Surgical Oncology Perspective of Melanoma

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DISCLOSURE

- Nothing to disclose
Discussion Objectives

• Surgical management of localized cutaneous melanoma

• Changes in management in sentinel lymph node positive patients

• Management of regional and recurrent melanoma

• Role of surgery in Stage IV melanoma
Melanoma Epidemiology

- Approximately 87,000 new cases and 10,000 deaths in 2017

- Highest rate of increased incidence in men, second-highest increase in incidence in women.
  - Female lifetime risk → 1 in 34
  - Male lifetime risk → 1 in 53

## Melanoma Epidemiology

### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Percentage</td>
</tr>
<tr>
<td>Prostate</td>
<td>161,360</td>
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<tr>
<td>Lung &amp; bronchus</td>
<td>116,990</td>
<td>14%</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>71,420</td>
<td>9%</td>
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<td>Urinary bladder</td>
<td>60,490</td>
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<tr>
<td>Melanoma of the skin</td>
<td>52,170</td>
<td>6%</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,610</td>
<td>5%</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,080</td>
<td>5%</td>
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<tr>
<td>Leukemia</td>
<td>36,290</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>35,720</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>29,200</td>
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<tr>
<td>All Sites</td>
<td>836,150</td>
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<table>
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<td>Breast</td>
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<tr>
<td>Lung &amp; bronchus</td>
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<td>Colon &amp; rectum</td>
<td>64,010</td>
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<tr>
<td>Uterine corpus</td>
<td>61,380</td>
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<td>Thyroid</td>
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<tr>
<td>Melanoma of the skin</td>
<td>34,940</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>32,160</td>
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<tr>
<td>Leukemia</td>
<td>25,840</td>
<td>3%</td>
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<tr>
<td>Pancreas</td>
<td>25,700</td>
<td>3%</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>23,380</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>852,630</td>
<td>100%</td>
</tr>
</tbody>
</table>

Melanoma Risk Factors

• Male sex

• Age >60

• Tendency to sunburn / sun-sensitive skin

• History of multiple or blistering sunburns
Melanoma Risk Factors

- History of non-melanoma skin cancers
- Immunosuppression
- Family or personal history of melanoma
- Tanning bed use; intermittent intense or chronic sun exposure
**Cutaneous Lesions Suspicious for Melanoma**

**THE ABCDE GUIDE TO POTENTIALLY CANCEROUS MOLES**

**CONSULT A DOCTOR IF ...**

**A = ASYMMETRY**
The two halves of the mole do not match when you draw a line through the middle.

**B = BORDER**
The mole has an uneven border.

**C = COLOR**
The mole has multiple shades of tan, brown or black or has unusual colors such as red, purple or blue.

**D = DIAMETER**
The mole is larger than 6mm in diameter (or the size of a pencil eraser).

**E = EVOLUTION**
The mole has changed in size, shape or color over time.
Biopsy Techniques for Melanoma

- Excisional biopsy with narrow margins
  - Elliptical excision, punch biopsy, saucerization

- Punch biopsy of thickest part of lesion

- Shave biopsy
Melanoma Pathology Report

- Components of minimum pathology reporting:
  - Melanoma
  - Breslow thickness / Clark level
  - Ulceration status
  - Mitotic rate
  - Microsatellitosis
Surgical Treatment of Localized Melanoma

• Wide local excision of the primary melanoma

• Sentinel lymph node dissection
Surgical Treatment of Localized Melanoma

- Diameter of wide excision depends on Breslow thickness

**PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA**

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended Clinical Margins$^2$</th>
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<tr>
<td>In situ$^1$</td>
<td>0.5–1.0 cm</td>
</tr>
<tr>
<td>≤1.0 mm</td>
<td>1.0 cm (category 1)</td>
</tr>
<tr>
<td>1.01–2 mm</td>
<td>1–2 cm (category 1)</td>
</tr>
<tr>
<td>2.01–4 mm</td>
<td>2.0 cm (category 1)</td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>2.0 cm (category 1)</td>
</tr>
</tbody>
</table>

