Clinical Case Conference
Melanoma
Epidemiology

- ~60,000 cases and 8,000 deaths per year in US
- Caucasian:African American = 10:1
- 15% arise from existing nevi
- 91% are cutaneous
- 15% are LN+ at presentation
- 5% are M1 at diagnosis
- Types: superficial spreading, desmoplastic, nodular, lentigo maligna, acral lentiginous
<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed (e.g., curettaged or severely regressed primary)</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Melanoma in situ</td>
</tr>
</tbody>
</table>
| T1               | $\leq 1.0$ mm  
     a: without ulceration and mitoses $<1/mm^2$  
     b: with ulceration or mitoses $\geq 1/mm^2$ |
| T2               | $1.01-2.0$ mm  
     a: without ulceration  
     b: with ulceration |
| T3               | $2.01-4.0$ mm  
     a: without ulceration  
     b: with ulceration |
| T4               | $>4.0$ mm  
     a: without ulceration  
     b: with ulceration |

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional metastases detected</td>
</tr>
</tbody>
</table>
| N1                       | One lymph node  
     a: micrometastases*  
     b: macrometastases* |
| N2                       | Two or three lymph nodes  
     a: micrometastases*  
     b: macrometastases*  
     c: in-transit met(s)/satellite(s) without metastatic lymph nodes |
| N3                       | Four or more metastatic lymph nodes, or matted lymph nodes, or in-transit met(s)/satellite(s) with metastatic lymph node(s) |

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No detectable evidence of distant metastases</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastases to skin, subcutaneous, or distant lymph node, normal serum LDH</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases, normal LDH</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to other visceral metastases with a normal LDH, or any distant metastases and an elevated LDH</td>
</tr>
<tr>
<td>Stage</td>
<td>Primary tumor (T)</td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td><strong>Clinical staging</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2b</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3b</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T4b</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Stage</th>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes (N)</th>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathologic staging</strong></td>
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<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IB</td>
<td>T1b</td>
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<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
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<td>T3a</td>
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<td>M0</td>
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<td>T3b</td>
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<td>M0</td>
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<td>T4a</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IIIA</td>
<td>T1&lt;4a</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1&lt;4b</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1&lt;4a</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1&lt;4b</td>
<td>N1a</td>
<td>M0</td>
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<td>T1&lt;4b</td>
<td>N2a</td>
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<td>T1&lt;4a</td>
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<td>N2b</td>
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<td>T1&lt;4a</td>
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<td>Stage IIIC</td>
<td>T1&lt;4b</td>
<td>N1b</td>
<td>M0</td>
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<td>T1&lt;4b</td>
<td>N2b</td>
<td>M0</td>
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<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Clark Levels

- Level I - Confined to epidermis (in situ); not an invasive lesion
- Level II - Invasion of papillary dermis; invasion past basement membrane
- Level III - Papillary dermis filled by tumor and reticular dermis compressed, but not invaded
- Level IV - Invasion of reticular dermis; subcutaneous tissue not involved
- Level V - Invasion of subcutaneous tissue
Principles of Surgery

• Minimum margins:
  • Tis = 5mm, T1 = 1cm, T2-T4 = 2cm

• Risk of regional recurrence is 30-50% if:
  • ECE, >4 LN+, >3cm of LN involved, Cervical LN+, cN+

• Odds of SLN+:
  • T1 = 5%, T2/T3 = 15-20%, T4 = 30-50%
• If SLN+, then 20% likelihood of other regional LN+

• If SLN+, recommend completion dissection. If not, RT recommended
**SLNB**

- Morton et al., NEJM 2006
- Prospective RCT
- 1,269 pts with melanoma undergoing WLE randomized to:
  - SLNB, and if positive -> completion LND
  - Observation, and if clinical LN failure -> LND
- No difference in OS, or DSS
- However, 5yr DSS better for SLN+ patients (72%) vs observed pts who became cLN+ ($p = .004$)
- 5-yr OS was 90% if SLN- vs. 72% if SLN+
- Conclusion: SLNB is a valuable staging tool
- Open: MSLT-II – randomizes pts with SLNB+ to completion LND vs. obs.

