Melanoma

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Melanoma - Outline

• General statistics and development
• Risk factors and patient assessment
• Pathology and prognosis
• Work-up and staging
• Surgical treatment
• Lymph node controversy/sentinel node
• Adjuvant therapy
Melanoma - Data

- Incidence increase fastest
- Mortality increase 2nd only to lung
- 5th most prevalent, incidence 7%/year increase
- 5% skin cancer, 75% skin cancer death
- 1/75 in 2000, 1/1500 in 1935
- 20% H&N, 51% facial, 26% scalp, 16% neck, 9% ear
Development of Nevi

- **Melanocytes**
  - dendritic, neural crest, basal cell layer
  - synthesis of melanin
  - 1/10 to keratinocytes
  - hyperplasia- tanning/lentigines, increased ratio

- **Nevus transformation**
  - poorly understood
  - dendritic- rounded
  - no longer lentiginous pattern- nests
Development of Nevi

• Junctional nevi
  – nests along dermal-epidermal junction

• Compound nevi
  – “invade” dermis, first as nests then cords and single cells

• Dermal nevi
  – junctional component lost
Evolution of Nevi
Melanocyte Hyperplasia
Junctional Nevi
Compound Nevi
Dermal Nevi
Developement of Melanoma

• Questionable
  – benign melanocytes
  – progressive hyperplasia/dysplasia

• Radial growth
  – in epidermis, lines of radii, no expansive nests or nodules
  – slow unrestricted, no metastatic potential
Development of Melanoma

• Vertical growth
  – vertically into dermis
  – expansive and coalescent nests and nodules
  – metastatic potential dermal lymphatic and vascular invasion

• Growth patterns
  – biphasic- slow radial months to years- rapid vertical growth
  – monophasic- rapid vertical growth only
Evolution of Melanoma
Dysplastic Nevi

- border melanocytic nevi and malignant melanoma
- clinical resembles malignant melanoma
- lentiginous compound nevus, prominent bridging across rete ridges
- aberrant in inter-rete spaces
- lamellar fibrosis of papillary dermis, variable lymphoid response
Dysplastic Nevi
Dysplastic Nevi
Types of Melanoma

- Acral lentiginous
- Mucosal melanoma
- Superficial spreading melanoma
- Lentigo maligna melanoma
- Nodular melanoma
Superficial spreading

• most common head and neck, 50%
• 4th to 5th decade
• clinical mixture of brown/tan, pink/white irregular borders, biphasic growth
• irregular nests in epidermis
• underlying lymphoid infiltrate
• enlarged nests and single cells in all epidermal layers
Superficial spreading
Lentigo maligna

- 20% of head and neck
- longest radial growth phase >15 yrs
- elderly sun exposed areas
- clinical dark, irregular ink spot
- contiguous lentiginous proliferation, dyshesive, variable shape, atrophic epidermis, infundibular basal cell layer of hair follicles
Lentigo maligna
Nodular melanoma

- 30% of head and neck
- 5th decade
- aggressive monophasic growth
- sun-exposed and nonexposed areas
- well circumscribed blue/black or nodular with involution in irregular plaque
- downward tumorigenic growth, expand papillary dermis into reticular dermis
Nodular melanoma
Mucosal melanoma

- 8% head and neck
- histologic staging little use
- local control predicts survival
- neck dissection for clinical N+
- XRT for histo N+
- adjuvant interferon alpha 2-b
Risk factors

- Type I or II skin
- atypical and congenital nevi
- actinic skin changes
- history of melanoma
- family history of melanoma, atypical nevi
- history of significant sun exposure (blistering)
Clinical

- early, increase in size, change in shape or color of pigmented lesion
- most common symptom pruritis
- late, tenderness, bleeding, ulceration
- ABCDE’s (asymmetry, border, color, diameter, elevation, surrounding tissue)
- Epiluminescence microscopy (ELM)
Biopsy

- excisional biopsy or saucerization if small
- incisional if large
- **Depth of biopsy must be to sub-Q fat**
- if melanoma a second excision must be performed
Pathology

- diagnosis, tumor thickness in millimeters, margins
- histologic subtype, anatomic site, Clark level, mitotic rate, growth phase, ulceration, regression, lymphocytes, angiolympathic spread, neurotropism, microsatellitosis, precursor lesion
Prognosis