- Margins may be modified to accommodate individual anatomic or functional considerations.
Surgical Treatment of Localized Melanoma

- Diameter of wide excision depends on Breslow thickness
Sentinel Lymph Node Biopsy

- The most important prognostic factor for localized melanoma is the status of the regional lymph nodes

- Sentinel lymph nodes (SLN) → the first lymph nodes in a region to receive lymphatic drainage from the primary tumor site
Sentinel Lymph Node Biopsy

• Discuss and offer sentinel lymph node biopsy to:
  
  – All patients with Breslow thickness ≥1 mm
  
  – Patients with Breslow thickness <0.8 mm with ulceration
  
  – Patients with Breslow thickness 0.8-1 mm ± ulceration
  
  – Patients with Breslow thickness <0.8 mm with other adverse features → mitoses ≥2/mm² or lymphovascular invasion
Sentinel Lymph Node Biopsy

Completion Lymph Node Dissection

- Previously, completion lymph node dissection recommended to all patients with positive SLN

- Rates of additional positive non-SLN are approximately 20%

- Two prospective randomized trials have been conducted to assess the impact of completion dissection on survival and local control
DeCOG-SLT Trial

- Randomized, multicenter, phase 3 trial from 41 German cancer centers.

- Patients with positive SLN randomized to completion lymph node dissection or observation
  - Stratified by primary tumor thickness, ulceration, intended use of interferon

DeCOG-SLT Trial

- Primary endpoint → distant metastasis-free survival
  - Secondary endpoints → recurrence-free survival, overall survival, regional lymph node recurrence, adverse events

- 233 patients in the observation group, 240 in the completion lymph node dissection group.

- Median follow-up 35 months

DeCOG-SLT Trial

- Distant metastasis-free survival at 3 years:
  - Observation group → 77%
  - Completion dissection group → 74.9%

DeCOG-SLT Trial

- Overall survival at 3 years:
  - Observation group → 81.7%
  - Completion dissection group → 81.2%

DeCOG-SLT Trial

- 24% of completion dissection group had adverse event
- Trial criticized for not meeting accrual goal and for being underpowered

Multicenter Selective Lymphadenectomy Trial (MSLT-II)

- International, multicenter, randomized, prospective phase 3 trial

- Patients randomized to completion lymph node dissection or observation with nodal ultrasound

- Primary endpoint → melanoma-specific survival

- Secondary endpoints → disease-free survival (DFS), rates of non-SLN metastasis.

Multicenter Selective Lymphadenectomy Trial (MSLT-II)

- 967 patients in both the completion dissection group and nodal observation group (intention to treat).
- Median follow up 43 months
Melanoma-specific survival at 3 years follow up:
- Nodal observation group → 86±1.2%
- Completion dissection group → 86±1.3%

Multicenter Selective Lymphadenectomy Trial (MSLT-II)

• Disease-free survival at 3 years follow up:
  – Nodal observation group → 63±1.7%
  – Completion dissection group → 68±1.7%

• Regional node disease control at 3 years follow up:
  – Nodal observation group → 77±1.5%
  – Completion dissection group → 92±1%

Multicenter Selective Lymphadenectomy Trial (MSLT-II)

• Adverse events more common in dissection group compared with observation group:
  – Lymphedema in dissection group → 24.1%
  – Lymphedema in observation group → 6.3%

Multicenter Selective Lymphadenectomy Trial (MSLT-II)

- Author conclusions:
  - No significant survival benefit conferred by immediate completion dissection in patients with SLN metastasis
  - Dissection may contribute to more accurate staging and disease control

