Sentinel Lymph Node Biopsy for Melanoma: Useful

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Table 3. Indications for Consideration of Sentinel Lymph Node Biopsy in Patients With Clinically Localized Melanoma*

<table>
<thead>
<tr>
<th>Lesion ≥1.0 mm</th>
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<tbody>
<tr>
<td>Lesion &lt;1.0 mm (0.75-1.0 mm) with any of the following:</td>
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<tr>
<td>Ulceration</td>
</tr>
<tr>
<td>Extensive vertical regression to at least 1.0 mm</td>
</tr>
<tr>
<td>Young patient age</td>
</tr>
<tr>
<td>High mitotic rate particularly in younger age</td>
</tr>
</tbody>
</table>

*Primary melanoma location and location or number of predicted draining nodal basins should not be used as exclusion criteria. Older patient age is not a contraindication in the case of high-risk lesions.

*From: Johnson: Arch Dermatol, Volume 140(1). January 2004. 107-113*
Sentinel Node Hypothesis

- **Theory** – an orderly progression of cancer cells occurs in the initial stage of the metastasis within the lymphatic system
- **Verse** – direct hematogenous spread
- **The first lymph node that cancer cells metastasize to is the SLN**
- **Hypothesis** – a tumor-negative SLN can predict the absence of metastatic disease
SLN Hypothesis

SLN really is the first draining node

• Correlation between the pathologic status of the SLN and the rest of the nodal basin

• Correlation between SLN status and overall disease-specific outcome

Morton. Interim results of the MSLT-1. ASCO.2005

- 237 SLNB
- Identified the SLN in 194 of the lymphatic basins
- 40 had metastatic disease
- Metastasis were present in 47(18%) of 259 SLN

- Elective lymphadenectomy –
- Non-sentinel nodes were sole site of metastasis in only 2/3079 nodes

- False negative rate <1%
Does the **SLNB** accurately identify the **SLN** in patients with primary melanoma?

- Combination of preoperative lymphoscintigraphy, intraoperative gamma probe interrogation, intraoperative injection of blue dye
- Consistently provides the highest success rate in accurately identifying the SLN


200 SLNB

- 139 (69.5%) SLN were blue dye stained
- 167 (83.5%) SLN were hot (radioisotope)

With both techniques

- 124 of 129 (96%) of SLN were identified
False Negative Finding

Presence of histological or clinically identified metastasis in non-SLN in patients with a negative SLN

Three main causes

1. Technical failure
2. Pathological failure
3. Biological failure
Technical failure

- Inexperience – evidence suggest a learning curve

**Sentinel Lymph Node Biopsy Learning Curves: Summary**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Identification rate 85% (n)</th>
<th>False-negative rate 5% (n)</th>
</tr>
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<tbody>
<tr>
<td>Moffitt</td>
<td>15</td>
<td>Not determined</td>
</tr>
<tr>
<td>Northwestern</td>
<td>20</td>
<td>Not determined</td>
</tr>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>ECU Multicenter</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Louisville Multicenter</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>
Technical failure

- SLNB after a wide excision is associated with a higher likelihood of false-negative
- potential lymphatic drainage disruption

Pathological failure

Lack of sensitivity of current histopathologic methods

- Evidence suggest that serial sectioning and immunohistochemistry, if H&E staining is negative, identifies a higher percentage of positive SLN – reducing false negatives

Biological failure

- Lymphatics obstructed by melanoma cells
- Inadequate initial excision is performed, leaving cells at or near the primary site that acquire the capability to disseminate secondarily to nodes other than the original SLN

This is reduced in centers with experienced multidisciplinary approaches

Vuylsteke, Clinical outcome of stage I/II melanoma patients after selective sentinel lymph node dissection. J Clin Onc. 2003
Does **SLNB** accurately predict outcome?

- Evidence supports **SLN** status as the most powerful independent factor predicting survival
- Evidence indicates that **SLNB** provides the highest sensitivity and specificity of any nodal staging test available


Morton. The case for lymphatic mapping and sentinel lymphadenectomy in the management of primary melanoma. Br J Derm. 2004


- 612 melanoma patients
- Univariate analysis
- Prognostic factors for disease free survival
- +SLN / tumor thickness / Clark level >III / ulceration

3 yr disease free survival for -/+ SLN patients - 88.5 and 55.8%

P=<=.0001 - SLN status was the strongest predictor
American Joint Committee on Cancer (AJCC)

- **TNM classification**
- **The number of positive lymph nodes and the tumor burden**
- Either subclinical (microscopic) or clinically apparent (macroscopic) nodal metastases, rather than nodal size—define the N category.
- Using tumor burden (microscopic/macroscopic) as a determinant of the N category allows incorporation of SLNB results into staging.

