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Melanoma Sentinel Lymph Node Biopsy–Is it the Gold Standard?

Paul K. Shitabata, M.D.
Dermatopathologist
Pathology Inc.
Technical details of intraoperative lymphatic mapping for early stage melanoma

<table>
<thead>
<tr>
<th>Sites</th>
<th>% Metastases</th>
<th>Method of detection</th>
<th>% Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN</td>
<td>18% (47/259)</td>
<td>H and E</td>
<td>21% (194/237)</td>
</tr>
<tr>
<td>Non-SLN</td>
<td>&lt;1% (2/3079)</td>
<td>IPOX</td>
<td>9%</td>
</tr>
</tbody>
</table>

John Wayne Institute for Cancer Treatment and Research, St John's Hospital and Health Center, Santa Monica, Calif 90404.
Preparation of Sentinel LN

- Bisect through longest meridian
- 10 full face sections-
  - 1, 3, 5, 10 for H and E
  - 2, 4, 6, for S100, HMB-45, Mart1
- 20% positive SN
Skip metastasis beyond the first node is rare
Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group

- 30-case learning phase
- Comparison group of JWCI patients
  - 551 pts. MSLT group
  - 584 pts. JWCI group
- Selection criteria:
  - Thickness $\geq 1$ mm
  - Clark level $\geq$ III, or
  - Thickness $<1$ mm with a Clark level $\geq$ IV

<table>
<thead>
<tr>
<th>Group</th>
<th>LM with blue dye</th>
<th>LM with blue dye/radiocolloid</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSLT</td>
<td>95.2%</td>
<td>99.1%</td>
</tr>
<tr>
<td>JWCI</td>
<td>95.2%</td>
<td>99.1%</td>
</tr>
</tbody>
</table>

Melanoma recurrence patterns after negative sentinel lymphadenectomy

- Median follow-up of 36.7 months, 69 (8.9%) of 773 patients with tumor-negative SNs had recurrent disease.
- 8.9% of patients with tumor-negative SNs will develop recurrence
- Low incidence (1.7%) of regional basin recurrence in patients with negative SNs

<table>
<thead>
<tr>
<th>Location of recurrence</th>
<th>3YR Survival after first recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional basin</td>
<td>63.5% (13 pts)</td>
</tr>
<tr>
<td>Local or in-transit</td>
<td>48.7% (19 pts)</td>
</tr>
<tr>
<td>Distant</td>
<td>17.1% (37 pts)</td>
</tr>
</tbody>
</table>

ELND failed to increase survival because it was applied to unselected patients.
Single-institution experience in the management of patients with clinical stage I and II cutaneous melanoma: results of sentinel lymph node biopsy in 240 cases

Breslow thickness of 0.99 mm was the optimal cutpoint for predicting the SLNB result.

- Stage I and II (AJCC 2002)
- Positive SLN 20.8%
- 24 pts. (12.3%) developed a locoregional or distant recurrence at a median follow-up of 31 months.
  - Recurrences were more frequent with positive SLN.
  - Recurrences with positive SLN were more likely to have distant metastases

Complete regional dissection in patients with positive SN would result in more effective cure by disrupting the metastatic cascade.
Sentinel lymphadenectomy does not increase the incidence of in-transit metastases in primary melanoma

- 4,412 patients who underwent WLE (n = 2,771), SLND (n = 1,016), or ELND (n = 625) for stage I/II melanoma (1971 through 2002)

- Incidence of ITM increased with:
  - Breslow depth, Clark level, and T stage.
  - No significant differences in ITM overall or as a first recurrence
  - Treatment groups matched by T stage, age, sex, Breslow depth, and primary location

No relationship between SLND and ITM.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>% ITM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENLD</td>
<td>6.56</td>
</tr>
<tr>
<td>WLE</td>
<td>3.36</td>
</tr>
<tr>
<td>SLN</td>
<td>3.64</td>
</tr>
</tbody>
</table>

J Clin Oncol, 2005 Jul 20;23(21):4764-70
Roy E. Coats Research Laboratories of the John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA
SLNB reduces the morbidity of ELND
Immediate dissection of nodes containing micrometastases improves prognosis…Does SNLB improve Survival?
Safe Landing
Fig 8. Multicenter Selective Lymphadenectomy Trial treatment algorithm. *CLND*, Complete lymph node dissection; *LM/SL*, lymphatic mapping and sentinel lymphadenectomy; *SLN*, sentinel lymph node.
Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial

- Clear survival benefit for immediate vs. delayed dissection of LN mets
  - 71% of those treated with LM/SNB and immediate lymph-node removal were alive at five years, compared with 53% of those in the “watch and wait” group.
  - “Watch and wait” group had more cancerous lymph nodes on average (3.4) than those in the LM/SNB group (1.6)

