Management of Early Stage Melanoma

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Why should you be interested in melanoma?

- 4% of all skin cancers
- 79% of all skin cancer-related deaths
- >65,000 new cases in the U.S.
- >132,000 worldwide
- Mortality: 9,000 deaths annually [25 per day]
- #1 cause of death in women 20-29
Early Stage Melanoma Treatment Outline

- What is Melanoma?
- Diagnosis (How do we know a patient has melanoma?)
- Staging (How advanced is the melanoma?)
- Treatment (How do we treat early melanoma?)
- Prevention (How do we prevent it from coming back?)
The skin consists of two layers: Epidermis and Dermis
What is Melanoma?

• Abnormal growth of melanocyte cells
• Typically starts in the skin
• Can occur anywhere there are melanocytes
  – Eye
  – Nail beds
  – Mucosal membranes
• Develops in a predictable fashion
  – Superficial growth
  – Deep growth
  – Spread to lymph nodes
  – Spread to other organs
Melanoma develops in a step-wise fashion

**Stage**

<table>
<thead>
<tr>
<th>Benign Nevus</th>
<th>Dysplastic Nevus</th>
<th>Radial-Growth Phase</th>
<th>Vertical-Growth Phase</th>
<th>Metastatic Melanoma</th>
</tr>
</thead>
</table>

**Biologic Events**

| Benign Limited growth | Premalignant Lesions may regress Random stipia | Decreased differentiation Unlimited hyperplasia Cannot grow in soft agar Clonal proliferation | Crosses basement membrane Grows in soft agar Forms tumor | Dissociates from primary tumor Grows at distant sites |

**Molecular Lesions**

- *BRAF* mutation
- *CDKN2A* loss
- *PTEN* loss

- Increased CD1
- E-cadherin loss
- N-cadherin expression
- αVβ3 integrin expression
- MMP-2 expression
- Survivin
- Reduced TRPM1
- Absent TRPM1

Metastasis to lung, liver, or brain
The ABCDEs of Melanoma Diagnosis

Asymmetry
One half of the lesion is shaped differently than the other

Border
The border of the lesion is irregular, blurred, or ragged

Color
Inconsistent pigmentation, with varying shades of brown and black

Diameter
>6 mm, or a progressive change in size

Evolution
History of change in the lesion
Is this melanoma?
Is this Melanoma?
Is this Melanoma?
Which of these is Melanoma?
The Point

• The diagnosis of melanoma can be difficult even for professionals
How do you make a diagnosis?

- **Self Examination**
- **Dermatologist examination** (“Screening”)
  - Mole mapping
  - Digital photography
  - Dermoscopy
- **Biopsy**
  - Removes piece of tissue
  - Requires pathologist
Biopsy

• Histologic confirmation and microstaging
• Excisional
  – Small lesions (<1.5 cm)
• Incisional
  – Large lesions (>1.5 cm)
  – Cannot exclude a diagnosis of melanoma
• Shave biopsy *discouraged*
What is important in the biopsy?

- Tumor thickness
- Ulceration
- Mitotic rate
- Regression
- Lymphocytes
- Vascular invasion
- Other factors?

- Requires a pathologist
What is the “Stage”? 

- Classification system
- Determines outcome (prognosis)
- Allows comparisons between patients
- Determines treatment
- Allows us to evaluate clinical studies
- Is based on the characteristics of each cancer
How do you know the stage?

- Biopsy information about the melanoma
- Examination of lymph nodes
- Blood tests
- X-rays
  - MRI brain
  - CT scan of chest, abdomen, and pelvis
  - PET scan
Melanoma Imaging

- X-ray department
- May require special contrast material
- Takes 20 minutes to 1 hour
- Results read by radiologist
- Best to use same machine for comparisons
Melanoma Stages

- Stage I: Skin only < 2mm
- Stage II: Skin only > 2mm
- Stage III: Lymph nodes
- Stage IV: Other body organs
Stage I Melanoma

- Melanoma in the skin (thin < 2mm)
- 95% curable
- Surgery is the treatment of choice
Stage II Melanoma

- Melanoma in the skin (thicker > 2mm)
- 80% curable
- Treatment is surgery and consider assessment of lymph nodes
How do you treat Stage I and II melanoma?

