Melanoma: Updates in Current Management

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Background

- **Melanoma** is a malignancy of pigment-producing cells located predominantly in the skin, but also eyes, ears, GI tract, mucous membranes
- Accounts for 4% of all skin cancers
- Causes the greatest number of skin cancer-related deaths worldwide
- Early detection is the best means of reducing mortality
American Cancer Society Statistics - 2013

76,690 new cases estimated (45,060 men and 31,630 women)

9,480 melanoma deaths estimated

Incidences Rates by Race
- Whites: 1:50
- Hispanic: 1:200
- Black: 1:1000

Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk skin</td>
<td>1000</td>
</tr>
<tr>
<td>Sun-exposed sites, prior melanoma</td>
<td>500</td>
</tr>
<tr>
<td>Past non-melanoma skin cancer</td>
<td>100</td>
</tr>
<tr>
<td>Melanoma in a first-degree relative</td>
<td>7-17</td>
</tr>
<tr>
<td>New moles</td>
<td>7-14</td>
</tr>
<tr>
<td>Changes in moles</td>
<td>10-51</td>
</tr>
<tr>
<td>Excellent Hispanic and Asian</td>
<td>17-60</td>
</tr>
<tr>
<td>Personal history of melanoma</td>
<td>9</td>
</tr>
<tr>
<td>Other skin cancers</td>
<td>9</td>
</tr>
</tbody>
</table>

Sun Exposure

UVA radiation (320-400 nm) - penetrates deeper into the dermis. Responsible for sun-induced changes in dermal connective tissue and loss of elasticity (wrinkles, signs of aging)

UVB (290-320 nm) - causes sunburn, induction of increased melanin production in skin

UVA and UVB carcinogenic

Also found in tanning beds

Melanoma: Diagnosis

- Early diagnosis is key to improved outcomes
- ABCDE
  - Asymmetry
  - Border irregularity
  - Color
  - Diameter
  - Evolution
### Asymmetry

- If you could fold the lesion in half, the 2 halves would not match.

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Benign Asymmetry" /></td>
<td><img src="image2" alt="Malignant Asymmetry" /></td>
</tr>
</tbody>
</table>

*Photos Courtesy of the Skin Cancer Foundation*

### Border

- Melanoma often has uneven or blurred borders.

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Benign Border" /></td>
<td><img src="image4" alt="Malignant Border" /></td>
</tr>
</tbody>
</table>

*Photos Courtesy of the Skin Cancer Foundation*

### Color

- Melanoma contains mixed shades of tan, brown and black; it can show traces of red, blue or white.

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image5" alt="Benign Color" /></td>
<td><img src="image6" alt="Malignant Color" /></td>
</tr>
</tbody>
</table>

*Photos Courtesy of the Skin Cancer Foundation*

### Diameter

- Melanoma is usually greater than 6 mm (the size of a pencil eraser)

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image7" alt="Benign Diameter" /></td>
<td><img src="image8" alt="Malignant Diameter" /></td>
</tr>
</tbody>
</table>

*Photos Courtesy of the Skin Cancer Foundation*
Evolution and other suspicious signs

- Changes in appearance, such as spreading of pigment into surrounding skin
- A mole that looks scaly, oozes or bleeds
- Itching, tenderness or pain in a mole
- Brown or black streak under a nail
- Bruise on the foot that does not heal

ABCD: asymmetry, borders, color, diameter > 6mm

Which lesion should you biopsy??

Malignant  Benign

Asymmetry
Border
Color
Diameter

Photos Courtesy of the Skin Cancer Foundation

**Histologic Subtypes of Melanoma**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading melanoma</td>
<td>Most common subtype (~70%) • Occurs anywhere on the body (non-chronic sun damaged skin) • Derives its name from histologic evidence of lateral growth for a period of time before vertical growth • High incidence of BRAF, PTEN mutations</td>
</tr>
<tr>
<td>Nodular melanoma</td>
<td>Comprise 15-30% of all melanomas • Discrete nodule with dark black pigmentation is typical clinically • Present with clinical and histologic evidence of vertical growth only</td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>~ 5% of melanomas • Arises from <em>in situ</em> melanoma on sun-damaged skin • Usually head or neck • High incidence of KIT mutations</td>
</tr>
<tr>
<td>Acral lentiginous melanoma</td>
<td></td>
</tr>
</tbody>
</table>

**Nodular melanoma**

- Comprise 15-30% of all melanomas
- Discrete nodule with dark black pigmentation is typical clinically
- Present with clinical and histologic evidence of vertical growth only

**Lentigo maligna melanoma**

- ~ 5% of melanomas
- Arises from *in situ* melanoma on sun-damaged skin
- Usually head or neck
- High incidence of KIT mutations
Acral Lentiginous Melanoma

