Melanoma

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• 1 in 55 individuals will be diagnosed with melanoma over their lifetime
• 2008 estimates
  ✓ 62,480 new cases
  ✓ 8,420 deaths


Melanoma: Diagnosis

• Early diagnosis is key to improved outcomes
• ABCDE
  ✓ Asymmetry
  ✓ Border irregularity
  ✓ Color
  ✓ Diameter
  ✓ Evolution

Melanoma: Incidence and Mortality

Asymmetry

• If you could fold the lesion in half, the 2 halves would not match.
<table>
<thead>
<tr>
<th>Border</th>
<th>Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Melanoma often has uneven or blurred borders</td>
<td>• Melanoma is usually greater than 6 mm (the size of a pencil eraser)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Color</th>
<th>Evolution and other suspicious signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Melanoma contains mixed shades of tan, brown and black; it can show traces of red, blue or white</td>
<td>• Changes in appearance, such as spreading pigment into surrounding skin</td>
</tr>
<tr>
<td></td>
<td>• A mole that looks scaly, oozes or bleeds</td>
</tr>
<tr>
<td></td>
<td>• Itching, tenderness or pain in a mole</td>
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<tr>
<td></td>
<td>• Brown or black streak under a nail</td>
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<tr>
<td></td>
<td>• Bruise on the foot that does not heal</td>
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</table>
Melanoma: Diagnosis

- Excisional biopsy (elliptical, punch, or saucerization): 1-3 mm margin, avoid larger margin to permit accurate lymphatic mapping
- Full thickness incisional or punch: attempt to perform in clinically thickest portion of lesion

Melanoma: Survival & Stage

<table>
<thead>
<tr>
<th>Stage Distribution at Diagnosis</th>
<th>5-year Survival rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Localized: 81%</td>
<td>✓ 98.7%</td>
</tr>
<tr>
<td>✓ Regional: 12%</td>
<td>✓ 65.1%</td>
</tr>
<tr>
<td>✓ Metastatic: 4%</td>
<td>✓ 15.5%</td>
</tr>
<tr>
<td>✓ Unstaged: 4%</td>
<td>✓ 77.4%</td>
</tr>
</tbody>
</table>


Work-up of newly diagnosed patient

- Complete history and physical exam, including complete skin exam and nodal exam
- Assessment of risk factors
  ✓ Family history
  ✓ Previous melanoma
  ✓ History of dysplastic nevi/atypical moles
  ✓ Tanning bed, peeling sunburns < 18

Melanoma: Diagnosis

- Avoid shave biopsy: may compromise pathologic diagnosis and complete assessment of thickness
- Path report should include depth of invasion in mm, Clark’s level, presence or absence of ulceration, mitotic count, and status of peripheral and deep margin
Melanoma: Surgical Care

• Excision of the primary lesion
• Nodal assessment

Guidelines for Nodal Assessment

• For tumors ≥ 1 mm, sentinel lymph node biopsy (SLN)
• For tumors < 1 mm, no SLN
• Consider if young age or high risk histology (ulceration, mitotic rate > 1/mm², Clark’s level IV)
• For any positive nodes, complete lymph node dissection

Surgical Margins

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ In situ</td>
<td>✓ 0.5 cm</td>
</tr>
<tr>
<td>✓ ≤ 1 mm</td>
<td>✓ 1 cm</td>
</tr>
<tr>
<td>✓ 1.01 – 2 mm</td>
<td>✓ 1 – 2 cm</td>
</tr>
<tr>
<td>✓ 2.01 – 4 mm</td>
<td>✓ 2 cm</td>
</tr>
<tr>
<td>✓ &gt; 4 mm</td>
<td>✓ 2 cm</td>
</tr>
</tbody>
</table>

History of Nodal Assessment

• Management of regional nodes in melanoma was controversial for many years
• Some favored elective node dissection, but morbid procedure and only 20% of individuals with intermediate thickness lesions have positive nodes
• For many, drainage pattern uncertain
Sentinel lymph node biopsy technique

- Introduced by Morton in 1990
- Dual injection technique
  - Technetium sulfur colloid
  - Lymphazurin/Isosulfan blue dye
- Lymphoscintigraphy
- Small incisions to remove nodes that are hot, blue, or clinically suspicious
Excision Alone

Cases
Locally advanced, clinically node negative
Locally advanced, clinically node negative, sentinel node positive

Follow-up

- Stage 0 (in situ)
  - At least annual skin exam for life
  - Monthly self skin exam

