Melanoma Update
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John Wayne Cancer Institute, Santa Monica, CA

Outline
- Biopsy
- Excision (Margins)
- Sentinel Node
- Complete Lymph Node Dissection
- Stage IV Treatment

Biopsy
- ABCD
  - Asymmetry
  - Border irregularity
  - Color variegation
  - Diameter (>5mm)

Margins
Current (NCCN) Recommendations
- Melanoma-in-situ 5 mm
- Breslow <1mm 1 cm
- Breslow 1.01-2mm 1-2 cm
- Breslow 2.01-4mm 2 cm
- Breslow >4mm 2 cm

How did we get here?
William Norris
- described the first case of melanoma in the English literature in 1820.

Recommended the surgeon:

"Should immediately not only remove the disease, but cut away some of the healthy parts. I would, after excising the part, touch the wound with caustic so as not to leave an atom of the disease, if possible, and occasionally apply the same remedy to the skin in the vicinity."

W. Sampson Handley

"On the pathology of melanotic growths in relation to their operative treatment."
Areas of abnormal melanocytes outside the primary tumor area strongly supports the need for wide excision (usually excluding primary closure) of these tumors.


Margin Recommendations: pre-1970*

2 cm – Cooling (1966)
5 cm – Handley (1907)
5 cm – Raveg (1953)
8 cm – Pack (1953)
15 cm – Petersen (1962)

“As wide as possible” – Veronesi (1966)

Randomized Trials: <2 mm

French
Swed
WHO #10

Randomized Trials: Intergroup

n=468, Median follow up >10 years

- No difference in local recurrence
  - 2.6% (4cm) vs. 2.1% (2cm)
  - Skin grafts 46% (4cm) vs. 11% (2cm)
  - Risk of LR based on primary tumor

Randomized Trials: UK Trial

n=900

- Increased locoregional recurrences in the narrow group (37 vs. 32%)
- But...
  - No SLN allowed
  - changed endpoints
  - these margins not current options
Randomized Trials: Swedish Thick

- n = 936 pts
- Med f/u 6.7 years
- OS hazard ratio 1.05 p=0.64
- OS at 5 years 65% in both groups

Gillgren et al, Lancet, November 2011

Margin Determination
Special Case: Head/Neck melanoma-in-situ

Regional Lymph Nodes

Regional Lymph Nodes

Intergroup ELND: Overall Survival

Balch, Ann Surg Oncol, 2000

Intergroup ELND: Subgroup
Problem: Identification of patients

- 80% of patients undergoing ELND had negative nodes
- Others have concomitant systemic spread – not cured by ELND
- Only a subset can benefit from nodal surgery

Sentinel Lymph Node Biopsy

Dermal Lymphatics

Intraoperative Identification

MSLT I: Trial Design

Melanoma ≥ 1 mm or ≥ Clark IV
(primary analysis 1.2-3.5 mm)

Randomization

Wide excision alone: 40%
Wide excision + SLN: 60%

CLND for Recurrence
Immediate CLND

No recurrence: observation

Overall Melanoma Related Survival
(Breslow 1.20 – 3.5 mm)

<table>
<thead>
<tr>
<th>Group</th>
<th>Event</th>
<th>Total N</th>
<th>5-year Estimate (95% CI)</th>
<th>10-year Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBS</td>
<td>90 / 500</td>
<td>95.7 ± 1.6 %</td>
<td>97.3 ± 2.3 %</td>
<td></td>
</tr>
<tr>
<td>SNB</td>
<td>116 / 769</td>
<td>88.6 ± 1.3 %</td>
<td>81.1 ± 1.7 %</td>
<td></td>
</tr>
</tbody>
</table>

HR: 0.85
P=0.2441
**MSLT I: Trial Design**

- Melanoma > 1 mm or > Clark IV (primary analysis 1.2-3.5 mm)
- Randomization
  - Wide excision alone (40%)
  - Wide excision + SLN (60%)
  - CLND for Recurrence
  - Immediate CLND
  - Observation

**DSS: Primary Endpoint**

**DFS: Secondary Endpoint**

**Latent Subgroup Analysis**

**Patient Characteristics by Intent to Treat Randomization – All Strata**

**Cumulative Incidence of Nodal Metastases:**

- **MSLT1**

**Melanoma Specific Survival – Node+ (All Breslow Thickness)**

- **Group**
  - SNB+
  - OBS

<table>
<thead>
<tr>
<th>Group</th>
<th># Event / Total N</th>
<th>5-year</th>
<th>10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBS, had nodal recur.</td>
<td>72 / 132</td>
<td>56.6 ± 4.4</td>
<td>49.8 ± 4.7</td>
</tr>
<tr>
<td>SNB+</td>
<td>70 / 193</td>
<td>66.5 ± 3.5</td>
<td>56.2 ± 4.2</td>
</tr>
</tbody>
</table>

**HR:** 0.66

**95% C.I.** (0.47, 0.91)

**Log Rank P=0.0117**

**Estimate S(t) ± SE #Event / Total N**

- **Group**
  - SNB+
  - OBS, had nodal recur.