- Wide local excision
- Minor procedure with quick recovery
- May require skin graft or special techniques
- Side effects few (bleeding, infection)
- Surgical oncologist
## Wide Excision: Prospective Randomized Trials

<table>
<thead>
<tr>
<th>Surgical Trial</th>
<th>n</th>
<th>Tumor Thickness</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Melanoma Program</td>
<td>612</td>
<td>&lt;2 mm</td>
<td>1 vs 3 cm</td>
</tr>
<tr>
<td>U.S. Intergroup Melanoma Trial</td>
<td>486</td>
<td>1 – 4 mm</td>
<td>2 vs 4 cm</td>
</tr>
<tr>
<td>French Cooperative Study</td>
<td>362</td>
<td>&lt;2 mm</td>
<td>2 vs 5 cm</td>
</tr>
<tr>
<td>Swedish Melanoma Study Group</td>
<td>989</td>
<td>0.8 – 2 mm</td>
<td>2 vs 5 cm</td>
</tr>
<tr>
<td>UK Melanoma Study Group</td>
<td>900</td>
<td>&gt; 2 mm</td>
<td>1 vs 3 cm</td>
</tr>
</tbody>
</table>
Treatment of Primary Melanoma

- Wide local excision
  
  In situ       0.5 cm
  Thin (<1mm)   1.0 cm
  Interm. (1-4mm) 2.0 cm
  Thick (>4mm)  2-3 cm
Stage III Melanoma

- Melanoma in nearby lymph nodes
- 50% curable
- Treatment is surgical removal
- Additional therapy may be helpful
How do you treat lymph nodes (Stage III melanoma)?

- If melanoma is thin it is not necessary

- If lymph nodes are enlarged surgical removal is necessary

- Other cases may benefit from sentinel lymph node biopsy
How do we handle the clinically node positive basin?

- Therapeutic lymph node dissection
  - Provides local control and survival benefit
  - Prognosis depends on number of involved lymph nodes
How do we handle the clinically node negative basin?

- Observation
- Elective lymph node dissection
- Sentinel node mapping
Intergroup Melanoma Surgical Program: All Patients

Overall Survival (%)

Regional Node Dissection (n = 379)

Observation (n = 361)

Arm 5-yr Survival
ELND* 86%
Obs 82%

P = 0.25

*Elective regional lymph node dissection

Rationale for Sentinel Node Biopsy

- Enhance accuracy of staging
- Improve regional disease control
- Prevent morbidity in patients who do not benefit from lymph node dissection
- Improve odds of survival?
Prognostic Implications of SLN Status on Disease-Free Survival

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN status</td>
<td>3.41</td>
<td>2.25 – 5.17</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Tumor thickness</td>
<td>1.21</td>
<td>1.11 – 1.31</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Clark level &gt;III</td>
<td>1.91</td>
<td>1.15 – 3.18</td>
<td>.013</td>
</tr>
<tr>
<td>Ulceration</td>
<td>1.73</td>
<td>1.13 – 2.65</td>
<td>.01</td>
</tr>
<tr>
<td>Axial location</td>
<td>1.20</td>
<td>0.76 – 1.87</td>
<td>.43</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.99 – 1.01</td>
<td>.88</td>
</tr>
<tr>
<td>Sex</td>
<td>0.84</td>
<td>0.54 – 1.31</td>
<td>.45</td>
</tr>
</tbody>
</table>

HR = Hazard ratio
CI = Confidence interval

Who should get a SLNB?

• Any melanoma > 1mm
• High risk patients with melanomas < 1mm
What is “High Risk”? 

• Thick primary tumors 
• Male sex 
• Young age 
• Truncal/head & neck location 
• High mitotic rate 
• High vertical growth phase 
• Ulceration 
• Acral lentiginous histology 
• Level of invasion 
• Regression 
• Lymphocytic infiltration

*Leiter et al. JCO 2004
¥Gimotty et al. JCO 2004
What is adjuvant therapy?