- Stage IA (thin, node neg, no ulceration)
  - H&P with emphasis on skin and nodes every 3-12 months for 5 years, then annually for life
  - Monthly self skin exam

Locally advanced, clinically node negative, sentinel node positive

Follow-up

- Stage IB-IV, NED
  - H&P with emphasis on skin and nodes every 3-6 mos for 2 years, then every 3-12 mos for 2 years, then annually
  - CXR, LDH, CBC annually (optional)
  - CT scans for symptoms, can be considered routinely for follow-up in higher stages
  - Monthly self skin exam and node exam
Surgery for Metastatic Disease

- Palliative procedures may be performed for relief of symptoms
- Predictors of success for metastectomy with curative intent:
  - Site of metastasis (skin, soft tissue, nodes>pulmonary>visceral)
  - Number of metastatic lesions
  - Disease-free interval

JWCI/SMU study:
- 5-yr survival of 29% in patients undergoing complete resection of liver mets
- 26204 patients with melanoma
  - 1750 (7%) with liver mets
    - Resection attempted in 34 (2%)
    - Complete resection only possible in 18
    - 5 patients (0.3%) experienced long-term disease-free survival

Melanoma

Kari Kendra MD, PhD
Assistant Professor of Medicine
The Ohio State University

Case 1

34 y/o female presented with a bleeding mole on her arm.
- Biopsy: nodular melanoma, 4.1 mm deep, with ulceration, mitotic rate 15/10 HPF
- Wide excision: no residual tumor
- Sentinel Node: positive for 2/2 LN
- Axillary LN dissection: 0/20 LN
### Case 1

**What is the next step?**

### Prognostic Indicators

- Thickness (Breslow depth)
- Nodal status
- Ulceration
- Satellite lesions
- In transit lesions

### Case 1

Our 34 y/o female has multiple poor prognostic indicators:

- Depth $> 1.0$ mm
- Lymph nodes positive
- Ulceration present
- Mitotic rate high

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Fifteen-year survival curves comparing localized melanoma (stages I and II), regional metastases (stage III), and distant metastases (stage IV)
### Adjuvant therapy for high risk patients

- **What therapies are available?**
- **How do we identify patients for treatment?**

### Systemic Therapy: Adjuvant

- **Biologic Agents**
  - IFN
  - GM-CSF
- **Chemotherapeutic agents**
  - Cisplatin, Vinblastine, DTIC (CVD)
  - Cisplatin, Vinblastine, DTIC, IL2, IFN (Biochemotherapy)

### Adjuvant Therapy with Interferon Alfa-2b (E1684)

**FDA approved**

- IFN-alpha 2b for adjuvant treatment of melanoma patients with thick primary tumors (> 4 mm) or resected nodal disease
- Positive response data is for node + patients only

### Adjuvant Therapy with Interferon Alfa-2b (E1684)

**Patient population**

- Breslows depth >4mm
- LN+ after ELND
- Clinical LN+ with synchronous primary
- Regional LN recurrence after surgery for primary

Kirkwood et al, JCO 1996;14:7
Adjuvant Therapy with Interferon Alfa-2b (E1684)

Treatment
- **High-dose IFNα-2b**: 20 MU/m² IV, 5 days per week for 4 weeks (induction phase) followed by 10 MU/m² SC TIW for 48 weeks (maintenance)
- **Observation**

<table>
<thead>
<tr>
<th>IFNα-2b</th>
<th>Observation</th>
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<tbody>
<tr>
<td>median DFS</td>
<td>1.7 yr</td>
</tr>
<tr>
<td>OS</td>
<td>3.8 yr</td>
</tr>
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</table>

* benefit greatest in LN+ patients

Adjuvant Therapy with Interferon Alfa-2b (E1684)

- **TOXICITIES:**
  - Constitutional
  - Myelosuppression
  - Hepatotoxicity
  - Neurologic

* 67% of all patients had severe (grade 3) toxicity at some point during treatment

* Supportive care is necessary

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* benefit greatest in LN+ patients
**Adjuvant Therapy with Interferon α-2b (E1690)**

**Treatment:**
1. High-dose IFNα-2b
2. Low dose IFNα-2b
3. Observation

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**Adjuvant Therapy with Interferon α-2b (E1690)**

**RESULTS (642 patients)**

- Relapsed free survival: HD > observation
- Overall survival: HD = LD = observation
- Post relapse survival effected by salvage therapy?

