Soft Tissue Sarcomas

Joshua M.V. Mammen, MD, PhD
Department of Surgery
University of Kansas
Epidemiology

- Relatively rare tumors: less than 1% of malignant neoplasms
- 4.5-6.5 cases / person years (SEER database)
- Slight male and African American predominances
- Increases with age
Types of Sarcoma

More than 50 subtypes:
Liposarcoma
Fibrosarcoma
Malignant Fibrous Histiocytoma/Pleiomorphic Sarcoma
Leiomyosarcoma
Neurofibrosarcoma
Rhabdomyosarcoma
Synovial sarcoma
Etiology

- Most are spontaneous
- Li-Fraumeni syndrome - breast cancer, leukemia, osteogenic sarcomas, melanoma, cancers of colon, pancreas, adrenal cortex, and brain
- Retinoblastoma - mutation of RB1 (tumor suppressor gene)
- Malignant nerve sheath tumors - NF1
Risk Factors

- Not well identified
- Chronic lymphedema (angiosarcoma)
- Viral - Kaposi’s sarcoma due to HHV-8
- Ionizing radiation
  - Tumor develop 7-10 years after exposure
Location

- 32 percent of sarcomas were found in a lower extremity
- 18 percent in the viscera (organs located within the chest and abdomen, such as the stomach, kidney, uterus, etc.)
- 15 percent in the retroperitoneal region (the area outside or behind the peritoneum, which is the tissue that lines the abdominal wall)
- 13 percent in an upper extremity
- 8 percent in the trunk
- 14 percent in other sites

MSKCC, Data from 1982-2009
Presentation

- Painless mass (often incorrectly attributed to trauma)
- Intraabdominal sarcomas may present with obstructive symptoms (early satiety, nausea, etc.)
Diagnosis

- Imaging

- Great care must be taken to avoid crossing multiple compartments

- Biopsy
  - Percutaneous
  - Incisional
  - Excisional
MRI

- Most useful imaging for treatment planning and surveillance
- Allows for understanding anatomy
- Gadolinium is critical to differentiate viable tumor from necrosis and scar
Treatment

- Surgical resection is the mainstay of treatment
- Variable response and benefit of chemotherapy
- Radiation may play a role; so far, the evidence is mixed
Management of Melanoma: Rationale and Strategy for Local, Regional, and Systemic Approaches

Joshua M.V. Mammen, MD, PhD
Department of Surgery
University of Kansas
Epidemiology

- Almost 70,000 new cases of melanoma annually
- More than 10,000 deaths from melanoma annually
- Incidence increasing by 2.6% every year (increasing faster than almost every other malignancy)
- Lifetime risk of developing melanoma is 1.88% (1 in 53)

Risk Factors (Inherent)

- **Skin type**
  - White racial background has ten times increased risk as blacks and seven times higher risk than Hispanics
  - Fair skin, red hair, blue eyes

- **Age**
  - Incidence increases with age

- **Gender**
  - 1.7 fold increase risk for men

- **Benign Nevi**
  - Large number (greater than 50 increases risk 5 to 17 fold)

- **Previous history of melanoma**
  - 900 fold increased risk (risk of second is 3% to 7%)
## Risk Factors (Inherent)

### Incidence Rates by Race

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>25.0 per 100,000 men</td>
<td>15.8 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>28.9 per 100,000 men</td>
<td>18.7 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>1.1 per 100,000 men</td>
<td>1.0 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1.6 per 100,000 men</td>
<td>1.3 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native a</td>
<td>3.9 per 100,000 men</td>
<td>2.8 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic b</td>
<td>4.6 per 100,000 men</td>
<td>4.7 per 100,000 women</td>
</tr>
</tbody>
</table>

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## Risk Factors (Inherent)

### Death Rates by Race

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>3.9 per 100,000 men</td>
<td>1.7 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>4.4 per 100,000 men</td>
<td>2.0 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>0.5 per 100,000 men</td>
<td>0.4 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0.5 per 100,000 men</td>
<td>0.3 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>1.6 per 100,000 men</td>
<td>0.9 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.9 per 100,000 men</td>
<td>0.6 per 100,000 women</td>
</tr>
</tbody>
</table>

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Risk Factors (Modifiable)

- Tanning bed use
  - Ten or more uses per week increases risk two fold
  - Classified by the World Health Organization as a carcinogen
- Sunlight exposure
  - Episodes of severe and painful sunburns
  - Ten or more episodes double risk
What about Sunscreen?