- An additional therapy applied in addition to the main treatment
- This may prevent recurrence of the disease
- This may improve the survival from the disease
Is there adjuvant therapy for Stage III melanoma?

- Yes
- Interferon-alpha
- Radiation Therapy
- Clinical Trials
The Interferon Cascade

Interferon-Alpha

Virus-Infected Macrophage

Virus-Infected NK CTL

IL-8

TNF

IL-1

IL-6

Neutrophil

Endothelial Cell

Liver

Hypothalamus

Muscle/Adipose

B-Cell
Rates of Recurrent Melanoma: High-Dose and Low-Dose IFN

- HDI reduced risk of disease recurrence by 26%, $P_2 = 0.00009$
- Trend for increased benefit with high dose, $P = 0.02$

**High Dose Trials**
- ECOG 1684
- Intergroup E1690 (H)
- NCCTG 83-7052
- ECOG 2696
- Subtotal:

**Low Dose Trials**
- WHO 16
- Intergroup E1690 (L)
- UKCCCR AIM-High
- French CGM
- Austrian MMCG
- Scottish MG

$P_2$=2-sided $P$
Melanoma Prevention
Uncontrollable Risk Factors: Genetics

- Skin and Hair Type
  - Freckles
  - Non-melanoma skin cancer
  - Skin color
  - Hair color
  - Many moles

- Genetics
  - Race (Caucasians)
  - Family history
  - Prior melanoma
Melanoma Prevention
Controllable Risk Factors:
Ultraviolet Rays
The UV Index

- <2       Low
- 3-5      Moderate
- 6-7      High
- 8-10     Very High
- >11      Extreme
Controllable Risk Factors:
Environment

1920

2004
Controllable Risk Factors: Environment

- More than 3 blistering sunburns before age 20
- Summer jobs in outdoors more than 3 years in adolescence
- Sunlamps and tanning beds
- Each risk factor increases risk additively
What affects sun exposure?

- Time of day
- Duration of exposure
- Season
- Elevation
- Place on earth
- Surface
- Cloud cover
- Clothing
What is Sunscreen?

• Physical Agents
  – Zinc oxide block both ultraviolet A and B rays

• Chemical Agents
  – Parsol 1789 blocks A rays
  – Eusolex 8020 block A and B rays
Sun Protection Factor (SPF)

- Skin burns in 10 minutes
- SPF 10 delays burns 10-fold or 100 minutes
- SPF 30 delays burns for 300 minutes (5 hours)

- Needs to be re-applied
- No proof of “waterproof sunscreen”
Tips About Sunscreen

- Sunscreen should not be used to prolong recreational sunbathing
- Product should block both UVA and UVB rays
- Use SPF ≥15
- Apply early
  - 30 min before exposure
- Even infants should wear sunscreen
- Reapply often
  - Every 2 hr, more often if sweating or swimming
  - Follow manufacturer’s guidelines

MMWR. 2002;51:17.
Why should you wear sunscreen?

- Reduces aging
- Reduces skin wrinkles
- Reduces incidence of basal cell skin cancer
- Reduces incidence of squamous cell skin cancer
- May reduce incidence of melanoma
Melanoma Prevention
Skin Self-Exam
Body Map
CDC Recommendations for Skin Cancer Prevention

- Avoid direct exposure to sunlight
- Wear a hat and protective clothing
- Wear sunglasses
- Use sunscreen
- Avoid sunlamps, tanning beds
- Perform frequent skin self-examinations
- See your dermatologist
Conclusions

What is Melanoma: A bad disease

Diagnosis: Early and by professional

Staging: Determined by biopsy and sometimes imaging

Treatment:
   Early stage is treated by surgery with excellent results
   Sentinel node biopsy if melanoma might have spread

Prevention of recurrence:
   Protection from uv radiation
   Skin self examination
   Skin surveillance by dermatologist