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**Adjuvant Therapy with Interferon α-2b (E1690)**

- **Patient population:**
  - T4cN0
  - T1-4cN0pN1
  - T1-4cN1
  - Recurrent LN+
- * Lymphadenectomy not required

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**Adjuvant Therapy with Interferon α-2b (E1690)**

- **High-dose IFNα-2b:**
  - 20 MU/m² IV, 5 days per week for 4 weeks (induction phase) followed by 10 MU/m² SC TIW for 48 weeks
- **Low dose IFNα-2b:**
  - 3 MU/m² SC TIW - maintenance phase for 2 years
- **Observation**

Kirkwood et al, JCO 2000;18:2444
**Adjuvant Therapy with GM-CSF**

- **Patient population:**
  - Stage III (>4 positive LN or nodal mass > 3 cm)
  - Stage IV
  - All rendered clinically disease-free by surgery before enrollment

- **Treatment:**
  - GM-CSF 125 mcg/m² sc days 1-14 followed by 14 days of rest
  - Duration - 1 year

*Spiller et al, JCO 2000;18:1614*

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**Adjuvant Therapy with GM-CSF**

<table>
<thead>
<tr>
<th></th>
<th>GM-CSF</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>37.5 mos</td>
<td>12.2 mos</td>
</tr>
<tr>
<td>1 yr</td>
<td>89%</td>
<td>45%</td>
</tr>
<tr>
<td>2 yr</td>
<td>64%</td>
<td>15%</td>
</tr>
</tbody>
</table>

* Well tolerated
* Phase 3 data is pending

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**Adjuvant Therapy with Interferon**

Currently *recommended* for:

1. *Ulcerated* primary lesions of any depth with or without a positive sentinel node
2. *Positive* lymph nodes
Case 1

34 y/o female presented with a bleeding mole on her arm.

- **Biopsy**: nodular melanoma, 4.1 mm deep, with ulceration, mitotic rate 15/10 HPF
- **Wide excision**: no residual tumor
- **Sentinel Node**: positive for 2/2 LN
- **Axillary LN dissection**: 0/20 LN

Clinical Trials

- **CALGB 500103**: Phase III Randomized Study of Four Weeks High Dose IFN-alpha 2b in Stage T3-T4 or N1 (microscopic) Melanoma
- **OSU 07033**: A Pilot Study of IFN-alpha-2b Dose Reduction with Dose Optimization

Case 1: Current Options

- IFN (1 yr of therapy)
- Observation
- Clinical trial

Metastatic Disease
Case 2

20 y/o male:
- Presents with SOB, CT: bilateral pulmonary nodules and axillary mass
- Biopsy of axillary mass: melanoma

What is his prognosis?
What treatments are available?

Metastasis

- Most frequent first distant sites include:
  ✓ Skin
  ✓ Subcutaneous tissues
  ✓ Distant lymph nodes

- Surveillance is important

Metastatic Melanoma: Treatment

Localized
- **Surgery** – isolated metastases, limited in size and number, rendered disease free
- **Radiation** – CNS mets, cord compression, pain control

Fifteen-year survival curves comparing localized melanoma (stages I and II), regional metastases (stage III), and distant metastases (stage IV)
Metastatic Melanoma

Surgery:
- Isolated metastases
- Limited in size and number
- Rendered disease free

Prognosis: Metastatic Melanoma

Resection can improve median survival

<table>
<thead>
<tr>
<th>Site of Metastasis</th>
<th>with resection (months)</th>
<th>without resection (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin/sc nodules</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>GI</td>
<td>49</td>
<td>6</td>
</tr>
<tr>
<td>Brain</td>
<td>9</td>
<td>2 - 4</td>
</tr>
</tbody>
</table>

Radiation Therapy

- CNS metastases
- Vertebral metastases with cord compression
- Pain control

Prognosis: Metastatic Melanoma

Single institution data (John Wayne Institute)

(548 patients)
- Site of metastasis
  - Skin/sc nodule (median survival 11 months)
  - GI (median survival 6 months)
  - Liver, bone, or brain (median survival 2 – 4 months)
Case 2

20 y/o male:
- Presents with SOB, CT: bilateral pulmonary nodules and axillary mass
- Biopsy of axillary mass: melanoma

What is his prognosis?
What treatments are available?

