Update on SLN and Melanoma:

DECOG and MSLT-II

Gordon H. Hafner, MD, FACS
• No disclosures
• The surgery of malignant disease is not the surgery of organs, it is …of the lymphatic system.

Lord Moynihan

• Lymph nodes are indicators, not governors, of metastatic disease

Blake Cady MD,FACS

• Early completion lymph node dissection did not increase survival

Conclusion, MSLT-II
Objectives

• Changing concepts of the role of lymph node dissection in malignant melanoma
• Rationale for DeCOG trial on CLND and results
• Rationale for MSLT-II and results
• Where do we stand now in treating patients with nodal involvement in malignant melanoma?
Historical Perspective

Risk of Metastases vs Tumor Thickness

- Thin
- Inter
- Thick

Regional
Distant
Historical Perspective

- Two reasons for lymph node dissection: control of nodal basin and improved survival
- Target group always intermediate thickness: higher risk regional disease, lower distant disease at presentation
- Regional node dissection considered appropriate therapeutic procedure
Historical Perspective

• Intergroup Melanoma Surgical Trial (2000): ELND vs observation (1-4 mm)
• No survival difference (15 yr followup)

• Dilution effect (~80% node negative)?
• Perhaps removal of more lymph nodes has no impact on disease progression?
Multicenter Sentinel Lymphadenectomy Trial I

- Primary endpoint MSS

- Secondary endpoints included MSS in node positive and node negative patients

- Evaluation of SLNB technique, and prognostic significance of the SLN
Sentinel Lymph Node

Tumor

Sentinel Lymph Node

LN  LN  LN  LN  LN  LN  LN  LN
MSLT-I Primary Analysis

1347 pts (intermediate thickness)

WLE + SLNB (60%)

SLN (+), Immediate CLND

SLN (-), observe

WLE plus Nodal observation (40%)

If nodal recurrence, Delayed CLND
MSLT-I Secondary Analysis

1347 pts (intermediate thickness)

- WLE + SLNB (60%)
  - SLN (+), Immediate CLND
  - SLN (-), observe
- WLE plus Nodal observation (40%)
  - If nodal recurrence, Delayed CLND
MSLT-I Conclusions

• No overall difference in MSS

• “Accelerated-failure-time latent-subgroup analysis”: improved survival in SLN(+) patients receiving CLND

• Controversial conclusion
DeCOG SLN Trial

• 483 SLN(+) pts randomized to immediate CLND vs observation
• Hypothesis: CLND improves survival
• Primary Melanoma at least 1mm thick; H/N primary, macroscopic/ distant disease excluded
• Primary endpoint: distant metastasis free survival
• Secondary endpoint: DFS, OS, nodal recurrence, complications
• Stratified on basis of tumor thickness, ulceration, and intended adjuvant interferon treatment
DeCOG Results: Distant Metastasis-Free Survival

Events/n 3-year distant metastasis-free survival (90% CI)

- **Observation group**: 55/233 77.0% (71.9–82.1)
- **Complete lymph node dissection group**: 54/240 74.9% (69.5–80.3)

HR 1.03 (90% CI 0.71–1.50); p=0.87

Number at risk:
- **Observation group**: 233 203 186 165 144 125 99 75 61 54 45
- **Complete lymph node dissection group**: 240 195 181 150 136 110 94 75 56 48 36
DeCOG Results: Overall Survival

Overall survival (%)

Events/n  3-year overall survival (90% CI)

- Observation group: 44/233, 81.7% (76.8–86.6)
- Complete lymph node dissection group: 40/240, 81.2% (76.1–86.3)

HR 0.96 (90% CI 0.67–1.38); p=0.87

Number at risk
- Observation group: 233, 206, 191, 178, 157, 136, 109, 81, 69, 60, 49
- Complete lymph node dissection group: 240, 197, 190, 162, 150, 119, 102, 82, 60, 50, 38
DeCOG: DFS Results

**Recurrence-free survival (%)**

**Events/n** 3-year recurrence-free survival (90% CI)

- Observation group: 73/233, 67.4% (61.6–73.2)
- Complete lymph node dissection group: 67/240, 66.8% (60.9–72.7)

HR 0.95 (90% CI 0.72–1.25); p=0.75

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Observation group</th>
<th>Complete lymph node dissection group</th>
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<td>Events/n</td>
<td>233</td>
<td>240</td>
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<tr>
<td>3-year</td>
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<tr>
<td>Survival</td>
<td>73/233</td>
<td>67/240</td>
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<tr>
<td>(90% CI)</td>
<td>67.4% (61.6–73.2)</td>
<td>66.8% (60.9–72.7)</td>
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<tr>
<td>HR</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>(90% CI)</td>
<td>0.72–1.25</td>
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<tr>
<td>p-value</td>
<td>0.75</td>
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**Time from randomisation (months)**

0 6 12 18 24 30 36 42 48 54 60
DeCOG: Complications from CLND

- 58/240 CLND pts (24%)
- Lymphedema (grade 3,4) in 20 pts
- Lymph fistula (grade 3,4) in 5 pts
- Seroma, wound infection, delayed wound healing in others
DeCOG Results: Nodal Recurrence

*Nodal mets more common in observation group (15%) than CLND group

*About half of nodal relapses occurred with distant disease

*Nodal failure rate did not lead to difference in the primary endpoint: distant metastasis free survival
Survival by SLN tumor burden: 1mm or less