- ~2-10% of melanomas
- Most common subtype in dark-skinned individuals
- Involves palms, soles, and nail beds
- More aggressive than other types – due to depth at diagnosis
- High incidence of KIT mutations

Mucosal Melanoma - where the “sun don’t shine”

- Rare, but can occur on almost any mucosal surface
- 2x higher in whites vs blacks
- Head/neck (ie nasal, sinus, mouth), female genital tract, anorectal region, urinary tract
- KIT mutations

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

**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

Image courtesy of Dermatology Online Journal © The Regents of the University of California, Davis campus. Individual articles © by their authors. All material is available under the Creative Commons BY-NC-ND license.
Phases of Growth

Radial Growth Phase - tumor cells proliferate at the dermal-epidermal junction, tumor expands radially
  - Lesions are confined to epidermis, may have superficial involvement of dermis

Vertical Growth Phase - lesion invades deeper into dermis, development of palpable nodule
  - *Nodular type of melanoma has only VGP

Prognostic Factors

- Localized disease:
  - Breslow thickness
  - presence of ulceration
  - Mitotic count

- Regional disease:
  - tumor burden (# of positive nodes)
  - Macroscopic vs microscopic positive nodes
  - Extension into extranodal soft-tissue

- Other (worse prognosis):
  mucosal/ocular lesions, male, older age

Survival & Stage

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Stage Distribution</th>
<th>5 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to primary site – stage I, II)</td>
<td>84%</td>
<td>98%</td>
</tr>
<tr>
<td>Regional (spread to regional LN -stage III)</td>
<td>8%</td>
<td>62.1%</td>
</tr>
<tr>
<td>Distant</td>
<td>4%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Unknown (unstaged)</td>
<td>4%</td>
<td>76%</td>
</tr>
</tbody>
</table>

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

Melanoma: surgical care

Wide Excision of the primary lesion

Nodal assessment

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>

Margins of >2cm do not improve rate of local recurrence, disease-free survival, or overall survival, but they do increase the risk of requiring a skin graft or flap closure of the defect.

Elective Versus Therapeutic Lymph Node Dissection

Therapeutic lymph node dissection

“watch and wait”

– Delayed until the time of nodal recurrence
– Avoided LND complications in node-negative patients.
– Strategy assumes there will be no evidence of distant metastatic disease at the time of nodal recurrence – not necessarily
**Elective Versus Therapeutic Lymph Node Dissection**

Elective lymph node dissection  
*“search and destroy”*  
– Performed at the time of WLE.  
– 80% of patients were node-negative.  
– Survival advantage in retrospective studies.

**REGIONAL LYMPH NODES**

Is it better to find nodal disease early?

- **Hypothesis:** Most patients with nodal disease already have distant disease.  
- **Removal of regional nodes** has minimal impact on survival

- **Hypothesis:** Orderly progression of disease from primary site to lymph nodes then distant sites  
- **Removal of lymph nodes** prevents mets, improves survival

**Revolution circa 1994: Sentinel lymph node biopsy**

**Video: Injection and Lymphoscintigraphy**
When do we do Sentinel Lymph Node Biopsy?

- NCCN recommendations:
  - SLN biopsy for patients with melanoma > 1mm regardless of characteristics. Standard of care.
  - For lesions 0.75-1.0 mm, consider SLN biopsy if there are aggressive features such as:
    - Ulceration
    - Clark level IV or V
    - (Satellitosis)
    - (Regression)
    - (Young Age)
    - (High Mitotic Rate)

Some consider SLNbx for these, too

The Case for Sentinel Lymph Node Biopsy

<table>
<thead>
<tr>
<th>Better pathologic examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powerful predictor of survival – risk stratification allows for individualization of Treatment</td>
</tr>
<tr>
<td>Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal Recurrence</td>
</tr>
<tr>
<td>Avoid complications from ELND for node negative patients</td>
</tr>
<tr>
<td>Survival benefit to SLNBx?</td>
</tr>
</tbody>
</table>

Increased cross-sectional area examined with serial sectioning.

1cm x 1.5mm = 39.9 mm³

1cm x 1cm = 94 mm³

1cm x 1.5mm = 134.9 mm³

IHC in Sentinel Lymph Node Biopsy

The Case for Sentinel Lymph Node Biopsy

Better pathologic examination
Powerful predictor of survival – risk stratification allows for individualization of treatment
Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence
Avoid complications from ELND for node negative patients
Survival benefit to SLNBx?

Prognosis Associated with Sentinel Node Status

SLN status is the most powerful independent prognostic factor predicting survival, individualizing treatment

Gershenwald et al, J Clin Oncol 1999

Disease-free survival stratified by SLN status
**Loss of Local Control**


**The Case for Sentinel Lymph Node Biopsy**

Better pathologic examination

Powerful predictor of survival

Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence

Avoid complications from ELND for node negative patients

Survival benefit to SLNBx?