Does SLNB accurately predict outcome? Cont…

• Accurate staging is the bases for counseling and therapeutic decision making by the physician

• Prognostic information helps patients to make an informed decision about their treatment options

USEFUL
Does **SLNB** result in improved regional disease control?

- There is no conclusive evidence that SLNB followed by immediate CLND improves overall survival
Hypothesis of immunologic down-regulation

The primary melanoma interacts with the SLN as an immunologic unit to create a local immunosuppression that favors melanoma metastasis and growth

- Cytokine-mediated SLN immunosuppression is associated with primary melanoma
- Melanoma SLNs show a significant decrease in T cell rich paracortical areas and a profound down-regulation of antigen-presenting dendritic cells
- CD8 T cells from metastatic lymph nodes are functionally tolerant to tumor progression

Manipulation of the local cytokine microenviroment may be able to reverse the local immunodysfunction

Cochran. Sentinel lymph nodes show profound downregulation of antigen-presenting cells of the paracortex. Mod Path. 2001
E (elective) LND Trails

• Do not show improvement in survival
• However, only 20% of the patients enrolled had nodal involvement
• So, the these studies were not adequately powered to make inferences about SLNB

Veronesi. Inefficacy of immediate node dissection in stage I melanoma of the limbs. NJM. 1977.
WHO – ELND Trial

- Randomized trial of ELND vs. observation
- 240 pts with melanoma >1.5mm
- No overall survival benefit noted
- Group within the ELND group that had positive nodes had a **48%** 5-yr survival
- Compared with the group with clinically positive nodes in the observation arm
  - **27%** survival (p=.04)

MSLT-I

- Multicenter Sentinel Lymphadenectomy Trial
- Presented at the American Society of Clinical Oncology in 2005
- 2001 pts
- 18 centers
- Mean follow-up – 59.5 months

Morton. Interim results of the MSLT-1. ASCO.2005
MSLT-I

- Primary cutaneous melanoma - Breslow thickness of 1.0 mm or more
- Clark level IV or higher
- Clinically negative nodes
- Randomized in a 60:40 ratio to WLE and SLNB vs. WLE only (observational)
- SLNB positive – immediate CLND
- WLE only group - underwent delayed CLND when nodes became clinically positive
Prognostic Benefit

• 7 year - melanoma specific survival
• WLE/SLNB arm –
• 88% - survival for patients with negative SLNB
• 71% - survival for patients with a positive SLNB
Survival Benefit

7-year melanoma-specific survival

- **WLE/SLNB arm** – SLN + - melanoma 1.2-3.5 mm thick - that underwent immediate CLND – **68%** survival
- **WLE-only** – node positive clinically – delayed CLND – **48%** survival
- **P=.0034**
Survival Benefit

• Patients with occult SLN metastasis

• Immediate CLND prolongs survival compared with delayed CLND when SLN metastasis become clinically evident
Clinical Benefit

- SLN tumor burden
- WLE/SLNB arm – total involved nodes after CLND was 1.6
- WLE only – clinically + nodes – CLND was 3.4
- Only 5% with +SLNB had 4 or more +nodes after immediate CLND vs. 27% in the delay CLND group

Suggest clinical benefit if tumor burden correlates with survival
Does lymph node metastasis become clinically evident?

- WLE/SLNB group – 19.8% had +SLN

- WLE-only – 20.3% - experienced clinically positive lymph node basin recurrence

SLNB finds this 20%, earlier
Morbidity of SLNB justified?

Sunbelt trial – 3600 patients in 79 center

- SLNB – **4.6%** complication rate (most minor)

- CLND after +SLNB - **23.2%** complication rate

Hematoma/seroma – **2.31%** was the most common complication

If the MSLT-I shows prognostic and/or survival benefit then – **YES!**
Conclusion

Current evidence supports the use of SLNB in the management of melanoma.
THE END