Objectives

- To identify new technologies for melanoma diagnosis
- To list recent changes in the melanoma staging
- To define adequate margins for excision of melanoma
- To describe indications for sentinel node biopsy and complete node dissection
- To discuss indications for adjuvant therapy in melanoma
Trends in Cancer Incidence

Male

- Prostate
- Lung & bronchus
- Colorectum
- Urinary bladder
- Melanoma of the skin
- Liver
- Thyroid

Female

- Breast
- Colorectum
- Lung & bronchus
- Uterine corpus
- Melanoma of the skin
- Liver
- Thyroid
Melanoma Survival by Stage and Race

Melanoma of the skin

- Localized: 98%
- Regional: 64%
- Distant: 23%
- All stages: 27%

Colorectum

- Localized: 90%
- Regional: 72%
- Distant: 14%
- All stages: 10%
**Melanoma Diagnosis**

• Biopsy is the gold standard
  • Dermoscopy may help direct biopsies

• New technologies
  • Melafind
    • Optical scanning device, off market
  • Reflectance confocal microscopy
    • Real-time imaging at cellular resolution
    • Much more specific than dermoscopy for equivocal lesions*
      • Avoid unnecessary biopsies

Melanoma Diagnosis

- **Other New tech**
  - Optical coherence tomography
    - Deeper penetration, lower resolution than LCM
  - High-frequency ultrasound
  - These need more data in cutaneous melanoma
    - Accuracy unclear
    - Lack of guidelines for diagnosis

- **Total body photography**
  - Screening high risk patients with multiple moles

![Figure 1. Prominent skin imaging modalities. The scale bars denote 200 μm. CM: Confocal microscopy; DS: Dermatoscopy; HFUS: High frequency ultrasound; MPT: Multiphoton tomography; μMRI: Micro MRI; OCT: Optical coherence tomography. Adapted from [J2,20].](image)
Melanoma Staging 2019

TX: Primary tumor thickness cannot be assessed
T0: No evidence of primary tumor
Tis (melanoma in situ)
T1  ≤1.0 mm  Unknown or unspecified
T1a <0.8 mm  Without ulceration
T1b* <0.8 mm  With ulceration
0.8-1.0 mm  With or without ulceration
T2  >1.0-2.0 mm  Unknown or unspecified
T2a >1.0-2.0 mm  Without ulceration
T2b >1.0-2.0 mm  With ulceration
T3 >2.0-4.0 mm  Unknown or unspecified
T3a >2.0-4.0 mm  Without ulceration
T3b >2.0-4.0 mm  With ulceration
T4 >4.0 mm  Unknown or unspecified
T4a >4.0 mm  Without ulceration
T4b >4.0 mm  With ulceration

* Mitoses removed from staging

Survival by T for Stage I-II Melanoma

<table>
<thead>
<tr>
<th>N Stage</th>
<th>Description</th>
<th>Presence</th>
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<tbody>
<tr>
<td>NX</td>
<td>Node path not assessed*</td>
<td>No in-transit**</td>
</tr>
<tr>
<td>N0</td>
<td>No regional metastases</td>
<td>No</td>
</tr>
<tr>
<td>N1</td>
<td>One node or in-transit met</td>
<td>Yes</td>
</tr>
<tr>
<td>N1a</td>
<td>One clinically occult***</td>
<td>No</td>
</tr>
<tr>
<td>N1b</td>
<td>One clinically detected</td>
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<tr>
<td>N1c</td>
<td>No lymph node disease</td>
<td>Yes</td>
</tr>
<tr>
<td>N2</td>
<td>2-3 nodes or in-transit with 1 node</td>
<td>Yes</td>
</tr>
<tr>
<td>N2a</td>
<td>Two or 3 clinically occult</td>
<td>No</td>
</tr>
<tr>
<td>N2b</td>
<td>2-3, ≥1 clinically detected</td>
<td>No</td>
</tr>
<tr>
<td>N2c</td>
<td>One or more nodes</td>
<td>Yes</td>
</tr>
<tr>
<td>N3</td>
<td>≥4 nodes or any in-transit with ≥ 2 nodes, or any matted nodes</td>
<td>Yes</td>
</tr>
<tr>
<td>N3a</td>
<td>≥4 clinically occult</td>
<td>No</td>
</tr>
<tr>
<td>N3b</td>
<td>≥4 nodes, ≥1 clinically or matted****</td>
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</tr>
<tr>
<td>N3c</td>
<td>≥2 or matted nodes</td>
<td>Yes</td>
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</table>