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**Risks vs Benefits: Lymphedema after ELND....lymph nodes were negative**


**The Case for Sentinel Lymph Node Biopsy**

Better pathologic examination

Powerful predictor of survival

Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence

Survival benefit to SLNBx?
Multicenter Selective Lymphadenectomy Trial - I

1-4 mm thickness cutaneous melanoma

- Wide local excision with Lymphatic mapping
- Wide local excision Alone

SLN Positive
- Perform Lymphadenectomy
- Follow for Survival

SLN Negative

Interim Results - MSLT I

2001 patients with melanoma >1.0 mm or Clark IV

1339 patients with melanoma between 1.2 and 3.5 mm

Melanoma Specific Survival

WLE + SLN
- LND for + SLN
  - 65% 7-year survival
  - P = 0.01
  - HR 0.66

WLE Alone
- LND for recurrent dz
  - 52% 7-year survival
  - + 20.3%

Average # nodes: 1.6
Pts. with >4 nodes: 5%
In Transit Recurrence: 8%
7.4% False Negative Rate

ASCO, 2005

Management of Positive Lymph Nodes

- Positive Sentinel Node
- Standard of Care = Completion Lymph Node Dissection
- Palpable Lymph Node in a patient with a primary melanoma, or a history of melanoma
- FNA to get a tissue diagnosis
- If confirmed to be melanoma, staging work-up indicated to rule out distant metastatic disease
- If no distant disease, lymph node dissection

Multicenter Selective Lymphadenectomy Trial - II

- + SLNbx patients randomized to CLND vs nodal observation (with clinical examinations and ultrasound) to determine if CLND improves relapse rate or survival
Adjuvant Therapy for Melanoma

- Risk of recurrence after surgery:
  - 60% for T4N0M0
  - 75% for regional node metastases
- Only proven therapy in the adjuvant setting is IFN-2b, but its use is controversial
  - Intergroup Trials E-1684, 1690, 1694 showed RFS benefit to high dose IFN-2b; OS benefit noted in E-1684 and E1694.
- Consider for patients with resected melanoma at high risk for recurrence (>4mm thick and/or node+)

Local Recurrence

In-Transit Melanoma

- Confirm pathologically with FNA, biopsy
- Treatment options:
  - Excise to clear margins, consider SLN bx
  - Intratumoral BCG or IFN or IL-2 or Rose Bengal, etc...
  - CO2 Laser Ablation
  - Hyperthermic Isolated Limb Perfusion
  - Radiation
  - Clinical Trial
  - Systemic Chemotherapy

Management of In-Transit Disease
Isolated perfusion circuit

Melanoma treated by melphalan ILP

Normal toxicity reaction

Iliac cannulation
Isolated Limb Infusion

Metastatic Disease

- M1a – skin, subcutaneous, distant lymph node basin
- M1b - pulmonary
- M1c – visceral mets OR any distant mets + elevated LDH

Management of Stage IV Melanoma

- Complete and thorough physical examination
- Radiologic Examination to Document Location and Number of Lesions
  - MRI of brain
  - CT of chest/abd/pelvis
  - PET scan (18F-PET)
- Consider Surgical Excision
- Systemic Therapy If Not Resectable
## Survival After Complete Resection of M1a Disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markowitz</td>
<td>LN</td>
<td>1991</td>
<td>72</td>
<td>38%</td>
</tr>
<tr>
<td>Markowitz</td>
<td>Soft Tissue</td>
<td>1991</td>
<td>60</td>
<td>49%</td>
</tr>
<tr>
<td>Gadd</td>
<td>LN</td>
<td>1992</td>
<td>199</td>
<td>11%</td>
</tr>
<tr>
<td>Barth</td>
<td>All Sites</td>
<td>1995</td>
<td>281</td>
<td>14%</td>
</tr>
</tbody>
</table>

Factor most predictive of survival: Disease-Free Interval (>12-18 months)

## Survival After Complete Resection of M1b Disease (Pulmonary)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karp</td>
<td>1990</td>
<td>29</td>
<td>5%</td>
</tr>
<tr>
<td>Gorenstein</td>
<td>1991</td>
<td>59</td>
<td>25%</td>
</tr>
<tr>
<td>Harpole</td>
<td>1992</td>
<td>98</td>
<td>20%</td>
</tr>
<tr>
<td>Tafra</td>
<td>1995</td>
<td>106</td>
<td>27%</td>
</tr>
<tr>
<td>Leo</td>
<td>2000</td>
<td>282</td>
<td>22%</td>
</tr>
</tbody>
</table>

Factors most predictive of survival: Disease-Free Interval and # of metastatic lesions excised