- **Observation group**: 31/158, 80.5% (74.6–86.4)
- **Complete lymph node dissection group**: 31/153, 79.5% (73.2–85.8)

HR 1.09 (90% CI 0.72–1.66)
Survival by SLN tumor burden: >1mm
DeCOG Conclusions

• Primary endpoint of distant metastasis free survival: **No survival benefit** for immediate CLND vs observation in melanoma pts with primary tumor >1mm and positive SLN

• No benefit for OS, DFS

• Better control of nodal basin (8% vs 15%)

• **CLND should not be recommended for SLN (+) pts, at least those with mets 1mm or smaller**
DeCOG: Limitations

- Did not meet accrual goal of 558 pts; given no difference in variables and the overlapping survival curves, unlikely further accrual would change results
- Small metastatic tumor burden (65% < 1mm); subset analysis showed no diff vs > 1mm
- Median f/u 35 months; MSLT-I showed median time to detection nodal mets 19.2 mo, while most relapses for St III disease occur within 2 years
DeCOG Limitations (cont)

- CLND removed =<5 nodes in 17% of pts
- CLND count not available in 25%
- Not optimal retrieval
- BUT: mets found in 18% of nonsentinel nodes (consistent with other studies)
- Suggests greater nodal yield probably wouldn’t change results
Multicenter Selective Lymphadenectomy Trial II (MSLT-II)

• Intermediate thickness melanoma pts with (+) SLN: CLND vs observation (CLND if clinical recurrence)
• Primary endpoint: Melanoma specific survival
• Secondary endpoints: OS, DFS, distant metastasis–free survival, extent of nodal involvement
• Trial also included set of pts SLN(-) but RT-PCR (+), stopped after 2012
MSLT-II Results: Melanoma Specific Survival

![Graph showing melanoma-specific survival over years after randomization with comparison between dissection and observation groups.](image)

- **Probabilities of Melanoma-Specific Survival**
  - Censored
  - Observation
  - Dissection

- **Years after Randomization**
  - P=0.55

**No. at Risk**
- Observation: 931, 856, 734, 564, 425, 304, 217, 151, 95, 55, 13
MSLT-II Results: MSS per detection method

![Graph showing probability of melanoma-specific survival over years after randomization.](image)

**Dissection, RT-PCR-positive**
- Probability of melanoma-specific survival is consistent with time after randomization.
- *P* = 0.35

**Observation, RT-PCR-positive**
- Probability of melanoma-specific survival is consistent with time after randomization.
- *P* = 0.47

**Observation, pathologically detected**
- Probability of melanoma-specific survival decreases over time after randomization.

**Dissection, pathologically detected**
- Probability of melanoma-specific survival decreases over time after randomization.

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<thead>
<tr>
<th>Years after Randomization</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<td>Probability of survival</td>
<td>1.0</td>
<td>0.85</td>
<td>0.7</td>
<td>0.55</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.05</td>
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**No. at Risk**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>682</td>
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<td>441</td>
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<td>214</td>
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<tr>
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<td>241</td>
<td>163</td>
<td>109</td>
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<td>73</td>
<td>69</td>
<td>63</td>
<td>61</td>
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<td>36</td>
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<td>105</td>
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<td>63</td>
<td>54</td>
<td>42</td>
<td>31</td>
<td>21</td>
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</table>
MSLT-II Results: DFS

A

Probability of Disease-free Survival

Years after Randomization

No. at Risk
Subgroup 1  744  606  465  343  260  174  114  77  41  15  5
Subgroup 2  820  629  477  346  249  171  124  87  50  28  6
Subgroup 3  80  73  69  63  59  56  42  32  26  17  6
Subgroup 4  111  103  93  81  73  59  49  36  27  18  4

P=0.66
P=0.02

Censored
MSLT-II Results: Distant Metastasis-Free Survival

![Graph showing distant disease-free survival probability over years after randomization with no significant difference between subgroups (P=0.66 and P=0.27).](image)

**No. at Risk**

<table>
<thead>
<tr>
<th>Subgroup 1</th>
<th>744</th>
<th>649</th>
<th>520</th>
<th>384</th>
<th>286</th>
<th>192</th>
<th>128</th>
<th>86</th>
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MSLT-II Results: Survival Without Nodal Recurrence

![Graph showing survival without nodal recurrence](image)

**Years after Randomization**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>1</td>
<td>744 662 552 412 308 201 138 89 50 21 6</td>
</tr>
<tr>
<td>2</td>
<td>820 659 525 386 282 194 137 96 56 31 7</td>
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<tr>
<td>3</td>
<td>80 75 72 67 62 59 47 36 30 18 7</td>
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<td>4</td>
<td>111 105 94 82 77 62 53 41 30 20 4</td>
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</table>

- CLND: P = 0.81
- Obs: P < 0.001
MSLT-II Results: Cumulative Rate of Nonsentinel Node Metastasis
MSLT-II Conclusions

- Immediate CLND increased regional control but did not increase melanoma-specific survival

*Question: does “less” regional control mean loss of regional control?

*Question: does a thicker metastatic burden warrant CLND?
Recent studies strongly support the concept that completion lymphadenectomy does not alter the course of metastatic melanoma to regional nodes.

Role of CLND: palpable lymph nodes, patients with recurrence limited to regional nodes.

Morbidity of CLND significant and in absence of clear survival improvement, is difficult to support.

Both studies: equivalent distant metastasis free survival in both CLND and obs groups.
Questions?