The New and Changing Role of Sentinel Lymph Node Biopsy for Melanoma

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2019 AAD Guidelines for SLNBx

- **<0.8mm**: SLNBx not recommended
- **<0.8mm***: Consider SLNBx with adverse histologic features
- **0.8-1mm**: Consider SLNBx
- **1mm or >**: Discuss and offer SLNBx

**Why?** These groups likely to have +nodes >5% of the time
Does removing the positive SLN help the patient in any way?

What’s the evidence?
Four Historic Roles for SLNBx in melanoma

1. **To improve survival** in patients with intermediate thickness melanomas or high risk thin melanomas by removing nodal deposits before spread systemically or before they are detected clinically.
2. To provide **prognostic information** as the most important predictor of death from melanoma
3. **To avoid long term complications** associated with complete dissection for palpable nodes by removing positive nodes early
Four Historic Roles for SLNBx in melanoma

4. To aid in the decision for systemic adjuvant therapy
What do Lymph Nodes do? They *Sample*

1. Direct invasion into blood vessels - arteries or veins
2. Enter lymphatics and bypass nodes
3. Enter sentinel node and deposit or pass through
4. Bypass sentinel node and enter other nodes in basin
5. **The LN samples local antigens, it is not a filter**
Let’s examine the evidence to support the 4 roles for SLNBx
1. Does SLNBx provide a Survival Benefit? No

- Electively removing clinically normal nodes has \textit{never} provided a survival benefit for any solid tumor.
- \textbf{MSLT-I} showed \textit{no survival benefit} for performing a SLNBx + CLND.
- \textbf{MSLT-II} (and DeCOG-SLT) showed \textit{no survival benefit} to remove positive lymph nodes further down the chain in patients with a positive SLNBx.
2. Is SLNBx the best prognostic test?  No

Most melanoma patients are not a candidate for the test:
- 70% of patients have melanomas less than 1mm thick
- Many of the remaining 30% of eligible patients choose not to have the test

The test fails most patients who have the test:
- The False negative rate is up to 14%, The False positive rate is 11-34%
- SLNBx only identifies one third of patients who will die from melanoma
- Twice as many SLN- patients die as SLN+ patients
The origin of SLNBx as the best prognostic test

**Confusing conclusion:** “SLN status was the strongest predictor of death from melanoma”

<table>
<thead>
<tr>
<th>Risk of death from melanoma</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLN Status</strong> (positive vs negative)</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Breslow Thickness</strong> (per 1-mm increase)</td>
<td>1.59</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
The origin of SLNBx as the best prognostic test

<table>
<thead>
<tr>
<th>10 yr melanoma-specific survival (MSS)</th>
<th>Risk of death from melanoma</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td>(+)</td>
<td>62%</td>
<td>38%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10 yr melanoma-specific survival (MSS)</th>
<th>Risk of death from melanoma</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mm</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>2mm</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>3mm</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>4mm</td>
<td>60%</td>
<td>40%</td>
</tr>
</tbody>
</table>
2. Is SLNBx the best prognostic test?

Two very important papers:

1. **Freeman**: (Meta-analysis) “SLNBx may not provide more accurate prognostic information than Breslow thickness for most melanomas.”

2. **Stiegel**: The only study to answer the question “if you know the thickness, does SLN status add significant prognostic information?”
Does SLNBx status give us more prognostic information than Breslow thickness alone?

<table>
<thead>
<tr>
<th>Thickness</th>
<th>SLN +</th>
<th>Breslow thickness</th>
<th>SLN –</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 – 1.00</td>
<td>85.7</td>
<td>90.3</td>
<td>90.8</td>
<td>0.54</td>
</tr>
<tr>
<td>1.01 – 2.00</td>
<td>82.0</td>
<td>87.2</td>
<td>88.1</td>
<td>0.0775</td>
</tr>
<tr>
<td>2.01 – 4.00</td>
<td>68.9</td>
<td>76.5</td>
<td>79.5</td>
<td>0.17</td>
</tr>
<tr>
<td>4.01+</td>
<td>72.2</td>
<td>73.5</td>
<td>75.3</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Stiegel – Cleveland Clinic Data Base - 896 patients*
### Better prognostic tools for melanoma patients

<table>
<thead>
<tr>
<th>Web-based models using known clinic-pathologic features – Breslow thickness plus other important data</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LifeMath.net</td>
</tr>
<tr>
<td>• Memorial Sloan Kettering Nomogram</td>
</tr>
<tr>
<td>• AJCCmelanomaprognosis.net</td>
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</tbody>
</table>

### Gene Expression Profile

| • GEP predicts metastatic events and death better than SLNBx or any other prognostic tool alone |
| • Combined with clinico-pathologic factors may be better |
3. Is the role of SLNBx to avoid the long-term complications associated with CLND?

