Melanoma

What We Should Know About

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# Skin Cancer in The U.S.

*(Estimated No. New Patients Per Year)*

- **Melanoma:** > 120,000 *(2013)*
  - Melanoma, invasive: 76,700
  - Melanoma, in situ: 51,000

- **NMSC:** > 1,300,000
  - Basal Cell Carcinoma: 700,000
  - Squam. Cell Carcinoma: 200,000
  - Bowen’s disease/SCC in-situ: 200,000
  - Keratoacanthoma: 200,000

- **Cut. T-Cell Lymphoma:** 2,500

- **Others:** 3,000
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How Big Is The Problem

- The Cost: **5 Billion** dollars/year by 2010
- The Impact: **14%** (Whites) would die (Life Time Risk)
  
  [in Comparison: 94% of lung CA pt would eventually die]
- Incidence of MM: 1/3 of Breast CA; 1/3 of Prostate CA
- Mortality of MM: equal to Breast CA or Prostate CA
### MELANOMA

*Incidence and Mortality, US Minorities, per 10⁶*

<table>
<thead>
<tr>
<th>SEER, 2006-10</th>
<th>Incidence</th>
<th>Case-fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>1.0/100,000</td>
<td>40%</td>
</tr>
<tr>
<td>Asians</td>
<td>1.3/100,000</td>
<td>30%</td>
</tr>
<tr>
<td>American Indians</td>
<td>3.7/100,000</td>
<td>24%</td>
</tr>
<tr>
<td>Hispanic/non-White</td>
<td>4.5/100,000</td>
<td>20%</td>
</tr>
<tr>
<td>Whites</td>
<td>29.2/100,000</td>
<td>12%</td>
</tr>
</tbody>
</table>
# MELANOMA

*Types & Distribution, Chinese Vs. Caucasians*

*(JAMA Derm 2013, 149:272; JAAD 2013, 68:568)*

<table>
<thead>
<tr>
<th>Types of Melanoma</th>
<th>Chinese</th>
<th>Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acral Lentiginous MM</td>
<td>45%</td>
<td>2%</td>
</tr>
<tr>
<td>Nodular MM</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>Mucosal MM</td>
<td>20%</td>
<td>1%</td>
</tr>
<tr>
<td>Superficial Spreading MM</td>
<td>8%</td>
<td>65%</td>
</tr>
<tr>
<td>Lentigo Maligna MM</td>
<td>4%</td>
<td>15%</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>1%</td>
</tr>
</tbody>
</table>
MELANOMA

Stage Distribution, US White, 2003-2009

Dx & Rx
MELANOMA

Risk Factors

- Atypical moles (as marker) + PH/FH of MM
- Atypical moles (as marker) + FH of MM
- Atypical moles without PH/FH of MM
- Giant Congenital nevi: 3%
- Personal history of prior MM: 10x risks
- Family history of MM among 1° relatives: >3x risks
- Number of nevi >100
- The “Sun Factor”: 
  - Intense/intermittent sun exposure;
  - skin color/skin type,
  - hair/eye color,
  - freckling [low capacity of DNA repair]
MELANOMA

Risk Factors - Melanoma Genetics

- Chromosome region: $9p_{21}$
- Defect in Tumor Suppressor Gene*: $p16^{INK4a}/CDKN2A : 60\sim 90\% \text{ would have MM in their life time.}$
- MC1R (melanocortin-1-receptor) gene:
  Variant form of MC1R + UV-induced mutation of $BRAF \rightarrow MM$

*Other def. genes: $BRAF (~80\% \text{ of MM}), CDK4(\text{and } P16), CCND1, P14ARE(\text{and } P53), PTEN/MMAC1 \& N-ras, N-ras alone, H-ras, MEK, MAPK[NF1]$

†In a study, 57\% melanoma families had $CDKN2A$ mutation
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Diagnosis – Started from Moles

- What does a mole look like?
- ABCDE of a mole
The Beauty Marks
The Beauty Marks
The Beauty Marks

Crawford
Mole - *Nevus*

Brown round and raised
Mole - *Nevus*

Brown round and raised
SIGN *(ABCDE)* of a BAD Mole:

