Malignant Melanoma: Morphology, Classification, and AJCC staging

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Malignant melanoma
• In situ
• Invasive

Malignant Melanoma In Situ

Invasive Melanoma
• Nontumorigenic:
  Radial Growth Phase
• Tumorigenic:
  Vertical Growth Phase

Radial Growth Phase
• In Situ: confined above basement membrane
• Microinvasive: biologically indolent and common
  [none of 161 patients showed metastases at a mean
  follow-up of 13.7 years]

Radial Growth Phase Characteristics

- Cells present individually or in small nests
- Dermal nests are no larger than epidermal nests
- Dermal mitoses are absent
- Dermal component usually confined to papillary dermis
- Papillary dermis is usually not expanded
- No single group of cells is substantially larger than any other group
- Dermal and epidermal cells are cytologically similar

Vertical Growth Phase
Vertical Growth Phase

- Dermal cells present in one or more expansile nodules
- Dermal nests are larger than nests in epidermis
- Dermal mitoses
- Dermal component often extends into reticular dermis
- Papillary Dermis is often expanded
- Dermal and epidermal cells are cytologically different

Four Common Forms of Malignant Melanoma

Three with a Radial Growth Phase [RGP]
- Superficial Spreading Melanoma 70%
- Acral Lentiginous Melanoma 8%
- Lentigo Maligna Melanoma 5%

One with only Vertical Growth Phase [VGP]
- Nodular Melanoma 15%
Malignant Melanoma: Superficial Spreading Type

Malignant Melanoma: Superficial Spreading Type

Malignant Melanoma: Acral Lentiginous Type

Malignant Melanoma: Acral Lentiginous Type

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Malignant Melanoma: Lentigo Maligna Type

Malignant Melanoma: Nodular Type?
Four Common Forms of Malignant Melanoma

Three with a Radial Growth Phase [RGP]
- Superficial Spreading Melanoma: BRAF/NRAS
- Acral Lentiginous Melanoma: CKIT
- Lentigo Maligna Melanoma: CKIT

Chronic Sun Damage (CSD)

One with only Vertical Growth Phase [VGP]
- Nodular Melanoma: ?BRAF/NRAS

Superficial spreading Malignant melanoma & BRAF mutant melanomas
- Intermittent sun exposure.
- High degree of pagetoid spread
- Prominent nesting
- Large epithelioid cells
- Circumscription
- Minimal solar elastosis.
- Heavy melanin pigmentation
- Epidermal thickening

BRAF-negative melanomas

- Acral lentiginous melanomas.
- Lentigo maligna melanomas (chronic sun damage skin melanomas).
- Mucosal melanomas.

### Mutation | Percentage | Phenotype | New Therapies
--- | --- | --- | ---
BRAF | 50% | Young, Intermittent Sun Exposure | BRAF and MEK inhibitors
NRAS | 15–20% | Intermittent Sun Exposure (weak association) | MEK, PI3K, and AKT inhibitors
CKIT | 10–20% of acral and mucosal melanomas | Acral and mucosal sites, melanomas with lentiginous spread, with marked lesions | CKIT Other tyrosine kinase inhibitors
GNAQ/GNA11 | 59% | Unusual melanomas | Other tyrosine kinase inhibitors

Modified from Scolyer et al, Molecular Oncology (2011)124-136

Unusual Vertical Growth Phase Components

- Balloon Cell
- Rhabdoid
- Myxoid
- Small cell
- *Unusual Phenotypic profile: etc...*
Small cell melanoma

PROGNOSTIC FACTORS
Staging Melanoma

1. Characterize tumor status.
2. Stratify the risk of recurrence and metastasis.
3. Prognostication.

Melanoma staging, as defined by the current AJCC staging system, reflects tumor biology and survival outcomes.

AJCC Cancer Staging Manual 8th Edition

- Gershenwald JE, et al
- Melanoma of the Skin
- Pages 563-85
- American Joint Committee on Cancer 2017

Measuring Breslow Thickness

- Using a calibrated ocular micrometer at a right angle to the adjacent normal skin:
  - The upper point of reference is:
    - The granular layer of the epidermis of the overlying skin.
    - In an ulcerated lesion use the base of the ulcer.
  - The lower reference point is the deepest point of tumor invasion.