*Pathological N category is not required for T1 melanomas

**Includes in-transit, microsatellite, and satellite

*** No micro or macroscopic

****Not pathologic extranodal extension
## M Staging 2019

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Tis</th>
<th>N0b</th>
<th>M0</th>
<th>0</th>
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<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>Tis</td>
<td>N0b</td>
<td>M0</td>
<td>0</td>
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<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>IA</td>
</tr>
<tr>
<td>M1a</td>
<td>Skin, soft tissue, nonregional node</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>IB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
</tr>
<tr>
<td></td>
<td>LDH* not elevated</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
</tr>
<tr>
<td>M1a(0)</td>
<td>LDH elevated</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
</tr>
<tr>
<td>M1a(1)</td>
<td>LDH elevated</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
</tr>
<tr>
<td></td>
<td>To lung with or without M1a</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
<td>IIC</td>
</tr>
<tr>
<td>M1b</td>
<td>LDH not elevated</td>
<td>T0</td>
<td>N1b, N1c</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>M1b(0)</td>
<td>LDH not elevated</td>
<td>T0</td>
<td>N2b, N2c, N3b or N3c</td>
<td>M0</td>
<td>IIIC</td>
</tr>
<tr>
<td>M1b(1)</td>
<td>LDH elevated</td>
<td>T1a/b-T2a</td>
<td>N1a or N2a</td>
<td>M0</td>
<td>IIIA</td>
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<tr>
<td></td>
<td>Non-CNS visceral sites</td>
<td>T1a/b-T2a</td>
<td>N1b/c or N2b</td>
<td>M0</td>
<td>IIIB</td>
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<tr>
<td>M1c</td>
<td>LDH not elevated</td>
<td>T2b/T3a</td>
<td>N1a-N2b</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>M1c(0)</td>
<td>LDH not elevated</td>
<td>T1a-T3a</td>
<td>N2c or N3a/b/c</td>
<td>M0</td>
<td>IIIC</td>
</tr>
<tr>
<td>M1c(1)</td>
<td>LDH elevated</td>
<td>T3b/T4a</td>
<td>Any N ≥N1</td>
<td>M0</td>
<td>IIIC</td>
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<td>M1d**</td>
<td>CNS</td>
<td>T4b</td>
<td>N1a-N2c</td>
<td>M0</td>
<td>IIID</td>
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<tr>
<td>M1d(0)</td>
<td>LDH not elevated</td>
<td>T4b</td>
<td>N3a/b/c</td>
<td>M0</td>
<td>IIID</td>
</tr>
<tr>
<td>M1d(1)</td>
<td>LDH elevated</td>
<td>Any T, Tis</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
</tr>
</tbody>
</table>

*LDH now included for all subcategories

**CNS now separate category
Staging Workup

- All Stages
  - H & P with focus on lymphatic exam
  - Imaging to evaluate specific symptoms

- Stages I – II
  - Routine imaging or lab tests not recommended

- Stage IIIA (Positive sentinel node)
  - Consider imaging for baseline staging

- Stage III B/C/D (SLN +) or Clinical Node + or In-transit
  - Needle biopsy of palpable lesions
  - Imaging for baseline staging (Contrast CT Chest/Abd/Pelvis or whole body PET/CT, + Brain MRI if ≥ IIIC)
Melanoma Staging
Margins of Resection

• WHO Trial (1988)*
  • Breslow thickness ≤ 2mm
  • 1 vs 3 cm margins
  • No difference in disease-free or overall survival
  • Possible increase in local recurrence if > 1mm

• Intergroup Melanoma Trial**
  • Breslow thickness 2-4 mm
  • 2 vs 4 cm margins
  • No difference in DFS or OS

• Others – Swedish, UK, French

Current Margin Recommendations

**Figure 1:** Recommended Surgical Margins for Excision of Melanoma

- Surface of the skin
- Epidermis
- Dermis
- Subcutaneous tissue

Measurements: 2 cm, 1-2 cm, 1.0 cm, .5 cm, 1 mm, 2 mm, 3 mm, 4 mm

*Measurements not to scale.

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Management of Lymphatic Basins

• Clinically positive nodes require complete lymphadenectomy

• Sentinel node biopsy indications (ASCO/SSO Guidelines) for patients with clinically negative nodes

  • Thin (≤ 1mm) - 5.2% nodal mets
    • T1a – Not routinely indicated
    • T1b – Consider, discussion with patient
  • Intermediate thickness (1 – 4 mm) – 16 – 20% with nodal mets
    • Indicated for all (T2 and T3)
  • Thick
    • Recommended, discuss with patient
Lymphatic Drainage Patterns

- Cervical lymph nodes
- Lymphatics of the mammary gland
- Cisterna chyli
- Lumbar lymph nodes
- Pelvic lymph nodes
- Lymphatics of the lower limb
- Thoracic duct
- Thymus
- Axillary lymph nodes
- Spleen
- Lymphatics of the upper limb
- Inguinal lymph nodes
Injection of blue dye and radioactive tracer around primary melanoma

Sentinel lymph node is removed and tested for cancer cells
Impact of SLN Biopsy

• MSLT-I trial*
  • 2001 patients with primary cutaneous melanoma
  • Randomized to WLE with SLN vs WLE and observation
  • Significantly improved survival in SLN+ compared to SLN-
    • Both intermediate and thick melanomas
  • ~20% of intermediate thickness had lymph node mets
    • Survival improved in SLN+CLND vs observation and therapeutic dissection
      • 56% vs 41.5% at 10 years
  • No effective adjuvant therapy available at that time (trial closed in 2002)

