Sentinel Lymph Node Biopsy: Current Evidence for its Role in Managing Melanoma

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Why is this topic important today? — You play an important role in management!

- Confusion, uncertainty, controversy about SLNBx
- Malpractice fears if you don’t refer
- Changing evidence of the benefit of SLNBx
- To have the evidence to advise your patients truthfully
- Do you know what type of informed consent your patients get?
Four suggested 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
Four suggested Roles for SLNBx in melanoma

2. To provide **prognostic information** as the most important predictor of death from melanoma
Four suggested Roles for SLNBx in melanoma

3. **To avoid long term complications** associated with complete dissection for palpable nodes by removing positive nodes early
Four suggested Roles for SLNBx in melanoma

4. To aid in the **decision for systemic adjuvant therapy**
Let's examine the evidence for these 4 roles for SLNBx.
First, let’s review how tumors metastasize

• Theory #1: Tumor cells follow an orderly progression from the primary site, **first** into lymphatics and then into vascular system to form distant metastatic deposits. (SLN is first site of metastasis)

• Theory #2: Tumor cells spread simultaneously through the lymphatic system and the vascular system. (SLN samples tumor cells and antigens flowing from regional lymphatics)
So 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**
How do cells metastasize?

• Dissemination of cancer cells is a very **early** event
• Early cancer cells are mostly dormant
• Dissemination of nodal and distant metastases are simultaneous.
• **The preponderance of evidence refutes the orderly progression theory**
Let’s examine the evidence to support these 4 roles for SLNBx
1. Is the Role of SLNBx a Survival Benefit? *No*

- Electively removing clinically normal nodes has **never** provided a survival benefit for any solid tumor.
- **MSLT-I** showed **no survival benefit** for performing a SLNBx + CLND.
- **MSLT-II** (and DeCOG-SLT) showed **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?

- The prognostic significance of SLNBx is the most common reason offered to justify the procedure.

- The 2017 American Society of Clinical Oncology (ASCO)-Society of Surgical Oncology (SSO) guideline for sentinel lymph node biopsy in melanoma states:
  - “The recommendation for staging with SLN biopsy in the intermediate-thickness population is ... based on the established prognostic significance of SLN status.”

- Where did the “established prognostic significance” come from?
### 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></td>
<td></td>
<td>1.59</td>
</tr>
<tr>
<td>3mm</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.52</td>
</tr>
<tr>
<td>4mm</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.02</td>
</tr>
</tbody>
</table>
2. Is SLNBx the best prognostic test?

Three important studies:

1. Zagarella. “SLNB as the ‘most powerful predictor’ .. cannot be substantiated.”

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

3. Stiegel: “SLN status does not offer better prognostic information compared to Breslow thickness alone.”
Does SLNBx give us any more info than Breslow Tx?

<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>0.075</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
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
**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>
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<tbody>
<tr>
<td>• LifeMath.net</td>
</tr>
<tr>
<td>• Memorial Sloan Kettering Nomogram</td>
</tr>
<tr>
<td>• AJCCmelanomaprognosis.net</td>
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<table>
<thead>
<tr>
<th>Gene Expression Profile</th>
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</thead>
<tbody>
<tr>
<td>• GEP predicts metastatic events and death better than SLNBx or any other prognostic tool alone</td>
</tr>
<tr>
<td>• Combined with clinico-pathologic factors may be better</td>
</tr>
</tbody>
</table>
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></td>
</tr>
<tr>
<td>SLN biopsy alone (800 patients)</td>
<td>3.6%</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy? *Not yet*

- **Most studies have been limited to unresectable, advanced metastatic melanoma, not Stage IIIA SLN+ patients**

- KEYNOTE-006: Pembrolizumab versus ipilimumab for advanced melanoma. This study enrolled only unresectable or advanced melanoma, not stage IIIA.
- CheckMate 238: Nivolumab versus Ipilimumab in resected stage III or IV Melanoma. This study enrolled only Stage IIIB, IIIC, or IV melanoma.
- 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 Stage III unresectable or Stage IV melanoma.
1. Ipilimumab (CTLA-4) alone is approved for Stage IIIA patients with SLN deposits >1mm in diameter {EORTC 18071}
   - Ipi prolonged survival in the entire group of stage III patients
   - “There was no apparent survival advantage for Stage IIIA patients with microscopic disease” Eggermont (author)
   - Cost for drug alone, first year of 3yr = $700,000.
   - Side effects severe (five deaths [1.1%] due to drug).
   - *Ipi is not a cost effective choice for Stage IIIA patients*
4. Can SLNBx identify patients who benefit from Adjuvant Systemic Therapy? *Not yet*

2. **Dabrafenib (BRAF) + Trametinib (MEK) in Stage III BRAF mutated melanoma:** (SLN+ with deposits > 1mm diameter only accounted for 18% pts) {COMBI-AD}
   - Few patients eligible: Only 20% of SLN patients are positive, only 50% of those have BRAF mutations, and only 20% of those have deposits > 1mm, so only 2% of SLN patients would be eligible.
   - The combination drug increased relapse-free survival compared to placebo, but the overall survival effect was not significant in the first interim analysis.
   - Cost - $250,000 / year for drugs alone.
   - **Mitogen-activated protein kinase inhibitors are not a cost-effective choice for Stage IIIA patients**
4. Can SLNBx identify patients who benefit from Adjuvant Therapy? *Not yet*

- To date, there is no systemic adjuvant therapy that prolongs survival in patients with clinically normal nodes, or patients who are SLNBx positive.
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
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.
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