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## Strategies for Systemic Therapy for Metastatic Melanoma

### Traditional Antineoplastic Chemotherapy

**Dacarbazine (DTIC)**
- Overall response rates 10-15%
- CR in up to 3%

**Temozolomide**
- a derivative of DTIC that is absorbed orally and possesses significant CNS penetration
Immunotherapy

We know that human tumors can be immunogenic
- Increased cancers in setting of immunosuppression – transplant recipients, HIV
- Improved survival in many cancers with increased lymphocyte infiltration
- Unknown primary melanoma thought to be due to immune eradication of primary tumor; improved survival stage-for-stage vs known primaries
- Reports of spontaneous resolution of tumors
- Dr. Coley’s toxins

Factors Responsible for the Antitumor Response

Innate Immunity (non-specific)
- Phagocytosis
- Complement fixation
- NK-mediated killing

Adaptive Immunity (specific)
- Cell-Mediated Immunity
- Humoral Immunity

Clinical Translation: Ways to Induce Antitumor Immunity

- Passive Immunotherapy
  - Adoptive transfer of tumor-specific activated T-cells
  - Administration of anti-tumor antibodies
    - Rituxan, Herceptin
- Active Immunotherapy
  - Non-specific
    - Interferon
    - BCG administered in 4 lymph node basins
  - Specific
    - Intrallesional BCG
    - Vaccination

High Dose IL-2

- Nonspecific, active immunotherapy
- Given by IV bolus injection q 8h
- Two cycles of a maximum of 14 doses each, separated by 2 weeks off
- Results in profound lymphocytic infiltrates in tissues, “cytokine cascade”
- Side effects:
  - General: initial fever/chills, hypotension, tachycardia, oliguria (capillary leak)
  - Organ specific autoimmune type reactions: nausea, vomiting, diarrhea, dermatitis, confusion, agitation, myocarditis,
- Overall Clinical Response rate of 15-16% in patients with metastatic melanoma; some long term CRs
**Proof of Principle: Specific Antitumor Immunity**

Mice immunized with an irradiated tumor and then challenged with live cells from the same tumor were able to reject these tumor cells.

Mice challenged with a live but unrelated tumor were not protected and developed tumor outgrowth.

**Protection Study**


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**Tumor Vaccination Strategies**

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous Tumor Cell Vaccine</td>
<td>Patient specific – potential to generate immunity against any antigens, known or unknown, expressed by the patient’s tumor. Possibility of generating humoral and cellular antitumor immunity.</td>
<td>Not widely applicable. Requires adequate tumor tissue for manufacture. Time-consuming and technically challenging manufacturing process. Fluctuations in the panel of antigens expressed on a patient’s tumor render the vaccine ineffective.</td>
</tr>
<tr>
<td>Allogeneic Tumor Cell Vaccine</td>
<td>Widely applicable. Patient’s tumor tissue need not be available. Potentially targets humoral and cellular immunity.</td>
<td>Not patient specific. Response may be dictated by the similarity of patient’s tumor cells to tumor cells comprising the vaccine. Moderately complex/demanding preparation.</td>
</tr>
<tr>
<td>Peptide Vaccine</td>
<td>Acellular technique. Possibility of developing an &quot;off the shelf&quot; vaccine. Potentially widely applicable. Potentially may simplify immunologic monitoring.</td>
<td>Not widely applicable. Important tumor regression peptides may be unknown. Tumor escape is problematic when only one or two peptides are administered as part of a vaccine. HLA restriction. Only generates cellular immunity.</td>
</tr>
<tr>
<td>Dendritic Cell (DC) Vaccine</td>
<td>Utilizes potent antigen-presenting cells that are the final common pathway for generation of antitumor immunity. Can be loaded with tumor antigens through a variety of techniques.</td>
<td>Requires leukapheresis and ex-vivo culture and processing with multiple opportunities for contamination. Vaccine can be variable and patient dependent.</td>
</tr>
</tbody>
</table>

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**Overcoming Tolerance to Self Antigens**

- **CTLA4-Blockade**
  - Cytotoxic T-lymphocyte antigen 4, attenuates and limits emerging T-cell responses, prevents autoimmunity.
  - Neutralizing antibody to CTLA-4 results in unopposed positive co-stimulation of T-cells which overcomes peripheral tolerance to self antigens.
  - Results in autoimmunity to normal self antigens (resulting in side effect profile – (-) itis), and also to "self" tumor antigens.
**Targeted Therapy for Melanoma**

**BRAF Inhibitors**
- Activating mutations in BRAF (V600E) in ~50% of melanoma patients
- Clinical trials showing tumor regression and stabilized disease in >50% of patients with advanced melanoma
- Resistance to BRAF inhibition is a problem, investigating combination with other pathway inhibitors such as MEK, PI3k/akt, mTOR