# Summary of DeCOG-SLT and MSLT-II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Multicenter Selective Lymphadenectomy Trial-II&lt;sup&gt;5&lt;/sup&gt;</th>
<th>German Dermatologic Cooperative Oncology Group&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point (CLND vs OBS)</td>
<td>Melanoma-specific survival (86% vs 86%; <em>P</em> = .42)</td>
<td>Distant metastasis-free survival (74.9% vs 77%; <em>P</em> = .87)</td>
</tr>
<tr>
<td>Overall survival (CLND vs OBS)</td>
<td>Not reported</td>
<td>81.2% vs 81.7%; <em>P</em> = .87</td>
</tr>
<tr>
<td>Median follow-up, mo</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td>Patient cohort characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSN positive, %</td>
<td>11.5</td>
<td>24</td>
</tr>
<tr>
<td>SLN micrometastasis ≤1 mm, %</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Patients declining randomization, %</td>
<td>After randomization, 3% in OBS arm and 14% in CLND arm declined assignment</td>
<td>After randomization, 1.2% in OBS arm and 14.9% in CLND arm declined assignment; 61% of screened (eligible) patients declined to be randomized</td>
</tr>
<tr>
<td>Regional nodal basin control (CLND vs OBS)</td>
<td>3-y Nodal basin control rate (92% vs 77%; <em>P</em> &lt; .001)</td>
<td>8% vs 15% Regional recurrence rate</td>
</tr>
<tr>
<td>Lymphedema (CLND vs OBS)</td>
<td>24.1% vs 6.3%</td>
<td>8% in CLND group (grade 3-4 adverse event)</td>
</tr>
<tr>
<td>Trial exclusions</td>
<td>Age &gt;75 y</td>
<td>Age &gt;75 y</td>
</tr>
</tbody>
</table>

Abbreviations: CLND, completion lymphadenectomy; NSN, non-sentinel node; OBS, observation; SLN, sentinel lymph node.

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Future Directions for Node-Positive Patients

• For SLN-positive patients, discuss and offer completion lymph node dissection, in context of
  – Probability of positive non-SLN
  – Prognostic information of positive non-SLN
  – Morbidity of the procedure
  – Ability of the patient and/or institution to undergo surveillance

• For clinically-positive patients without evidence of metastatic disease after staging, completion/therapeutic lymph node dissection should be performed
Recurrent Melanoma – Satellite, In-Transit

- Biopsy must be performed to confirm recurrence.
- Biopsy will not have *in situ* component or radial growth phase, lacks epidermal component.

Recurrent Melanoma – Satellite, In-Transit

- Baseline staging recommended with PET/CT and brain MRI
- In-transit disease is at least pathologic Stage IIIB
Treatment of In-Transit Disease

• Options for treatment:
  – Local therapy
  – Regional therapy
  – Systemic therapy

Treatment of In-Transit Disease

- For limited resectable in-transit disease, surgical excision to clear margins ± SLNB is recommended

- SLNB identification is reliable and may have prognostic significance
  - 30 patients with recurrence, all SLN identified
  - Median DFS with negative SLN 36 months
  - Median DFS with positive SLN 16 months

Treatment of In-Transit Disease

• Options for unresectable Stage III in-transit melanoma:
  – T-VEC injection
  – IL-2 injection
  – Other injections and local therapies
  – Regional therapy with limb perfusion or infusion
Talimogene Laherparepvec (T-VEC)

- The first FDA-approved oncolytic viral therapy

- A modified herpes simplex 1 virus that causes tumor cell death and local delivery of GM-CSF
  - Two viral genes deleted allowing for selective replication in tumor cells
  - Human GM-CSF gene inserted
Talimogene Laherparepvec (T-VEC)

1. Inside a healthy cell, the virus (●) is unable to replicate, leaving the cell unharmed.

2. Inside a cancer cell, the virus replicates and secretes GM-CSF (●) until the cell lyses, releasing more viruses, GM-CSF, and antigens (●●).

3. GM-CSF attracts dendritic cells to the site, which process and present the antigens to T cells. The T cells are now "programmed" to identify and destroy cancer cells throughout the body.

Talimogene lahерparepvec: proposed mechanism of action for systemic immunological effect.