Recommendations
Indications for Radiotherapy

• **For the primary site:**
  • R2, R1 or close margin
  • Recurrent disease
  • Perineural invasion

• **For regional LNs:**
  • ECE
  • LN $\geq$ 3cm in size
  • $>4$ involved LNs
  • Recurrent disease after LND
  • See ANZMTG 01.02/TROG 02.01
Studies
Adjuvant RT to Lymph Nodes

- Ballo et al. – MDACC – IJROBP 2006
- Retrospective
- 466 pts with melanoma and +LN, s/p WLE and LND
- High risk features for inclusion:
  - ECE
  - LN > 3cm in size
  - >4 involved LNs
  - Recurrent disease after LND
- RT was given as 6Gy x 5, at 2fx per week
- Median f/u 4.2 years

Ballo et al., IJROBP 2006 Jan 1;64(1):106-13
Adjuvant RT to Lymph Nodes

- 5-yr rate of freedom from regional failure in the nodal basin was 89%, which compares favorably to historical controls of an untreated high-risk group (50-70%)

- 5-yr distant-metastasis free survival was only 44%

- 5-yr rates of symptomatic lymphedema were (p = .0001):
  - Epitrochlear = 0%, cervical = 1%, axillary = 20%, inguinal = 27%

Ballo et al., IJROBP 2006 Jan 1;64(1):106-13
Dose Per Fraction

• Sause et al. – RTOG 83-05 – IJROBP 1991
• Prospective RCT
• 121 patients with melanoma (gross disease) treated with palliative intent
• Stratified by disease site
• Randomized to
  • 8Gy x 4fx, with 1fx per week
  • 2.5Gy x 20, with 5fx per week
• Electron or MV photons

- No difference in response rate between the 2 dose schedule
- Study closed early due to statistical futility
- Grade 3/4 toxicity may have been higher in the 8Gy/fx arm (n=3/3) than the 2.5Gy/fx arm (n=4/0), although no statistical analysis was performed
Adjuvant RT to Lymph Nodes

- **ANZMTG 01.02/TROG 02.01**
- Prospective RCT
- Burmeister et al. – Sydney – Lancet Oncology 2012
- RTOG 9302 (similar design) failed to accrue
- 217 pts with melanoma s/p WLE and LND
- Required at least one of the following:
  - >1 parotid LN
  - >2 cervical/axillary LNs
  - >3 inguinal LNs
  - ECE
  - Cervical LN > 3cm
  - Axillary/inguinal LN > 4cm
- RT was 2.4Gy x 20fx (as in the phase II TROG 96-06 study)
- Median f/u 40 months

RT improved regional control in intent-to-treat analysis (HR = .56, p = .041) and analysis by treatment received (HR = .47, p = .005)
RT did not affect RFS or OS
RT was generally well-tolerated
Treatment of the Primary Site

• Harwood et al. – Princess Margaret – Cancer 1981
• Retrospective
• 37 patients with nodular or superficial melanoma of H&N
• Indications:
  • R2 Margin
  • R1 or close margin
  • Recurrent disease
• Local control was 93% for microscopic disease, 67% for gross disease, and 12% for recurrent disease.
• Local control was higher with larger dose per fraction:
  • <4 Gy = 25% vs >4 Gy = 71%

Desmoplastic Melanoma

- Arora et al. – Univ. of Mich. – Cancer 2005
- Retrospective
- 65 patients with desmoplastic melanoma
- This was believed to be a subtype with high rate of local recurrence and LN involvement
- Treated with WLE alone (no adjuvant RT)
- Neurotropism was seen in 32% overall
- Local recurrence rate was 4% overall, contrary to prior series
- Of these cases of desmoplastic melanoma, LN involvement was seen in 4% of those without neurotropism vs. 28% of those with neurotropism.

Arora A, Cancer. 2005 Oct 1;104(7):1462-7
Lentigo Maligna of the face

Dancuart et al., Cancer 452279-2283, 1980
Emerging Topics:  SBRT followed by IL-2

“Our 71% response rate is statistically significant because its 95% confidence interval does not include the historical response rate of IL-2 monotherapy in melanoma of 16% (2) (P = 0.05 with a power of 80%)”
• **Additional References:**
  • Halperin, Perez & Brady “Principles and practice of Radiation Oncology” 5th ed.
  • AJCC cancer staging handbook 7th ed.
  • Hansen and Roach III “Handbook of evidence-based Radiation Oncology” 2nd ed.
  • http://en.wikibooks.org/wiki/Radiation_Oncology
  • Hall and Giaccia “Radiobiology for the radiologist” 6th ed.