• Breslow (thickness in millimeters) strongest predictor

Fig. 1. Kaplan-Meier survival curves for more than 5000 patients. Patients are stratified into groups based on lesion thickness: less than 0.76 mm (squares); 0.76 to 1.5 mm (plus signs); 1.5 to 4 mm (diamonds); 4 or greater (triangles). The curve for patients with lesions smaller than 0.76 mm is corrected for referral bias; only patients referred before development of recurrent or metastatic disease are included in this subset. (From Slingluff CL Jr, Dodge RK, Stanley WE, et al. Cancer 1992;70:1924.)
## Prognosis

- Clark level less predictive, thin skin useful

| Level of Invasion | Tumor Thickness (mm) | 0.76-1.49 | 1.50-2.49 | 2.50-3.99 | ≥4.0 |
|-------------------|----------------------|-----------|-----------|-----------|
| II                | 92% ± 3%             | (230)     |          |          |      |
|                   | 90% ± 6%             | (48)      |          |          |      |
| III               | 83% ± 7%             | (81)      | 76% ± 6% | 51% ± 7% | 53% ± 9% |
|                   |                      | (145)     | (108)    | (50)     | (17) |
| IV                | 83% ± 9%             | (46)      | 70% ± 7% | 62% ± 5% | 43% ± 6% |
|                   |                      | (192)     | (181)    | (145)    | (92) |
| V                 |                      |           |          |          | 47% ± 15% |
|                   |                      |           |          |          | (20) |
| Total patients    | 357                  | 388       | 295      | 218      | 184   |
Prognosis

- anatomic site, ulceration, gender, histologic type, nodal disease
  - head and neck - scalp worse
  - extremity better trunk
  - women better men
  - lymph node +
    - Breslow thickness, ulceration, # pos. nodes
    - Cohen 10 yr survival # nodes positive
Work-up

• H&P
  – entire skin, inguinal, axillary, supraclavicular, H&N nodes, especially primary drainage
  – brain, bone, GI, constitutional symptoms
  – palpable nodes FNA

• Labs and imaging
  – vary, CXR to routine CT chest and LFT
  – H&N CT neck routine
  – If stage III (regional) or IV (distant) - CT head, chest, abdomen, pelvis
Work-up

• FDG-PET
  – some use in distant disease
  – sensitivity 17% in study with SLN biopsy
Staging-Clark

- **Level I** - in situ at basement membrane
- **Level II** - through basement membrane into papillary dermis
- **Level III** - spread to papillary/reticular interface
- **Level IV** - spread to reticular dermis
- **Level V** - sub-Q invasion
Staging-Breslow

- <0.76 mm - thin
- 0.76 - 1.49 - intermediate
- 1.50 - 4.00 - intermediate
- >4.00 mm - thick
Staging

- CS/PS (I, II, III)
- AJCC- Stage I and II - local, III - regional
  IV - distant
# AJCC Staging

<table>
<thead>
<tr>
<th>Primary tumor (pT)</th>
<th>TNM STAGING OF MELANOMA</th>
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<tbody>
<tr>
<td>pTX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>pTO</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>pTis</td>
<td>Melanoma in situ (atypical melanocytic hyperplasia, severe melanocytic dysplasia), not an invasive lesion (Clark level I)</td>
</tr>
<tr>
<td>pT1</td>
<td>Tumor 0.75 mm or less in thickness and invading the papillary dermis (Clark level II)</td>
</tr>
<tr>
<td>pT2</td>
<td>Tumor more than 0.75 mm but not more than 1.5 mm in thickness and/or invades to the papillary-recticular dermal interface (Clark level III)</td>
</tr>
<tr>
<td>pT3</td>
<td>Tumor more than 1.5 mm but not more than 4 mm in thickness and/or invades the reticular dermis (Clark level IV)</td>
</tr>
<tr>
<td>pT3a</td>
<td>Tumor more than 1.5 mm but not more than 3 mm in thickness</td>
</tr>
<tr>
<td>pT3b</td>
<td>Tumor more than 3 mm but not more than 4 mm in thickness</td>
</tr>
<tr>
<td>pT4</td>
<td>Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue (Clark level V) and/or satellite(s) within 2 cm of the primary tumor</td>
</tr>
<tr>
<td>pT4a</td>
<td>Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue</td>
</tr>
<tr>
<td>pT4b</td>
<td>Satellite(s) within 2 cm of the primary tumor</td>
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</tbody>
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<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>STAGE GROUPING</th>
</tr>
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<tbody>
<tr>
<td>NX</td>
<td>Stage I</td>
</tr>
<tr>
<td>N0</td>
<td>pT1 pT2</td>
</tr>
<tr>
<td>N1</td>
<td>pT3 pT4</td>
</tr>
<tr>
<td>N2</td>
<td>Any pT</td>
</tr>
<tr>
<td>N2a</td>
<td>Any pT</td>
</tr>
<tr>
<td>N2b</td>
<td>Any pT</td>
</tr>
<tr>
<td>N2c</td>
<td>Any N</td>
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</table>