T cells destroy cancer cells throughout the body, including those not directly injected with the virus.
OPTiM Trial

• Phase 3 multicenter prospective trial

• Inclusion criteria:
  – Stage IIIB to IV melanoma
  – Not surgically resectable
  – At least one (or more) cutaneous, subcutaneous, or nodal lesion ≥10 mm

OPTiM Trial

• Primary endpoint durable response rate (DRR)
  – rate of complete response (CR) plus partial response (PR)
    lasting ≥ 6 months continuously and beginning within the first 12 months

• T-VEC given once to seroconvert, then three weeks later, then every two weeks
OPTiM Trial Results

- DRR significantly higher in T-VEC arm compared with GM-CSF arm, 16.3% vs 2.1%, P<0.001

- ORR significantly higher in T-VEC arm compared with GM-CSF arm, 26.4% vs 5.7%, P<0.001
OPTiM Trial Results

- OS not significantly increased in the T-VEC group

OPTiM Trial Results

- OS benefit seen in earlier-stage disease, Stage IIIB, IIIC, IVM1a

OPTiM Trial Results

• Abscopal effect seen: 15% of uninjected visceral lesions has ≥50% decrease in size

• Significantly higher grade ≥3 AE in T-VEC arm, 36% vs 21%, P=0.003

• Common AE pyrexia, injection site pain, chills
T-VEC

- Further trials with T-VEC ongoing, including trials of neoadjuvant therapy and in combination with checkpoint inhibitors
Regional Therapy – Isolated Limb Perfusion and Infusion

- Isolated limb perfusion (ILP) designed in 1956
- Designed to achieve high concentrations of chemotherapy in a limb
Regional Therapy – ILP

• ILP technically more challenging than ILI

• The vessels leading to a limb are surgically exposed and cannulated along with lymphadenectomy

• The limb is perfused with hyperthermic melphalan under oxygenated conditions
Regional Therapy – ILP

Regional Therapy – ILP

• With hyperthermia and melphalan:
  – Overall response rates 80-90%
  – Complete response rates 25-60%

Regional Therapy – Isolated Limb Infusion

- ILI technically much simpler than ILP; introduced in the mid-1990s

- The vessels leading to an extremity are accessed percutaneously from the contralateral side

- The limb is infused with melphalan under normothermic but hypoxic conditions
Regional Therapy – ILI Data

- US multi-institutional data from 8 centers

- 128 patients reported:
  - CR 31%
  - PR 33%
  - No response 36%

- AE grade ≥3 in 36%
  - 1 amputation

Regional Therapy – ILI Data

• Recent Australian multi-institutional report

• 316 ILI procedures reported:
  – CR 33%
  – PR 42%
  – Stable disease 18%, progression 7%

• AE grade ≥3 in 30%
  – No amputations

Regional Therapy – Australian Multicenter ILI Study

- For CR patients, median survival 80 months, PR patients 36 months

Regional Therapy – ILI and ILP Future Directions

• Trials ongoing examining regional therapy in combination with immunotherapy
Metastasectomy in Melanoma

• There is a role for resection in Stage IV disease

• Site of metastatic disease must be biopsied
  – Test for BRAF, also c-KIT mutations

• Imaging with PET/CT and brain MRI in metastatic disease
## Stage IV M1a Metastasectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Median survival (mo)</th>
<th>5-year survival (%)</th>
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<td>Feun et al⁴</td>
<td>1982</td>
<td>64</td>
<td>23</td>
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<td>Overett and Shiu⁵⁸</td>
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<td></td>
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<td>24</td>
<td>38</td>
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<td></td>
<td></td>
<td>60</td>
<td>50</td>
<td>49</td>
<td>SQ</td>
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<td>Gadd &amp; Coit⁵³</td>
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<td>Karakousis et al⁵²</td>
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<td>33</td>
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<tr>
<td>Barth et al¹</td>
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<td>15</td>
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<tr>
<td>Howard et al⁵⁵</td>
<td>2012</td>
<td>26</td>
<td>&gt;60</td>
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# Stage IV M1b Metastasectomy