AJCC 8th:

Tumor Thickness (Breslow’s thickness)

- Tumor thickness ranges maintained
- T1a subcategorized (threshold 0.8 mm)
- Primary determinant of T staging:
  - T1a: non-ulcerated and < 0.8 mm
  - T1b: 0.8 to 1.0 mm regardless of ulceration, or < 0.8 mm if ulcerated
  - T2: 1.1-2.0 mm
  - T3: 2.1-4.0 mm
  - T4: >4.0 mm
AJCC 8th:
Measuring Breslow Thickness

- For tumors > 1 mm: Recorded to the nearest 0.1 mm (not 0.01 mm)
- Tumors ≤ 1 mm: May be measured to the nearest 0.01 mm but should be reported rounded to the nearest 0.1 mm
  - e.g. melanoma measured in the range of 0.75 to 0.84 mm are reported as 0.8 mm in thickness: T1b

FACTORS ASSOCIATED WITH AGGRESSION IN THIN MELANOMAS

- Early vertical growth phase
- Ulceration
- Level IV
- Mitosis
- Extensive regression

THESE FACTORS SHOULD LEAD TO CONSIDERATION OF SENTINEL LYMPH NODE BIOPSY.
**AJCC 8th: Primary Tumor Mitotic Rate**

- No longer used as a T-category criterion
- Remains a major determinant of prognosis
- Should be assessed and recorded
- May play a role in future prognostic models
- Count dermal mitoses only.
- Number of mitoses per mm2.
- 1mm2 = approx. 4 to 5 HPF’s (40X).

**Primary Tumor Mitotic Rate**

- Count dermal mitoses only.
- Number of mitoses per mm2.
- 1mm2 = approx. 4 to 5 HPF’s (40X).

**Prognostic Factors: Dermal Mitoses (Hot Spot)**

**AJCC 8th: Primary Tumor Ulceration**

- Is the second criterion for determining T category.
- Full-thickness absence of an intact epidermis with associated host reaction above the primary melanoma (based on histopathologic examination)
Primary Tumor Ulceration

Defined as the combination of:
- full-thickness epidermal defect
- evidence of reactive changes (fibrin exudation and neutrophilic debris)
- thinning, effacement, or reactive hyperplasia of the surrounding epidermis without trauma or evidence of a recent surgical procedure


CHARACTERISTICS OF ULCERATED MELANOMA

5 year survival decreased from 80% to 55% in Stage I/II; 53% to 12% in Stage III
- Majority of melanomas > 4.0 mm are ulcerated
- Median ulcer depth is 0.8 mm (range: 0.01- 1.2 mm)
- Width of ulcer > 6 mm. associated with even worse prognosis

Balch CM et al. J Surg Oncol. 2011

AJCC 8th: Microsatellites

Microscopic cutaneous and/or subcutaneous metastasis adjacent or deep to a primary melanoma on pathological examination of the primary tumor site.

AJCC 8th: Microsatellites

- The (metastatic) tumor cells must be discontinuous from the primary tumor.
- The “separating” tissue must not contain fibrosis and/or reactive inflammatory changes.
- There is no minimal size threshold or distance from the primary tumor.
- Multiple levels may be necessary to confirm that the focus is indeed separate from the tumor.
**AJCC 8th: Microsatellites**

- The presence of microsatellites indicates poor prognosis.
- Equivalent to patients with clinical satellites or in-transit metastasis.
- Patients with microsatellites in the primary tumor site are considered Stage III even in the absence of clinically involved lymph nodes, or grossly visible satellite or in-transit metastases.

**Prognostic Factors: Microsatellites**

<table>
<thead>
<tr>
<th>Survival</th>
<th>With satellites</th>
<th>Without satellites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five year survival</td>
<td>36%</td>
<td>89%</td>
</tr>
<tr>
<td>Ten year survival</td>
<td>37%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Reference: Harrist TJ, Rigel DS, Day CL Jr. et al: “Microscopic satellites” are more highly associated with regional lymph node metastases than is primary melanoma thickness. Cancer. 53 (10)2183-7. 1984 May 15


**Microscopic Satellites**

- **Five year survival**
  - with satellites: 36%
  - without satellites: 89%

Reference: Harrist TJ, Rigel DS, Day CL Jr. et al: “Microscopic satellites” are more highly associated with regional lymph node metastases than is primary melanoma thickness. Cancer. 53 (10)2183-7. 1984 May 15

**Ten year survival**

- With satellites: 37%
- Without satellites: 65%


**AJCC 8th: Regional lymph node metastasis**

- **Clinically occult:** Patients with microscopically documented nodal disease (lymphatic mapping and SLN biopsy) and without clinical or radiographic evidence of regional lymph node metastases (7th ed: “microscopic”)
- N1a, N2a, or N3a, based on the number of tumors involved
  - N1c, N2c, or N3c, if microsatellites, satellites, or in-transit metastases are present.
- **Clinically detected:** Patients with clinical or radiographic evidence of regional lymph node metastasis.