<table>
<thead>
<tr>
<th>Distant metastasis</th>
<th>Stage grouping</th>
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<tbody>
<tr>
<td>MX</td>
<td>Stage I</td>
</tr>
<tr>
<td>M0</td>
<td>Stage I</td>
</tr>
<tr>
<td>M1</td>
<td>Stage I</td>
</tr>
<tr>
<td>M1a</td>
<td>Stage I</td>
</tr>
<tr>
<td>M1b</td>
<td>Stage I</td>
</tr>
<tr>
<td>M2</td>
<td>Stage I</td>
</tr>
</tbody>
</table>

*In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the regional lymph nodes.
Surgical Treatment

• Recommended margins vary

• Rule of thumb
  – <1mm then 1 cm
  – 1-4mm then 2 cm
  – >4mm then 3 cm

• All depths to underlying muscle fascia
Nodal Disease

• CS-II remove regional lymphatics depending on location of primary and presence of distant metastasis
CSI- The Debate

• Balch study- nonrandomized
  – 5 and 10 yr survival intermediate thickness (0.76-3.99) doubled with ELND
  – 5 and 10 yr survival for thin (<0.76) and thick (>4.0) no change with ELND
Balch Study
CSI - The Debate

• Four prospective randomized trials
  – Mayo clinic 3 groups stage I (ELND, delayed, none) no survival difference, increased complications if none, criticized not looking at subgroups to benefit
  – WHO no survival benefit, criticized no subgroups, largely extremity lesions in females
Four prospective randomized trials

- Balch - no overall 5 yr difference, improved in patients, 60 yrs with ELND, 1-2 mm tumors, no ulceration, or both benefited,

- WHO trunk 1.5 mm or more immediate or delayed no significant survival benefit, however was between ELND with occult metastasis and later developers with delayed LND
The Debate - PRO ELND

- sequential dissemination theory
- 30% stage I & II occult disease
- Once palpable 70-80% distant disease, 10 yr survival 15-25%, 5 yr 1-2 nodes micrometastasis 65%
- Balch’s non-randomized study
The Debate - CON ELND

- randomized trials
- 70% no occult disease
- sequential dissemination only theory
Balch’s recommendations

- Three groups
  - local, local plus micro, local plus distant
- Thin - 95% cure rate no benefit to ELND
- Intermediate - 60% regional, 20% distant, benefit ELND
- Thick - >60% regional, >70% distant, no benefit
- Should consider other factors as well
Sentinel Node Theory

- Essence of debate to identify those with occult metastasis
- Morton- first node in group to receive flow from tumor site
SLN - procedure

- isosulfan blue injection at tumor site, follow channels to node
  - studies with ELND 80% sensitivity, specificity 99%

- preoperative lymphscintigraphy, intra-operative radiolymphoscintigraphy, and isosulfan blue dye
  - 69.5% SLN excised blue dye, 83.5% “hot”, combined success 96%, location matters
SLN - Utility

- prognostic indicator - study SLN status, most significant indicator of disease-free and disease-specific survival
- pathology
  - H&E, S-100, HMB-45 limited by # sections
  - reverse transcription with polymerase chain reaction (RT-PCR) - peripheral blood and nodes, (mRNA tyrosinase) 29 ELND 38% path positive, 66% RT-PCR positive
Adjuvant Therapy

- **Radiation**
  - high dose (400-500 cGy) bulky, residual, recurrent, unresectable, ill
  - lentigo maligna 5 yr cure 80% (disfiguring, debilitating location)
  - adjuvant- trend toward improved regional control in N+ dissected necks
  - palliate - especially bony mets
Adjuvant Therapy

- Chemotherapy
  - response 25%, durable control 1%
  - consider in CSI with >1.5 mm, CSII with WLE, TND
  - no survival advantage demonstrated
  - single agent dacarbazine (DTIC)
  - multiple combinations carmustine, cisplatin, DTIC, tamoxifen
Adjuvant Therapy

• **Immunotherapy**
  – unusual behavior, no survival benefit

• **Interferon**
  – ECOG 1684, >4mm or N+, 6.9 yrs high dose IFN-alpha-2b, improved disease-free and overall survival approx. 1 yr. 26% dropout rate toxicity
Summary

• Incidence and deaths on rise
• Survival rates increasing due to detection and thorough treatment
• Depth and nodal status most important prognostic indicators
• ELND still debated
• SLD useful
• Other modalities therapy further research