td>
<td>17</td>
<td>50</td>
<td>85.0</td>
<td>31.5</td>
<td>0.171</td>
</tr>
<tr>
<td>Irregular and confluent nests</td>
<td>17</td>
<td>18</td>
<td>85.0</td>
<td>75.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Single melanocytes predominating</td>
<td>18</td>
<td>40</td>
<td>90.0</td>
<td>45.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Absence of maturation</td>
<td>19</td>
<td>0</td>
<td>95.0</td>
<td>100.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Suprabasal melanocytes</td>
<td>19</td>
<td>4</td>
<td>95.0</td>
<td>94.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asymmetrical melanin</td>
<td>10</td>
<td>1</td>
<td>50.0</td>
<td>98.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Melanin in deep cells</td>
<td>6</td>
<td>7</td>
<td>30.0</td>
<td>90.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Cytological atypia</td>
<td>20</td>
<td>10</td>
<td>100.0</td>
<td>86.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mitoses</td>
<td>12</td>
<td>0</td>
<td>60.0</td>
<td>100.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1</td>
<td>0</td>
<td>5.0</td>
<td>100.0</td>
<td>0.215</td>
</tr>
<tr>
<td>Dermal lymphocytic infiltrate</td>
<td>19</td>
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Mother’s Little Helpers

Valium
Ancillary Techniques

- HMB-45
- Mib1
- p16
- FISH
HMB-45

Benign Nevus

Spitz Nevus

Blue Nevus

Residual Nevus

Malignant Melanoma
HMB-45: No Maturation
HMB-45: Breslow?

Residual Nevus: HMB-45 negative
Benign Nevus: <2%

Spitz Nevus: <10%

Blue Nevus: <2%

Malignant Melanoma: >10%
Irregular distribution. Ki-67 + cells in the deep dermis.

Residual Nevus: negative

Of note:
Only evaluate the dermal component!
Do not count Ki-67 + inflammatory or endothelial cells!
<table>
<thead>
<tr>
<th>Average MIB1 Index</th>
<th>0.5%</th>
<th>2.6%</th>
<th>6.9%</th>
<th>23.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compound nevi</td>
<td>Dysplastic nevi</td>
<td>Spitz nevi</td>
<td>Malignant melanomas</td>
</tr>
<tr>
<td>Average number of MIB1-positive nuclei (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>0.69 ± 0.14†</td>
<td>4.31 ± 1.07†</td>
<td>8.78 ± 3.75†</td>
<td>27.45 ± 2.52</td>
</tr>
<tr>
<td>Middle</td>
<td>0.44 ± 0.11†</td>
<td>2.12 ± 0.61†</td>
<td>7.34 ± 3.41†</td>
<td>23.48 ± 2.54</td>
</tr>
<tr>
<td>Deep</td>
<td>0.26 ± 0.07†</td>
<td>1.06 ± 0.33†</td>
<td>5.42 ± 2.16†</td>
<td>20.63 ± 2.64</td>
</tr>
<tr>
<td>All zones</td>
<td>0.48 ± 0.10†</td>
<td>2.58 ± 0.73†</td>
<td>6.92 ± 2.85†</td>
<td>23.74 ± 2.21</td>
</tr>
<tr>
<td>Maximal number of MIB1-positive nuclei (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>1.30 ± 0.29†</td>
<td>6.30 ± 1.75†</td>
<td>12.19 ± 4.66†</td>
<td>35.52 ± 2.61</td>
</tr>
<tr>
<td>Middle</td>
<td>0.78 ± 0.21†</td>
<td>2.94 ± 0.78†</td>
<td>9.55 ± 3.91†</td>
<td>30.31 ± 2.53</td>
</tr>
<tr>
<td>Deep</td>
<td>0.52 ± 0.14†</td>
<td>1.42 ± 0.38†</td>
<td>7.98 ± 2.27†</td>
<td>29.68 ± 2.92</td>
</tr>
<tr>
<td>All zones</td>
<td>0.90 ± 0.19†</td>
<td>3.93 ± 1.19†</td>
<td>9.93 ± 3.63†</td>
<td>32.16 ± 2.36</td>
</tr>
</tbody>
</table>

* Results were expressed as Mean ± SE.
† Value was significantly different from the corresponding value in malignant melanoma (p < 0.05 by Scheffé method).
Ki-67

Residual Nevus

Residual Nevus

Inflammatory Infiltrate

Melanoma
**Sentinel Node**

**Nodal Nevus:**
- Bland cytology
- Involves nodal capsule or trabeculae
- HMB-45 mostly negative (or very focal)
- Melan A positive
- No mitoses
- Ki-67 negative or <0.2%

**Nodal Metastasis:**
- Atypical melanocytes (may be bland)
- Involves nodal parenchyma
- HMB-45 60-75% positive
- Melan A positive
- Mitoses
- Ki-67 2-82%, most >10%

Intratumoral Heterogeneity of Chromosome 9 Loss and CDKN2A (p16) Protein Expression in a Morphologically Challenging Spitzoid Melanoma

Chr. 9p most commonly lost genomic region in melanomas:
- 10% homozygous loss with complete loss of p16 expression
- 50% heterozygous loss with retained p16 expression
- Methylation of promoter region with loss of p16 expression

**Problems:**
Intratumoral heterogeneity
Small dermal component
Cell size
Melanin pigment
Residual nevus
Melanoma is not a single entity
Polyploidy
Borderline remains borderline
Chromosome 9 not included
Cutoffs?
Time consuming

# FISH Interpretation

## Histology favors benign
- **FISH positive**: may be malignant, recheck histology
- **FISH negative**: supports the histologic diagnosis of a benign nevus

## Histology favors malignant
- **FISH positive**: supports the histologic diagnosis of melanoma
- **FISH negative**: unhelpful, no change of therapy

## Equivocal histology
- **FISH positive**: in favor of melanoma, but may be false positive
- **FISH negative**: unhelpful
A false-negative diagnosis of melanoma was the single most common reason for filing a malpractice claim against a pathologist.

Arch Pathol Lab Med. 2006 May;130(5):617-9.
Medicolegal aspects of error in pathology.
Troxel DB.