- **A** symmetry
- **B** order irregularity
- **C**olor variability
- **D**iameter > 6mm
- **E**levated
MELANOMA

Diagnosis of Melanoma

- Clinical Features
- Dermatoscopy/Episcopy
- Histopathology:
  - H&E, S-100 *(high sens, low spec)*;
  - HMB45 *(75% sens, high spec)*;
  - Melan-A/Mart-1 *(80% sens, high spec)*;
  - Tyrosinase *(T311)*;
  - MIB-1 *(for Ki-67)*
- Confocal Scanning Laser Microscopy:
  - *low sensitivity, limited specificity, high cost*
- Ultrasound, high-resolution
- Computerized Image Analysis System
- Spectrophotometric intracutaneous analysis
MELANOMA

*Dermatoscope*

**Pattern analysis:**
- global features, local features and site related features - *More sensitive and specific than others but need “experience”*

**ABCD algorithm**

**Menzies method:** two neg. and one pos.

**7-point checklist:** ≥ 3 is required for Dx.

**Saida patterns:** for Acral Volar Skin
MELANOMA

Histopathology

H&E

$S-100$ *(high sens, low spec)*

$HMB45$ *(75% sens, high spec)*

$Melan-A/Mart-1$ *(80% sens, high spec)*

$Tyrosinase(T311)$

$MITF$ *(microphthalmia transcription factor)*

$MIB-1$ *(for Ki-67)*

*For children’s melanoma:* reliability of Dx is poor

*For adults:* world-leading experts cannot agree upon the Dx of
  “classic” nevus/melanoma in 65% of cases!
  *(Farmer et al, Hum Pathol. 1996, 27:528)*
MELANOMA

What You Should Do - SURGICAL

**MM Thickness**

- in-situ

**Recommend Margin**

.5 cm
MELANOMA

What You Should Do - SURGICAL

**MM Thickness**
- 0.01 - 2.00 mm

**Recommend Margin**
- 1 cm

Dx & Rx
Appraisal of Evidence

Melanoma 0.3mm

Melanoma 0.59 mm
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What You Should Do - SURGICAL

MM Thickness

- .01 - 2.00 mm

Recommend Margin

- 1 cm

Melanoma 1.15mm  Melanoma 1.65mm
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What You Should Do - SURGICAL

**MM Thickness**
- > 2.00 mm

**Recommend Margin**
- 2 cm

Melanoma 2mm

Melanoma 3mm
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What You Should Do - SURGICAL

**MM Thickness**

- > 2.00 mm

**Recommend Margin**

- 2 cm

Dx & Rx

Appraisal of Evidence

Melanoma 4mm

Melanoma ~ 5 cm
Metastatic Melanoma
Metastatic Melanoma
Metastatic Melanoma
Metastatic Melanoma on skin graft
Metastatic Melanoma along blood vessels and under the graft
MELANOMA

What You should do before it happens

PREVENTION

- Avoid the Sun between 10Am-3PM
- Sunscreen/Sunblocker
- Sun blocker clothings, hat and cap.
- Don’t be a sun-worshiper!
- Stay in the shade
The Grace Lines
Sun-induced Wrinkles!

SUNDOWN VS. SUN DAMAGE
The Grace Lines

Sun-induced Wrinkles!

Sun! Sun! Sun!
The Grace Lines

Sun-induced Wrinkles!

Sun! Sun! Sun!
Age spots/Liver spots -
*Lentigo Simplex or Solaris*
The Best Sunscreens

Helioplex
Active photobarrier complex
Mexoryl SX
MELANOMA

What You Could Do

**MEDICAL [for Advanced MM]**

- IFNα2b s/p Surgery: toxic/costly
- IFNα2b + IL-2 s/p Surgery: toxic/costly
- Chemotherapy:
  - DTIC [dacarbazine] alone,
  - Dartmouth [cisplatin, carmustin, DTIC, tamoxifen],
  - CVD [cisplatin, vinblastine, DTIC]
- Aldara cream (5% imiquimod) for MM in situ
MELANOMA TREATMENT