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<tr>
<th>Study</th>
<th>Year</th>
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<th>Median survival (mo)</th>
<th>5-year survival (%)</th>
<th>Prognostic factors</th>
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<td>Feun et al⁴</td>
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<tr>
<td>Overett and Shiu⁵⁸</td>
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<td>Karp et al⁶⁸</td>
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<td>Gorenstein et al⁷⁰</td>
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<td>84</td>
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<td>106</td>
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<td>282</td>
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<td>Meyer et al⁶⁰</td>
<td>2000</td>
<td>10</td>
<td>28</td>
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<tr>
<td>Dalrymple-Hay et al⁶⁷</td>
<td>2002</td>
<td>121</td>
<td>16</td>
<td>22</td>
<td>No. of lesions, DFI, PET usage</td>
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<tr>
<td>Essner et al⁵⁶</td>
<td>2004</td>
<td>364</td>
<td>28</td>
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<td>Antecedent nodal disease, DFI, no. of lesions</td>
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<td>Petersen et al⁶⁵</td>
<td>2007</td>
<td>249</td>
<td>19</td>
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<tr>
<td>Neuman et al⁶⁶</td>
<td>2007</td>
<td>26</td>
<td>40</td>
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<td>No. of lesions</td>
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<td>2012</td>
<td>27</td>
<td>17.9</td>
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</table>

IRLM, International Registry of Lung Metastases; DFI, disease-free interval; TDT, tumor-doubling time.

Melanoma GI Tract Metastases

- Recent large single-institution report of 1623 patients with abdominal metastatic melanoma from 1969-2014.

- Median overall survival improved in surgical patients:
  - Surgery (n=392) → 18 months
  - No surgery (n=1231) → 7 months (P<0.001)

- Metastasectomy and GI tract metastasis significantly associated with improved overall survival.

Melanoma GI Tract Metastases

- Greatest benefit to patients with intestinal metastasis after complete resection → median OS 64 months

- Treatment in modern era of immunotherapy after 2004 not significantly associated with survival.

- Surgical resection may allow for durable long-term survival despite advances in systemic therapy.

Melanoma GI Tract Metastases – Overall Survival

Melanoma GI Tract Metastases – Overall Survival

Melanoma Liver Metastases

• Median survival with melanoma liver metastases 4-6 months

• In very selected patients with favorable disease biology, e.g. long doubling time, liver resection may lead to improved survival
Melanoma Liver Metastases

- Report from JWCI, 5.8% of 1078 patients underwent liver resection ± ablation

- On multivariable analysis, overall survival significantly related to:
  - Completeness of resection
  - Stabilization of disease before resection
Melanoma Liver Metastases

Melanoma Liver Metastases – Completeness of Resection

Melanoma Liver Metastases – Stabilization of Disease

Screening for Melanoma

**GET NAKED AND CHECK YOUR SKIN.**

*What you'll need:*
- A bright light
- A full-length mirror
- A hand mirror
- Two chairs or stools
- A blow dryer

Research shows catching melanoma in its earliest stages is one of the most important factors in improving the outcome of a melanoma diagnosis. In its early stages, melanoma can often be treated with simple surgery. In its later stages, when it spreads to other body organs, melanoma can be deadly.

Increase your chances of catching melanoma early by carefully examining your skin once a month and visiting a dermatologist once a year.

---

**Examine head and face, using one or both mirrors. Use blow dryer to inspect scalp.**

**Focus on neck, chest and torso. Women: check under breasts.**

**Check hands, including nails. In full-length mirror, examine elbows, arms and under-arms.**

**Use mirror to inspect back of neck, shoulders, upper arms, back, buttocks and legs.**

**Check legs and feet, including soles, heels and nails. Use hand mirror to examine genitals.**
Prevention of Melanoma

• Protecting skin from further solar damage
  – Daily use of broad-spectrum sunscreen
    • SPF ≥30
  – Avoiding extended sun exposure from 10AM to 4PM
  – Protective clothing: long sleeves, long pants, hat with circular brim
  – NO TANNING BEDS
Questions?