<table>
<thead>
<tr>
<th>Group 1000 patients</th>
<th>Complication rate</th>
<th>Number of patients with complications</th>
<th>Total number of patients with complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLND for palpable disease (195 patients)</td>
<td>20%</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>CLND for SLN+ biopsy (160 patients)</td>
<td>12.4%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>CLND for false (-) SLN (40 patients)</td>
<td>20%</td>
<td>8</td>
<td>58</td>
</tr>
<tr>
<td>SLN biopsy alone (800 patients)</td>
<td>3.6%</td>
<td>30</td>
<td></td>
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</table>
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

- “Dramatic results with new immune therapies”

- Survival and progression in patients with melanoma is improved with:
  - Nivolumab
  - Ipilimumab
  - Dabrafenib
  - Trametinib
  - Vemurafenib
  - Pembrolizumab
  - Talimogene laherparevic
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

- Most studies have been limited to unresectable, advanced melanoma, not patients with no clinical evidence of metastases

- KEYNOTE-006: Pembrolizumab versus ipilimumab for advanced melanoma. This study enrolled only **unresectable** or advanced melanoma, not stage IIIA.
- CheckMate 066: Nivolumab in **unresectable** Stage III or IV melanoma BRAF native melanoma.
- CheckMate 067: Nivolumab and Ipilimumab in advanced melanoma. This study enrolled only **unresectable** Stage III or Stage IV melanoma.
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

- What studies have looked at clinically node negative patients?

- Stage IIIA: Patients with no palpable nodes and a +SLN
- Stage IIIB: Patients with no palpable nodes and a +SLN and:
  - Ulcerated primary tumors any thickness
  - Thin melanomas less than 1mm thick with a Mitotic rate $\geq 1$
- Stage IIIC: Patients with melanoma of any thickness, no palpable nodes and:
  - Satellite metastases
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

1. **Ipilimumab (CTLA-4):** no apparent survival advantage for IIIA patients with microscopic disease. Possible subgroup benefit for IIIB. (EORTC 18071).
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

1. **Ipilimumab (CTLA-4):** no apparent survival advantage for IIIA patients with microscopic disease. Possible subgroup benefit for IIIB. (EORTC 18071).

2. **Dabrafenib (BRAF) + Trametinib (MEK):** no survival benefit for stage IIIA or IIIB patients (COMBI-AD)
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

1. **Ipilimumab (CTLA-4):** no apparent survival advantage for IIIA patients with microscopic disease. Possible subgroup benefit for IIIB. (EORTC 18071).

2. **Dabrafenib (BRAF) + Trametinib (MEK):** no survival benefit for stage IIIA or IIIB patients (COMBI-AD)

3. **Vemurafenib (BRAF):** No significant reduction in relapse free survival for stage IIIA or IIIB (BRIM8)
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

4. **Nivolumab (PD1):** did not offer better recurrence free survival than Ipilimumab for stage IIIB. (CheckMate 238), but Ipilimumab had shown possible benefit for IIIB.
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy?

4. **Nivolumab (PD1):** did not offer better recurrence free survival than Ipilimuab for stage IIIIB. (CheckMate 238), but Ipilimumab had shown possible benefit for IIIB.

5. **Pembrolizumab (PD1):** no significant benefit in relapse free survival on forest plots. (EORTC 1325)
4. Can SLNBx identify patients who benefit from Adjuvant Therapy? Summary

- To date, there is no systemic adjuvant therapy that prolongs survival in patients with clinically normal nodes, even those who are SLNBx positive.
- However, patients with ulcerated primaries (IIB) may have some unproven benefit, at a great cost and side effects.
What would JZ do if he had an ulcerated primary melanoma, Stage IIIIB?

- **GEP**
  - **Class 1a:** Observe
  - **Class 2b:** Consider SLNBx
    - **Positive:** Discuss PD1 therapy with medical oncology
    - **Negative:** Observe
Summary of the evidence for the role of SLNBx

1. Not a procedure that provides a survival benefit
2. Not the best prognostic test
3. Does not reduce the long term complications of complete lymph node dissection
4. *Does not select patients for systemic adjuvant therapy – yet*
5. Future studies may support SLNBx for adjuvant Rx for patients:
   1. GEP Class 2 melanomas
   2. Ulcerated primary melanomas (potential stage IIIB)
The last word: *Your role*

1. **Provide true informed consent.** 32% of patients believe it would prevent disease-spread.
2. **Offer Clinical trials** for systemic adjuvant therapy. Know what is available locally.
3. **Pay attention to the literature:** Watch for adjuvant therapy indicated for patients at high risk for metastasis staged by SLNBx, Class 2b Gene Expression Profile test results, or other prognostic tests.


References (cont)

- **Slide 12:**
  
  
• Slide 16:


• Stiegel E, Xiong D, Ya J, Funchain P, et al. Prognostic value of sentinel lymph node biopsy according to Breslow thickness for cutaneous melanoma. Accepted for publication to the Journal of the American Academy of Dermatology January 2018.
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• Slide 17:
  Mitra A. Melanoma SNBx and prediction models for relapse and overall survival. Br J Cancer 2010;103:1229-1236
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Slide 18:

Slide 19:


References (cont)

- **Slide 23:**

- **Slide 24:**

- **Slide 27:**