What’s New Treatment

- Yervoy (ipilimumab): anti-CTLA-4 monoclonal antibody for Stage IV
- Zelboraf (Vemurafenib): anti-BRAF; for Stage IV
- Tafinlar (Dabrafenib): anti-BRAF V-600-E;
- Mekinist (Trametinib): Anti-MEK

*All extend the survival 3-4 months longer*
MELANOMA 2002 Staging System

- Stage 0: in-situ
- Stage IA: ≤1 mm w/o ulcer
- Stage IB: ≤1 mm w ulcer or 1.01~2 mm w/o ulcer
- Stage IIA: 1.01~2 mm w ulcer or 2.01~4 mm w/o ulcer
- Stage IIB: 2.01~4 mm w ulcer or >4 mm w/o ulcer
- Stage IIC: >4 mm w ulcer
- Stage IIIA: 1~3 LNs w “micro”meta, w/o ulcer
- Stage IIIB: 1~3 LNs w “micro”metastasis w ulcer, or
  1~3 LNs w “macro” metastasis, or
  in-transit met(s)/satellite(s) w/o metastatic LNs
- Stage IIIC: 1~3 LNs w “macro” metastasis w ulcer, or
  ≥4 LNs, or matted LNs, or
  in-transit met(s)/satellite(s) w metastatic LNs
- Stage IV: distant meta in (a) skin, SQ, LNs; (b) Lung; and
  (c) other viscera, or distant met(s) w elevated LDH
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Prognosis - Second Melanoma

- Among patients who had melanoma, 10% would have a 2nd in 5-10 yrs.

- A 2nd melanoma will occur in:
  - In the 1st year (60%)
  - At the same anatomic site (50%)

*JAMA 2005; 294: 1647*
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Prognostic Factors
- While MM already developed

- Thickness (and Level) of melanoma
- Ulceration of melanoma
- Age (60 yrs) & Sex (male) of patients
- Site of melanoma (Axial vs. Limbs)

Balch et al. CA Cabcer J Clin 2004, 54:131

- Tumor-infiltrating lymphocytes (TILs)
- Mitotic rate (> 6/mm²)
- Vertical growth phase
- Sentinel lymphnode (DFS, DMFS & OS)
- LDH for Stage IV/Metastasis
- Tumor regression (no inter-observer concordance)
MELANOMA

Prognosis - Bad Markers

- **C-myc oncogen:**
- **TA90-IC** (a 90-kDa glycoprotein immune complex)
- **MIA** (Melanoma-inhibiting activity)
- **S-100 beta & LDH:** makers for metastasis
**MELANOMA**

*Prognosis*

10 Yr Survival based on the thickness of MM

- **<1 mm:** >90%
- **<2 mm:** ~75%
- **<4.0 mm:** ~60%
- **> 4.0 mm:** ~50%

10 Yr Survival based on the No. of LN

- One LN: 55%
- 2–4 LNs: 40%
- >4 LNs: 26%

*In general, 5-yr survival in patients with metastasis is 10%*
**MELANOMA**

*Follow-up*

<table>
<thead>
<tr>
<th>Thickness</th>
<th>F/U</th>
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<tbody>
<tr>
<td>In-Situ</td>
<td>1/y up to 10y</td>
</tr>
<tr>
<td>.01-1.00mm</td>
<td>2/y for the 1st 3y, then 1/y up to 10y</td>
</tr>
<tr>
<td>1.01-2.00mm</td>
<td>3/y for the 1st 3y, then 1/y up to 10y</td>
</tr>
<tr>
<td>2.01-4.00mm</td>
<td>4/y for the 1st 3y, 2/y for the 4th y, then 1/y up to 10y</td>
</tr>
<tr>
<td>&gt;4mm/LN+</td>
<td>4/y for the 1st 3y, 3/y for the 4th y, then 1/y.....</td>
</tr>
<tr>
<td>Metastasis</td>
<td>6/y for the 1st 3y, 4/y for the 4th &amp; 5th y, then 2/y...1/y...</td>
</tr>
</tbody>
</table>

*W/U*  
Hx & PE [each visit]; Sentinel LN for MM ≥1mm; LDH, CXR [every 1-2 yr]; CT, MRI, PCR [depends]