- General recommendation of SPF equal or greater than 15
- SPF 15 blocks 93% of UVB, SPF-45 blocks 98%
- However, SPF only measures UVB protection, not UVA protection (no good measure)
What about Sunscreen?

- Important that sunscreen is effective after use (sweating, swimming, etc.)
- Water resistant: effective after 2x 20 minute immersions
- Very water resistant: 4 x 20 minute immersions
What about Sunscreen?

- Controversial if sunscreen is effective at reducing the incidence of melanoma
- Good data in reducing rates of basal cell cancers, squamous cell cancers, and solar keratoses
Risk Factors (Familial/Genetic)

- **Genetic anomalies**
  - Genes located on chromosomes 1p, 6q, 7, 9, 10, and 11
  - B-RAF (mutated in 60-70% of melanomas)

- **Family history**
  - Increase risk 3-8 fold
Risk Factors (Familial/Genetic)

- Atypical mole and melanoma syndromes
- Dysplastic nevus syndrome: large number of abnormal nevi
Clinical Presentation

- A: Asymmetry
- B: Border irregularity
- C: Color variegation
- D: Diameter greater than 6mm
- E: Evolving or enlarging
Evaluation

- Physical examination
  - Skin survey: remember to look at scalp, between fingers and toes, etc.
  - Lymph node basins
  - Subcutaneous tissues
Tissue is the issue: How to biopsy

- Excisional biopsy
  - Most accurate to determine thickness
  - 1-3mm of skin removed around lesion
  - Orient elliptical incision in direction of potential wide local excision (vertical incisions for extremities, horizontal incisions on the trunk and neck)
Punch biopsy

- Consider when lesions are too large to completely excise or complete excision would be cosmetically undesirable
- Attempt to complete excise nevus (6mm punch)
- Biopsy raised or most pigmented area
- Biopsy must extend to subcutaneous tissue for staging
Tissue is the issue: How to biopsy

- Shave biopsy
  - Not optimal
  - Larger area to remove later
  - Often fails to accurately predict thickness
Summary

- Attempt to remove entire lesion if possible as part of biopsy
- Need to obtain all layers of skin to obtain accurate staging
Immunohistochemistry

- S-100: Expressed by 90% of melanomas as well as some other cell types
- HMB-45: Monoclonal antibody specific for melanoma
- Anti-MART-1
Major Categories

- Superficial Spreading
  - 70%
  - Originates from nevus
Major Categories

- Nodular
  - 15-30%
  - Becomes invasive more quickly
Major Categories

- Lentigo maligna
  - 4-10%
  - Strongly associated with sun exposure
  - Slowly becomes invasive
  - Usually greater than 3cm in diameter
Major Categories

- Acral lentiginous
  - 2-8%
  - Palmar, plantar, or subungual locations
  - 34-60% of non-white melanomas
  - 3cm average diameter
Major Categories

- Amelanotic
  - Lack pigmentation
  - Challenge in diagnosis

www.molemap.net
Staging

- Clarke’s depth of invasion

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*Cancer Medicine, 5th Edition*
## T Staging (Breslow thickness)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T1</td>
<td>( \leq 1.00 )</td>
<td>a: Without ulceration and mitosis &lt; 1/mm² ( b: ) With ulceration or mitoses ( \geq 1/mm² )</td>
</tr>
<tr>
<td>T2</td>
<td>1.01-2.00</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>2.01-4.00</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.00</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
</tbody>
</table>
T Staging

A graph showing survival rate (proportion) over time (years) for different T staging categories:

- T1a (n = 9,452)
- T1b (n = 2,389)
- T2b (n = 1,517)
- T2a (n = 6,529)
- T3a (n = 3,127)
- T3b (n = 2,164)
- T4a (n = 1,064)
- T4b (n = 1,397)

The graph indicates a decrease in survival rate with increasing T staging.
# N Staging

<table>
<thead>
<tr>
<th>N</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N1</td>
<td>1</td>
<td>a: Micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis†</td>
</tr>
<tr>
<td>N2</td>
<td>2-3</td>
<td>a: Micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: In transit metastases/satellites without metastatic nodes</td>
</tr>
<tr>
<td>N3</td>
<td>4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes</td>
<td></td>
</tr>
</tbody>
</table>
N Staging
## M Staging

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>NA</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>metastases</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

*Journal of Clinical Oncology*
M Staging

![Graphs showing survival rates](VOLUME 27 - NUMBER 36 - DECEMBER 20 2009)