- 2001 pts
- Clinically localized intermediate thickness primary melanoma
- Randomize to WE with CLND if mets develop or WE plus LM/SNB with immediate complete dissection if SN+
- 20% had SLN+
- One cancerous node were 2.6 times more likely to die of melanoma within five years

- 10.1% complication rate for LM/SNB vs. 37.2%
- LM/SNB were 26% less likely to have a recurrence of melanoma after five years than those treated with the “watch and wait” approach

SLNB is a derivative of an ineffective therapy
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>DESIGN</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup Melanoma Trial</td>
<td>Melanoma 1-4 mm ELND</td>
<td>ELND with slightly better survival at 10 yrs</td>
</tr>
<tr>
<td>WHO #1*</td>
<td>Extremity melanoma</td>
<td>ELND no difference in survival</td>
</tr>
<tr>
<td></td>
<td>No lymphoscintigraphy</td>
<td></td>
</tr>
<tr>
<td>WHO #14*</td>
<td>Trunk melanoma</td>
<td>ELND with slightly better survival at 10 yrs</td>
</tr>
</tbody>
</table>
THE TRUTH IS OUT THERE
THE SMALLEST SPECIMEN YET.
Lymphatic mapping identifies the first node receiving lymphatic drainage from a given skin area in over 95% of cases.
Role of lymphoscintigraphy for selective sentinel lymphadenectomy

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>LN Basins</th>
</tr>
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<tbody>
<tr>
<td>Base of scalp</td>
<td>Base of the neck up</td>
</tr>
<tr>
<td></td>
<td>Occipital or upper cervical areas</td>
</tr>
<tr>
<td></td>
<td>Neck base</td>
</tr>
<tr>
<td>Upper limb</td>
<td>Above axilla</td>
</tr>
<tr>
<td>Post. Body wall</td>
<td>Para-aortic</td>
</tr>
<tr>
<td></td>
<td>Paravertebral</td>
</tr>
<tr>
<td></td>
<td>Retroperitoneal</td>
</tr>
<tr>
<td>Hand and arm</td>
<td>Epitrochlear region</td>
</tr>
<tr>
<td>Foot and leg</td>
<td>Popliteal</td>
</tr>
</tbody>
</table>

- SNs outside the axilla, which occur in about 50% of patients
  - Internal mammary chain
  - Supraclavicular region
  - Interpectoral region
  - Intramammary interval nodes

Cancer Treat Res. 2005;127:15-38
Uren RF, Howman-Giles RB, Chung D, Thompson JF. Nuclear Medicine and Diagnostic Ultrasound, RPAH Medical Centre and Discipline of Medicine, The University of Sydney, Sydney, NSW, Australia.
Proportion of melanoma-positive sentinel nodes is higher in patients with thicker tumors.
Factors predictive of tumor-positive nonsentinel lymph nodes after tumor-positive sentinel lymph node node dissection for melanoma

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Probability % of SN+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12.3%</td>
</tr>
<tr>
<td>1</td>
<td>30.9%</td>
</tr>
<tr>
<td>2</td>
<td>41.9%</td>
</tr>
</tbody>
</table>

- 1,599 patients
- 19.5% underwent CLND for tumor-positive SN.
- Forty-six (24%) patients had tumor-positive NSN
- Risk Factors
  - Breslow \(> \text{or } \geq 3 \text{ mm}\)
  - SN tumor size \(> \text{or } \geq 2 \text{ mm}\)
Presence of histologically and/or histochemically detectable tumor cells in the lymphatic basin is a more informative predictor of early relapse than Breslow thickness.
Sentinel node biopsy provides more accurate staging than elective lymph node dissection in patients with cutaneous melanoma

- Sentinel node biopsy identified more nodal micrometastases than ELND but did not influence survival*
- Preop LS with more detailed pathologic examination of the appropriate lymph nodes
- SNB (n = 672) or ELND (n = 793).

- Patient factors that influenced nodal positivity included:
  - Age
  - Breslow thickness
  - Ulceration
  - Head or neck primary
  - Operation type (SNB or ELND)

Ann Surg Oncol. 2004 Sep;11(9):829-36.
Doubrovsky A, De Wilt JH, Scolyer RA, McCarthy WH, Thompson JF
Sydney Melanoma Unit, Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia.
If an extremely sensitive test could detect any tumor cells, it may lead to a higher proportion of positive findings but with a much lower prognostic value.
Quantification of melanoma micrometastases in sentinel lymph nodes using real-time RT-PCR

<table>
<thead>
<tr>
<th>Assay</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology + mRNA of one or both markers</td>
<td>17%</td>
</tr>
<tr>
<td>Histology – positive RT-PCR</td>
<td>28%</td>
</tr>
</tbody>
</table>