Metastatic Melanoma

Systemic therapy:
- *Chemotherapy* – directly target the tumor
- *Immunotherapy* – activates the immune system to recognize and destroy the cancer

Biologic Therapy: HD IL2

- Cycle: 600,000 IU/kg every 8 hours x 14 doses, repeated after 6 – 9 days of rest
  - RR 16%
  - CR 6%, PR 10%
- Median response duration for CR, not reached 6 years after completion of the study
- 28% of responding patients remained disease free

*Atkins et al, JCO 1999*
**Biologic Therapy: IFN α**

- RR 10 – 24%
- Dose:
  - 10 MU/m² TIW
  - 20 MU/m² QD x 5 /week
- Delayed responses observed
  - Initial progression, CR at 12 months

**Case 2**

20 y/o male:
- Presents with SOB, CT: bilateral pulmonary nodules and axillary mass
- Biopsy of axillary mass: melanoma

**Biologic Therapy (IL2, IFN)**

- Potential benefits:
  - Durable responses
- Limitations:
  - Toxicity

(Kirkwood et al, Ann Int Med 1985)
Chemotherapy: Single Agents

<table>
<thead>
<tr>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTIC</td>
</tr>
<tr>
<td>Vindesine</td>
</tr>
<tr>
<td>Vinblastine</td>
</tr>
<tr>
<td>Carmustine</td>
</tr>
<tr>
<td>Taxanes</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>Temozolamide</td>
</tr>
</tbody>
</table>

Best studied:

- **Dacarbazine (DTIC)**
  - RR 10% – 20%
  - Responders survive longer than nonresponders
  - Responses most frequent in skin, subcutaneous tissue, lymph node, and lung metastases

Single Agent: DTIC

RR 20%

- Median duration of response is 5 – 6 months
- CR 5% (phase III trials with 580 pt)
- CR predominantly in sc nodules and lymph node metastases
- Liver, bone, and brain, respond infrequently

Chemotherapy: Single Agents

Single Agent: Temozolamide

- Active metabolite of DTIC
- Phase II studies show similar RR to DTIC
- Oral
- Dose: 150 mg/m²/d, D 1 – 5, q 28 days
- CNS penetration
### Chemotherapy: Combination Regimens

- Dartmouth regimen
  - DTIC, BCNU, cisplatin, tamoxifen
- CVD
  - Cisplatin, vinblastine, dacarbazine
- CVT
  - Cisplatin, vinblastine, temodar
- Taxol/carboplatin

### Chemotherapy:

- Single agents:
  - Dacarbazine
  - Temodar
- Combination agents:
  - CVD
  - Taxol/carboplatin

### Combination chemotherapy: Paclitaxel and carboplatin

N = 31 patients

- 2 previous therapies, including temodar or DTIC
- Taxol 100 mg/m², carboplatin AUC 2
  - On day 1, 8, and 15 of a 28 day cycle
- 26% PR, 19% SD = clinical benefit of 45%
- Median TTP 3 months, median OS of 7.9 months
- In responders median OS = 5.7 months

### Biologic Therapy:

- Interleukin 2
- Interferon
## Case 2

20 y/o male:
- Presents with SOB, CT: bilateral pulmonary nodules and axillary mass
- Biopsy of axillary mass: melanoma

## Clinical Trials

- **OSU 0132**: A Phase 2 Study of Bevacizumab and Interferon-alpha-2b in Metastatic Malignant Melanoma
- **OSU 04105**: A Phase I Study of PS-341 (Bortezomib, Velcade) and Interferon-alpha-2b in Malignant Melanoma

## Case 2

What treatments are available?
- Immunotherapy with Interleukin 2
- Chemotherapy with dacarbazine
- Clinical trial

## Clinical Trials

- **OSU 06006**: A Phase I Study of Bolus High Dose IL2 with Sorafenib in Patients with Unresectable or Metastatic Melanoma
- **OSU 07137**: A Phase I, Open-label, dose escalation study of ANA773 Tosylate, an Oral Prodrug of a Toll-Like Receptor-7 Agonist, in Patients with Advanced Cancer
**Clinical Trials (opening soon)**

- **OSU 08054**: A Randomized, Double-blind, Phase 3 Trial of STA-4783 in Combination with Paclitaxel versus Paclitaxel Alone for Treatment of Chemotherapy-Naïve Subjects with Stage IV Metastatic Melanoma (SYMMETRY)

- **OSU 08059**: A Phase II Trial of Intravenous Administration of Reovirus Serotype 3 - Dearing Strain (Reolysin®) in Patients with Metastatic Melanoma.

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**MODIFY RISK!!!**

- Risk behaviors
  - >3 sunburns
  - Episodic excessive sunlight exposure
  - Long term continuous sunlight exposure
  - UV exposure at tanning salons

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**Early Detection!**

Five-year survival curves comparing localized melanoma (stages I and II), regional metastases (stage III), and distant metastases (stage IV).