**Journal of Clinical Oncology**
# TNM Staging

<table>
<thead>
<tr>
<th>Pathologic Staging†</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-4a</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4a</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1-4b</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4b</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4a</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4a</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4a</td>
<td>N2c</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1-4b</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4b</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4b</td>
<td>N2c</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
TNM Staging
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness</td>
<td>Primary determinant of T staging</td>
<td>Same</td>
<td>Thresholds of 1.0, 2.0, and 4.0 mm</td>
</tr>
<tr>
<td>Level of invasion</td>
<td>Used only for defining T1 melanomas</td>
<td>Same</td>
<td>Used as a default criterion only if mitotic rate cannot be determined</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Included as a secondary determinant of T and N staging</td>
<td>Same</td>
<td>Signifies a locally advanced lesion; dominant prognostic factor for grouping stages I, II, and III</td>
</tr>
<tr>
<td>Mitotic rate per mm²</td>
<td>Not used</td>
<td>Used for categorizing T1 melanoma</td>
<td>Mitosis ≥ 1/mm² used as a primary criterion for defining T1b melanoma</td>
</tr>
<tr>
<td>Satellite metastases</td>
<td>In N category</td>
<td>Same</td>
<td>Merged with in transit lesions</td>
</tr>
<tr>
<td>Immunochemical detection of nodal metastases</td>
<td>Not included</td>
<td>Included</td>
<td>Must include at least one melanoma-associated marker (e.g., HMB-45, Melan-A, MART-1) unless diagnostic cellular morphology is present</td>
</tr>
<tr>
<td>0.2 mm threshold of defined N+</td>
<td>Implied</td>
<td>No lower threshold of staging N+ disease</td>
<td>Isolated tumor cells or tumor deposits &lt; 0.1 mm meeting the criteria for histologic or immunohistochemical detection of melanoma should be scored as N+</td>
</tr>
<tr>
<td>Number of nodal metastases</td>
<td>Primary determinant of N staging</td>
<td>Same</td>
<td>Thresholds of 1 ≤ 2-3 ≤ 4+ nodes</td>
</tr>
<tr>
<td>Metastatic volume</td>
<td>Included as a second determinant of N staging</td>
<td>Same</td>
<td>Clinically occult (microscopic) nodes are diagnosed at sentinel node biopsy; clinically apparent (macroscopic) nodes diagnosed by palpation or imaging studies, or by the finding of gross (not microscopic) extracapsular extension in a clinically occult node</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>Separate category as M1b</td>
<td>Same</td>
<td>Has a somewhat better prognosis than other visceral metastases</td>
</tr>
<tr>
<td>Elevated serum LDH</td>
<td>Included as a second determinant of M staging</td>
<td>Same</td>
<td>Recommend a second confirmatory LDH level if elevated</td>
</tr>
<tr>
<td>Clinical vs pathologic staging</td>
<td>Sentinel node results incorporated into definition of pathologic staging</td>
<td>Same</td>
<td>Large variability in outcome between clinical and pathologic staging; sentinel node staging encouraged for standard patient care, should be required prior to entry into clinical trials</td>
</tr>
</tbody>
</table>
Summary

- T staging: thickness, ulceration, and mitotic rate are critical.
- N staging: differentiate between number of lymph nodes involved and micro versus macroscopic disease.
- M staging: location of metastases and LDH levels are important.
Preoperative Evaluation

- Stage I and II: Chest X-ray, LDH, ultrasound evaluation of lymph node basin
- Stage III and IV: PET/CT, CT (chest/abdomen/pelvis), MRI (brain)
Surgical Excision

- Wide local excision is the primary treatment of melanoma
- Rationale is melanocytes found surrounding melanoma
- 1907, Handley recommended 5cm margin
- 1962, Paterson recommended 15cm margin
Surgical Margins

- World Health Organization Melanoma Group
- Evaluated melanomas up to 2mm thickness
- Randomized 1cm or 3cm margins for wide local excision
- Identical DFS and OS

Surgical Margins

- Swedish Melanoma Study Group
- 989 patients with tumor thickness between 0.8mm and 2mm
- Randomized to 2cm and 5cm wide local excision
- No difference in recurrence free and overall survival

Surgical Margins

- British Trial
- Melanomas of at least 2mm in thickness
- Total of 769 patients evaluated
- Evaluated 1cm versus 3cm margins
# Surgical Margins