- 139 patients with 235 SLN were assessed for Melan-A and tyrosinase expression by real-time quantitative RT-PCR
- Tumor recurrences were demonstrated (median 29 months)
  - Eight patients (35%) with histopathologically positive SLN
  - Four patients (10%) with submicroscopic tumor cells detected exclusively by real-time RT-PCR
  - *None of the patients negative by both methods*
- RT-PCR for the detection of minimal residual melanoma in SLN improves the prediction of disease-free survival

Fig 9. Sunbelt Melanoma Trial treatment algorithm. CLND, Complete lymph node dissection; LM/SL, lymphatic mapping and sentinel lymphadenectomy; RT-PCR, reverse transcriptase polymerase chain reaction; SLN, sentinel lymph node.
...The only drawback of SNLB is the side effects of mini-invasive surgery...
Sentinel-lymph-node biopsy (SLNB) for melanoma is not complication-free

- Neck SLNB—highest rate of identification failure
- Prognostic factors of morbidity
  - Patient age
  - Basin location
  - Number of excised nodes
- Three hundred and nine lymphatic basins of 250 patients
- Overall complication rate was 20%.
- Sensory morbidity was significantly associated with axillary SLNB (p=0.04) and was more prevalent in younger patients.


Wasserberg N, Tulchinsky H, Schachter J, Feinmesser M, Gutman H. Department of Surgery B, Rabin Medical Center, Beilinson Campus, Petah Tiqwa 49100 and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
Immune System Alterations

- Resecting SN may remove the critical first defense

- Nodal mets may occur years after resection implying active nodal immune response

- Few tumor cells may provide a natural vaccine
Should All Patients with Melanoma undergo SNLB?
Sentinel lymph node biopsy for the T1 (thin) melanoma: is it necessary?

- LN mets in 2/24 pts (8.3%) in whom the thickness of the melanoma was 0.9 mm and 1 mm.
- Both patients have died of metastatic melanoma.
- No recurrence has been demonstrated in the remaining 22 patients at the 2 to 5-year follow-up.
- Superficial spreading or nodular melanoma larger than 0.9 mm should include sentinel lymph node biopsy regardless of other associated histological factors.

- Retrospective analysis of 34 patients with T1 melanoma was completed over a 3-year period.
- Selection criteria:
  - Breslow thickness of less than or equal to 1 mm
  - Clark level of III or IV tumor ulceration, or tumor regression

- Mean tumor thickness for all patients:
  - 0.69 mm (range, 0.3-1.0 mm)
  - 0.61 mm for the Clark level III patients (N = 15)
  - 0.72 mm for the Clark level IV patients (N = 9).
  - Tumor ulceration-1 patient
  - Regression-2 patients


Nahabedian MY, Tufaro AP, Manson PN
Division of Plastic and Reconstructive Surgery, Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA.
Sentinel node biopsy for thin melanomas: which patients should be considered?

- Cutaneous melanomas less than 1.00 mm in Breslow thickness
- Pts with melanomas between 0.75 and 1.00 mm are appropriate candidates

<table>
<thead>
<tr>
<th>Clark Level*</th>
<th>Pts. n=409</th>
<th>SLN+</th>
</tr>
</thead>
<tbody>
<tr>
<td>II or III</td>
<td>252 (62%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>IV</td>
<td>157 (38%)</td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>

Cutaneous Oncology Division, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA.
No indication for performing sentinel node biopsy I melanoma patients with a Breslow thickness of less than 0.9 mm.

Melanomas thinner than 0.90 mm, no positive SN was found (95% confidence interval 0-5%).

- 348 patients stages I or II cutaneous melanoma with a Breslow thickness $\geq 0.5$ mm
- 75 patients (22%), with a median follow-up of 31 months.

False Positives and False Negatives
Nodal Nevus Cells
HMB-45, S-100, NK1/C3, and MART-1 in metastatic melanoma

- S-100 and NK1/C3 were the most sensitive stains for detecting metastatic melanoma; however, they both also stain other nontumor cells in lymph nodes.

- MART-1 did not stain histiocytes and exhibited a more frequently intense and diffuse staining pattern than NK1/C3.

- HMB-45 was less sensitive and demonstrated less diffuse staining than MART-1.

<table>
<thead>
<tr>
<th>Stain</th>
<th>Cases</th>
<th>%</th>
<th>Diffuse Staining Pattern % Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100</td>
<td>123/126</td>
<td>98</td>
<td>56</td>
</tr>
<tr>
<td>HMB45</td>
<td>95/125</td>
<td>76</td>
<td>34</td>
</tr>
<tr>
<td>NK1-C3</td>
<td>117/125</td>
<td>93</td>
<td>48</td>
</tr>
<tr>
<td>MART-1</td>
<td>103/126</td>
<td>82</td>
<td>83</td>
</tr>
</tbody>
</table>

Size of the Micrometastases

- <1mm subcapsular deposits, no survival different from cases without mets (N0)
- Current AJCC staging is $\leq 0.2$ mm

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References

- Kirkwood JM, et al. ASCO 1999 (Abstract)