Management of Lymphatic Basins

- Role of completion lymphadenectomy with positive SLN
  - Not recommended unless more extensive nodal involvement
    - Trials randomized for CLND vs no CLND
    - Patients without dissection all followed with frequent ultrasound
    - Regional control improved
    - No difference in disease-specific or overall survival
  - ~ 65% of mets under 1mm
    - DeCOG-SLT (German)*
      - Some patients got adjuvant interferon
    - MSLT-II (International)**
      - Positive non-sentinel nodes strongly associated with recurrence
      - 12% of patients RT-PCR positive only
  - Role of CLND with more extensive nodal involvement is still unclear


Adjuvant Systemic Therapy

• Interferon
  • No clear benefit in overall survival

• Anti-CTLA4 (Ipilimumab/Yervoy, FDA approved 2015)
  • Enhance effector T cell function
  • EORTC 18071 – significantly improved RFS and OS (HR 0.76 and 0.72)
    • Significant toxicity due to high dose regimen
    • Trial of high vs low dose in progress

• BRAF/MEK inhibitors (dabrafenib/trametinib, FDA 2018)
  • Only effective in V600E or V600K BRAF mutant melanoma (50% of cases)
  • COMBI-AD – Significant improvement in 3 year RFS and OS (0.47 and 0.57)
Fig 4. Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) blockade prevents downregulation of T cells. (A) CTLA4 receptors are upregulated after T-cell activation and bind to B7, sending an inhibitory signal that downregulates T-cell activation. (B) Anti-CTLA4 antibodies have a greater affinity for CTLA4 than B7 and inhibit the interaction of B7 and CTLA4. Thus, the inhibitory signal produced by B7 binding to CTLA4 is blocked, and T-cell activation is prolonged. MHC, major histocompatibility complex; TCR, T-cell receptor; mAb, monoclonal antibody.
BRAF-MEK Inhibitors

Adjuvant Therapy

- **Anti-PD-1**
  - Block PD-1/PD-L1 interaction, decreases blocking of immune recognition
  - Pembroluzimab (Keytruda) – FDA approved 2019
    - EORTC1325/KEYNOTE-054
      - Pembrolizumab vs placebo
      - Improved RFS (HR 0.57)
      - PDL-1 status did not matter
  - Nivolumab (Opdivo) – FDA 2017
    - CHECKMATE-238
      - Nivolumab vs Ipilumimab
      - Improved RFS (HR 0.65)
Mechanism of Anti-PD-1

Management of In-transit Metastases

- Disease in the subdermal lymphatics
- Occur in up to 6% of patients
- May have multiple lesions and/or recurrences
- Surgical resection is first option
  - Patients are stage III and therefore candidates for adjuvant systemic therapy
Unresectable Stage III

- **Limb Perfusion/infusion**
  - Good response rates of 75% or more
    - Complete responders have improved survival
  - Indications unclear in light of new systemic options
  - ILI less morbid/minimally invasive

- **Radiation**
  - Mainly used in palliation

- **Systemic**
  - Limited data in Stage III
  - Combination therapy
T-VEC (talimogene laherparepvec) injection

- Modified herpes virus preferentially targets cancer cells
- Oncolytic and causes GM-CSF production

Role of Adjuvant Radiation in Melanoma

- Very little data is available from randomized trials
  - Historical bias against XRT in melanoma
  - No data in patients who received modern adjuvant systemic therapy

- Potential current indications*
  - Regional nodes after dissection for clinically palpable/bulky disease
    - May decrease local recurrence, but no effect on survival
  - Nodal recurrence after regional dissection
  - Local control of desmoplastic or other melanomas with neurotropism
    - In patients with <8 mm margins, XRT halved LR (hazard ratio: 0.48)**
  - After resection of brain metastases with no or oligo-metastatic disease

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Current Adjuvant Studies

• Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716, Merck) - Recruiting
  • Recurrence-free survival is primary outcome
  • DDFS and OS secondary outcomes

• Neoadjuvant PD-1 Blockade in Patients With Stage IIB/C Melanoma (University of Pennsylvania) – Not open yet
  • Single dose of pembrolizumab preop
  • Continued treatment postop up to 1 year
  • Evaluate effect on sentinel node positivity
  • Secondary outcomes include DFS and OS
Current Adjuvant Studies

• Neoadjuvant L19IL2/L19TNF (Pivotal) - Recruiting
  • Intratumoral injections of cytokines, stage III
  • Outcome is RFS

• Vaccine trials
  • 6MHP, With or Without Systemic CDX-1127 (Celldex) - Recruiting
    • Peptide vaccine (6MHP) with adjuvants and monoclonal antibody (CDX-1127)
    • Endpoints are adverse events and level of immune response
  • MART-1 Antigen With or Without TLR4 Agonist GLA-SE in Treating Patients With Stage II-IV Melanoma That Has Been Removed by Surgery - Active
    • Outcome is immune response
Future Directions

- New diagnostic tools
- Further refinement of staging and indications for SLN
- New immunotherapy and targeted therapy agents
- Adjuvant therapy for stage II
- Neoadjuvant therapy for stage III
- Continue defining the role of completion lymphadenectomy