<table>
<thead>
<tr>
<th>End Point</th>
<th>1-cm Margin of Excision</th>
<th>3-cm Margin of Excision</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>168</td>
<td>142</td>
<td>1.26 (1.00–1.59)</td>
<td>0.05</td>
</tr>
<tr>
<td>Recurrence or death</td>
<td>220</td>
<td>195</td>
<td>1.21 (0.99–1.46)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local or in-transit recurrence</td>
<td>37</td>
<td>25</td>
<td>1.51 (0.91–2.51)</td>
<td>0.1</td>
</tr>
<tr>
<td>Regional-node recurrence</td>
<td>149</td>
<td>129</td>
<td>1.21 (0.96–1.53)</td>
<td>0.1</td>
</tr>
<tr>
<td>Death from melanoma</td>
<td>128</td>
<td>105</td>
<td>1.24 (0.96–1.61)</td>
<td>0.1</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>144</td>
<td>137</td>
<td>1.07 (0.85–1.36)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Surgical Margins

![Graph showing overall survival rates for 3-cm and 1-cm margin surgeries.](image)

- **Overall Survival (%)**
- **Year since Randomization**
- **No. at Risk**
  - 3-cm Margin: 443, 413, 345, 271, 213, 151, 94, 58, 22
  - 1-cm Margin: 447, 417, 341, 260, 210, 144, 87, 56, 23

*P = 0.6*
Surgical Margins
Surgical Margins

- Integroup Melanoma Surgical Trial
- 468 patients with melanoma of thickness from 1-4mm
- Randomized to 2cm or 4cm margins
- No difference in local recurrence or overall survival

## Surgical Margins: Summary

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 1mm</td>
<td>1cm</td>
</tr>
<tr>
<td>1-2mm</td>
<td>1-2cm</td>
</tr>
<tr>
<td>2-4mm</td>
<td>2cm</td>
</tr>
<tr>
<td>&gt;4mm</td>
<td>2cm</td>
</tr>
</tbody>
</table>
Wound closure

- Attempt primary closure if possible
- Usually longitudinal axis must be three times length of short axis
- Sometimes can make a hurricane pattern to facilitate closure
Wound Closure

- Skin graft
  - Used when primary closure is not possible
  - Almost always necessary in the scalp
  - Split thickness skin graft except in the face
  - Remove from a site remote from the melanoma
Summary

- Attempt primary closure if possible
- Skin graft is next option if closure is not possible
Sentinel Lymph Node Biopsy
Sentinel Lymph Node Biopsy
Sentinel Lymph Node Biopsy

- Who should get it?
  - 1mm or greater thickness lesions
  - 0.75mm melanoma with negative prognostic markers (high mitotic rate, high Clark level)
  - Controversy with regards to thin melanoma
Lymph Node Dissection

Indications

- Positive sentinel lymph node (17% of total sentinel lymph node biopsies)
  - 80% will have additional disease

- Clinical evidence of regional nodal disease
Lymph Node Dissection

- **Contraindications**
  - Inability to tolerate general anesthesia
  - Most patients with widespread extraregional metastatic disease
Lymph Node Dissection

- Cervical
- Axillary
- Inguinofemoral
- In transit basins
Cervical Lymphadenectomy

- Usually metastases from head, neck, or upper trunk
- Modified radical neck dissection (levels II, III, IV, and V) with sparing of the sternocleidomastoid, spinal accessory nerve, and internal jugular vein
Axillary Lymphadenectomy

- Usually metastases from upper extremity or trunk
- Complete axillary dissection (levels I-III)
  - Different than breast cancer
- 10% will have complication of lymphedema
  - Lower incidence than breast cancer (20%)
Inguinofemoral Lymphadenectomy

- Usually metastases from the lower extremity or trunk
- Superficial groin dissection and biopsy of Cloquet’s node for positive SLN
- Deep groin dissection if Cloquet’s node is positive
- Superficial and deep groin dissection for clinically palpable lymph node disease
Inguinofemoral lymphadenectomy

European Urology Volume 56, issue 5, pages 753-890, November 2009
Inguinofemoral lymphadenectomy
Inguinofemoral Lymphadenectomy

- Additional considerations:
  - Rotation of the sartorius muscle for coverage
  - Sparing the saphenous vein
  - High risk of DVT and wound infections
Summary

- Sentinel lymph node biopsy should be used to assess lymph node basins in clinically node negative patients.
- Lymph node dissection is indicated in patients with clinically evident disease and sentinel lymph node positive disease.
In Transit Melanoma