**Breslow 1.2 – 3.5 mm**

- Clinical Recurrence (false neg. SNB)
  - 20.5%

- Clinical Detection Following Nodal Observation
  - 19.8%
### Melanoma Specific Survival – Node+ (All Breslow Thickness)

- **HR:** 0.66
- **95% C.I.:** (0.47, 0.91)
- **Log Rank P:** 0.0117

#### Predictors of SLN Involvement

- **Breslow**
- **Clark**
- **Ulcration**
- **Gender**
- **Primary Site**
- **Age**

#### Predicted probabilities of Nodal Recurrence

| Breslow | Age | Sex | Prob of Recurrence (%)
|---------|-----|-----|------------------------
| 0.0     | <30 | female | 0.9
| 0.0     | <30 | male | 1.6
| 0.0     | 30-39 | female | 1.5
| 0.0     | 30-39 | male | 2.3
| 0.0     | 40-49 | female | 2.1
| 0.0     | 40-49 | male | 2.8
| 0.0     | 50-59 | female | 2.8
| 0.0     | 50-59 | male | 3.5
| 0.0     | 60-69 | female | 3.2
| 0.0     | 60-69 | male | 3.9
| 0.0     | >=70 | female | 3.9
| 0.0     | >=70 | male | 4.6

Concordance index = 0.79

#### MSLT II: Trial Design

- **Melanoma > 1.2 mm or Clark IV, n=3500**
- **LM/SL: standard and molecular assessment**
- **Stratification: MSLT1 Center**
- **Breslow**
- **Ulceration**
- **SLN H&E vs. PCR**

#### Is CLND necessary in SN(+) LN basins?

- **Melanoma Patients with Positive Sentinel Nodes Who Did Not Undergo Completion Lymphadenectomy:**

#### Disease Specific Survival

- **Group:** SLN+/ NSLN+ 77.8%
- **SLN+ NSLN+ 46.4%**
- **P:** 0.0001
**Pre-SLN Ultrasound**

Preoperative ultrasound assessment of sentinel nodes in melanoma patients does not provide reliable staging.
- 49 (1.7%) True Positives (558 False Negative)
- Sensitivity was 8.1%
- Specificity 97.5%
- Negative Predictive Value: 80.5%
- Median area for US detected metastases = 4.80mm²
- Median overall SLN metastasis area = <0.5mm²
- Sensitivity doubles (13% → 23%) after first 100 cases
- Sensitivity and PPV increase with increasing tumor thickness
SLN excision may be therapeutic (i.e. no need to proceed to CLND)

**Interferon-α2b**

- Recurrence-free survival
- Overall survival

Kirkwood et al, Clin Cancer Res, 2004
Pegylated interferon

Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial

Stage IV Melanoma

Surgery for Metastatic Melanoma
Multiple single institution series indicate long-term survival following resection of multiple distant mets for melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Survival (mos)</th>
<th>5-Yr OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gorenstein</td>
<td>56</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Karakousis</td>
<td>39</td>
<td>14</td>
<td>14</td>
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<tr>
<td>Harpole</td>
<td>84</td>
<td>19</td>
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<tr>
<td>Tafra</td>
<td>106</td>
<td>18</td>
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<tr>
<td>Wong</td>
<td>38</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>La Hei</td>
<td>83</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Leo</td>
<td>282</td>
<td>19</td>
<td>22</td>
</tr>
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</table>

Median 19 mos | Median 5 Yr OS 22%

Overall Survival after Resection

Southwest Oncology Group – M1a/M1b/M1c

Complete Surgical Resection At Risk Deaths Median (Months)

Approx. 15%

0 24 48 72 96 Months After Registration

MMAIT IV Canvax™ Survival vs JWCI Phase II Canvax™ and SWOG

Complete resection

There is no survival benefit to leaving disease behind.
**Tumor Volume Doubling Time**

- Tumor Doubling Time: A Selection Factor for Pulmonary Resection of Metastatic Melanoma
- n=129 total pulmonary resections
- n=45 with calculated doubling time

**Metastasectomy: Prognostic Factors**

- n=129 total pulmonary resections
- n=45 with calculated doubling time

**The Dawn of “The Era of Effective Drugs”**

- Objective Response 10.9%
- Disease Control Rate 28.5%
- i.e. >70% of patients progress
- Not without toxicity
  - 14 (2.1%) study-drug related deaths
  - 7 (1%) death due to autoimmunity

**The Era of Effective Drugs: Ipilimumab**

- Prior Stage III
- Disease-Free Interval
- Metastasis Site

**Limitations of New Drugs: PLX4032**

- Curtin NEJM 2005
  - Without chronic sun damage 22/40
  - With chronic sun damage 3/30
  - 25/70 = 36%

**Overall Survival**

- MMAUT Vax Phase 3
- SWOG JWCI Vax Phase 2
- SWOG JWCI non-Vax
- Ipilimumab
- Vemurafenib
- Ipi +/- gp100