**Other important considerations**

- Even focal nodal disease (including isolated tumor cells) can be associated with poorer outcomes.
- Immunohistochemistry is more sensitive for identifying melanoma cells, (HMB-45, Melan A, and MART 1).
Prognosis of SLN Micrometastases

- Location & extent of melanoma SN deposits predictive of
  - Regional non-SN metastases
  - Clinical outcome
- Parameters include
  - % nodal cross sectional area
  - Microanatomical location
  - Tumour penetrative depth
  - Size

Regression

- Area of epidermis without recognizable tumor flanked by obvious melanoma. Deep to the tumor free epidermis, the papillary dermis is also free of tumor and usually widened because of delicate fibrous tissue with increased vascularity and scattered melanophages.

Prognostic Factors: Regression

Thin melanomas with extensive regression >70 to 75% of the surface area are highly associated with metastatic behavior.
Prognostic Factors: Lymphovascular Invasion

Tumor Infiltrating Lymphocytes (TILs)

System for classifying TILs, as developed by Clark, Elder et al.

<table>
<thead>
<tr>
<th>TIL Subclassification</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Absent</td>
<td>No lymphatics directly apposed to tumor cells</td>
</tr>
<tr>
<td>Nonbrisk</td>
<td>Isolated, multifocal and segmental TIL infiltrate in the tumor</td>
</tr>
<tr>
<td>Brisk</td>
<td>Entire base of tumor infiltrated by TILs or TILs diffusely meeting tumor</td>
</tr>
</tbody>
</table>

System for classifying TILs, as developed by Clemente et al.

- **Diffuse**
  - Peripheral
  - Focal in one third of VGP
- **Multifocal**
  - Perivascular
- **Not apposing tumor**
  - Absent in one of the biphasic VGPs
- **Within fibrosis**
  - Absent in one of the biphasic VGPs
Absent Host immune Response
Tumor Infiltrating Lymphocytes

- The study by Azimi et al, of the Melanoma Institute of Australia, emphasized the importance of density of lymphocytes with the best survival in densely and briskly infiltrated tumors.
- 10 years ago, the European Organization for the Research and Treatment of Cancer (EORTC) began a study to examine infiltrates with more detailed attention to distribution and pattern in 1080 cases with 30 year follow-up.

Advancing Edge of the Tumor

- The EORTC study emphasizes the significance of the advancing edge of the tumor (Brisk-Peripheral).
- Four other studies support the significance of the advancing edge:
  1. The pERK and high Ki67 staining of the advancing edge*
  2. The significance of Sox2 expression as evidence of epithelial-mesenchymal transition (EMT) in the advancing edge of malignant melanoma**
  3. Nestin depletion and its relationship to invasion***

TILs and Metastasis: Lymph nodes

- A study in 1996 correlated melanoma survival with brisk infiltrates in draining lymph node deposits compared to non-brisk or absent TILs*
- A recent study of metastatic melanoma in sentinel lymph nodes showed a positive correlation between recurrence and overall survival related to the number of CD3, CD4, and CD8 positive TILs**

Tumor Infiltrating Lymphocytes: Metastatic Melanoma

- The importance of TILs has recently been emphasized in the work of Ribas and colleagues who demonstrated that the presence of clonal CD8+/PD1+/PD-L1+ lymphocytes at the periphery of the tumor showed a remarkable response to Pembrolizumab in metastatic melanoma biopsies, resulting in regression.
- A predictive model based on CD8 expression at the invasive margin was proposed (Tumeh et al).
- This study emphasizes the importance of pathologists’ role in evaluating TILs in primary and metastatic disease.

AJCC 8th Edition: International Melanoma Database

- Only patients treated since 1998
- >49,000 patients (one third from MIA Sydney)
- Patients from Australia, USA, Italy, Greece, Spain
- Chair: Jeff Gershenwald
- Vice Chair: Richard Scoller
- Statistician: Ken Hess
- Expert Panel: 28 other members worldwide
Importance of Histopathological Reporting

- Melanoma pathology report should
  - Document key diagnostic criteria
  - Provide the pathological parameters important for
    - Prognosis
    - Management

Conclusions

- Pathologist should produce a report with sufficient information to allow
  - Evidence-based management plan be established
  - Reliable estimate of prognosis to be made
- Structured report format can facilitate this
- More accurate prediction of prognosis in future
  - Web-based tools
  - Integrating other prog factors & complex data
  - Molecular predictive and prognostic markers

Thank you!