- Regional metastases that present as nodules in the dermis or subcutaneous tissue
- Includes local recurrence, satellite lesions, or true in transit disease
- Typically develops between primary site and regional lymph node basin
In Transit Melanoma

- Incidence of 3-10% of all melanoma patients
- Very uncommon in Stage I and II disease
- Risk factors: increased tumor thickness, ulceration, lower extremity site, nodal metastases
- Likelihood of distant relapse is determined by the burden of in transit disease
In Transit Melanoma

- No clear standard of care

- Options considered: surgical excision, intratumoral injections, palliative external beam radiation, laser ablation, electroporation
In Transit Melanoma

- Surgical excision
  - Useful in patients with limited nodules in which negative margins can be achieved
  - Little morbidity and relatively inexpensive
  - High relapse rate at other sites
  - 50% rate of distant relapse
  - Should be combined with systemic chemotherapy
  - If no distant relapse, may consider excising any additional in transit lesions
In Transit Melanoma

- Regional Chemotherapy
  - Isolated limb perfusion or isolated limb infusion
  - Arterial and venous catheters are placed to isolate the extremity from systemic circulation to deliver high dose chemotherapy
- Indications:
  - Multiple in transit metastases not amenable to resection
  - Staging usually reveals no distant disease (except for palliation)
In Transit Metastases
In Transit Metastases

- **Toxicity**
  - Compartment syndrome (5%)

- **Results**
  - Response rates from 80-90%
  - Complete response rate is 25-60%
  - Durability of 18-24 months
Summary

- In transit disease develops between the primary site and the regional lymph node basin
- Surgical excision can be considered when there are only a few lesions amenable to resection
- Regional chemotherapy should be considered when there are multiple lesions confined to one extremity
Distant Metastases and Surgery

- Systemic therapies have dismal responses with 5 year survival usually of 5%
- Response rates for agents are well under 50%
- May be able to improve survival with a complete surgical metastectomy (removing all clinically or radiographically detected melanoma)
Distant Metastases and Surgery

- 5-year survival by site after complete metastectomy
  - Pulmonary
    - Harpole (1992) 20%
    - Tafra (1995) 27%
    - Leo (2000) 22%
  - Skin, soft tissue, and lymph nodes
    - Markowitz (1991) 38%
    - Gadd and Coit (1992) 22%
    - Barth (1995) 14%
Distant Metastases and Surgery

- Gastrointestinal
  - Ricaniadis (1995) 28%
  - Ollila (1996) 41%
  - Agrawal (1999) 38%
Surgery for Palliation

- Skin, soft tissue, and lymph node disease can lead to pain, limited function, and bleeding
  - Attempt complete excision for palliation
- Abdominal disease can lead to obstruction or bleeding
  - Resection even if not complete
- Intracranial disease
  - Consider stereotactic radiosurgery
Complete surgical metastectomy may improve survival in patients with Stage IV disease.

Still need a randomized prospective clinical trial, but challenging to organize due to the variability in number and sites of metastases.

Resection of lesions may be needed for palliation.
Adjuvant Systemic Therapy

- Chemotherapy has very poor activity
- The best chemotherapy, DTIC, has approximately 10% activity against melanoma
- Other agents to consider include cisplatin and alkylating agents
Interferon

- Only FDA approved treatment for melanoma
- Melanoma has a 15% response rate with high dose interferon (5% complete response rate)
- Has been shown to increase DFS and maybe OS (Stage IIb to III disease)
- Toxicities: fatigue, anorexia, weight loss, fever, myalgia, transaminitis, depression, vertigo, confusion, thrombocytopenia, anemia, leukopenia
- 15-30% develop autoimmune disorders
Adjuvant Radiation

- Used to reduce regional lymph node basin recurrence
- More useful in those with higher failure rates: extracapsular extension, greater than 4 positive lymph nodes, greater than 3cm lymph node
- May reduce recurrence rate by 5-20%
- Complication: lymphedema (10%)
Summary

- Adjuvant chemotherapy is generally ineffective
- Some patients may benefit from high dose interferon
- Radiation to the lymph node basins may reduce local recurrence in patients with history of palpable nodal disease
Conclusions

- Melanoma is increasing in incidence
- Several modifiable risk factors deserve physician attention
- Wide local excision is an important component of treatment
- Lymph node basins need assessment to accurately determine the stage of disease and to provide therapeutic benefit
Conclusions

- Management of in transit disease includes surgical excision and regional chemotherapy
- Stage IV disease may benefit from complete surgical metastectomy
- Options for adjuvant treatment are limited