Patient Outcomes and Recurrence Patterns Following Sentinel Node Biopsy in Melanoma

"Zogakis, M.D.
Assistant Professor of Surgery
Division of Surgical Oncology
UT Southwestern
Outline

• SN biopsy (SNB)
• Prognostic implications of the tumor status of the SN
• Recurrence patterns
• Treatment of recurrences
• Time to recurrence
• The first node (nodes) in the lymphatic basin to which the primary melanoma consistently drains.

• The tumor status of the SN reflects the tumor status of the entire nodal basin.
Lymph Node Dissection
<table>
<thead>
<tr>
<th>Complication</th>
<th>LND (%)</th>
<th>SNB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>7</td>
<td>1.6</td>
</tr>
<tr>
<td>Lymphadema</td>
<td>11.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Seroma</td>
<td>5.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Nerve injury</td>
<td>2.2</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Sentinel Node Biopsy

- Minimally invasive surgery
- Accurately detects lymphatic metastases
- Stages melanoma
- Predicts outcome
- Determines need for adjuvant therapy
- Directs enrollment into clinical trials
Identification Rates of SN Biopsy

- Blue dye + radiocolloid improve identification:
  - 99% (blue dye and radiocolloid) vs. 95% (blue dye alone)

- Surgeon Experience
  - About 30 cases are required to accurately perform the technique.
SN Biopsy is Highly Accurate at Detecting Occult Nodal Disease

• Determine the frequency of missed positive nodes following SN(-) biopsy.
  – Of 34 pts who received CLND following SN (-) biopsy, none had missed positive nodes.

• Compare % of SN(+) patients to % of observed patients who develop lymph node metastases in the draining nodal basin. MSLT1: SN (+) 19.8% vs. observation 20.3%
  Morton DL et al. ASCO 2005
## Incidence of SN(+) Biopsy for Clinical Stage I/II Melanoma Patients

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>No. Pts</th>
<th>Percent SN (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gershenwald et al</td>
<td>1999</td>
<td>580</td>
<td>15</td>
</tr>
<tr>
<td>Jansen et al</td>
<td>2000</td>
<td>200</td>
<td>24</td>
</tr>
<tr>
<td>Chao et al</td>
<td>2002</td>
<td>1183</td>
<td>19.7</td>
</tr>
<tr>
<td>Wagner et al</td>
<td>2003</td>
<td>408</td>
<td>20.8</td>
</tr>
<tr>
<td>Vuylsteke et al</td>
<td>2003</td>
<td>209</td>
<td>19</td>
</tr>
<tr>
<td>Fincher et al</td>
<td>2003</td>
<td>198</td>
<td>19.2</td>
</tr>
<tr>
<td>Morton et al</td>
<td>2005</td>
<td>1204</td>
<td>19</td>
</tr>
</tbody>
</table>
How Does the Tumor-Status of the SN Impact Outcome?
# Tumor-status of the Sentinel Node and Survival

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>No. Pts</th>
<th>SN (-)</th>
<th>SN (+)</th>
<th>F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gershenwald et al.</td>
<td>1999</td>
<td>612</td>
<td>96.8</td>
<td>69.9</td>
<td>3 years</td>
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<tr>
<td>Jansen et al.</td>
<td>2000</td>
<td>200</td>
<td>93</td>
<td>67</td>
<td>3 years</td>
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<tr>
<td>Vuylsteke et al.</td>
<td>2003</td>
<td>209</td>
<td>92</td>
<td>67</td>
<td>5 years</td>
</tr>
<tr>
<td>Morton et al.</td>
<td>2005</td>
<td>1159</td>
<td>88</td>
<td>71</td>
<td>5 years</td>
</tr>
<tr>
<td>Investigator</td>
<td>Year</td>
<td>Total No. Pts</td>
<td>SN (-)</td>
<td>SN (+)</td>
<td>F/U</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>-------</td>
</tr>
<tr>
<td>Chao et al.</td>
<td>2002</td>
<td>1183</td>
<td>6.0%</td>
<td>15.5%</td>
<td>1.3 years</td>
</tr>
<tr>
<td>Wagner et al.</td>
<td>2003</td>
<td>408</td>
<td>12.1%</td>
<td>36.5%</td>
<td>2.6 years</td>
</tr>
<tr>
<td>Gershenwald et al.</td>
<td>1999</td>
<td>580</td>
<td>11.5</td>
<td>44.2</td>
<td>3 years</td>
</tr>
<tr>
<td>Jansen et al.</td>
<td>2000</td>
<td>200</td>
<td>12%</td>
<td>42%</td>
<td>3 years</td>
</tr>
<tr>
<td>Vuylsteke et al.</td>
<td>2003</td>
<td>209</td>
<td>12%</td>
<td>50%</td>
<td>5 years</td>
</tr>
</tbody>
</table>
Factors That Influence Recurrence

- Clark level
- Tumor thickness
- Tumor ulceration
- Positive SN

Types of Recurrence

- Local
  - At the site of the primary
- In-transit
  - In-between the primary and the nodal basin
- Nodal
  - Draining the primary site
- Distant
  - Lung
  - Liver
  - Brain
  - Bowel
Local Recurrence
Local Recurrence

• Local recurrence happens infrequently.
  – About 1-2% of patients over 3 years.

• Why does it happen?
  – Cells left behind at the time of resection.
    • Margins of resection are important.
Risk Factors for Local Recurrence

- Increasing tumor thickness
  - 1.0-2.0 mm 2.3%
  - 2.01-3.0 mm 4.2%
  - 3.01-4.0 mm 11.7%

- Presence of tumor ulceration
  - 1.1% (absent) vs. 6.6% (present)

- Head and neck primary location

Detection of Local Recurrence

- Good physical exam.
- Continued follow-up is important.
  - 40% of local recurrences can occur 5 or more years after melanoma excision.

Management of Local Recurrence

• Excision

• Other
  – Isolated Limb Perfusion
  – Intra-tumoral therapy
  – Radiation
  – Systemic therapy
In-transit Recurrence

• In-transit melanoma can occur in 4 - 7% of clinical stage I/II melanoma patients who undergo SNB and are followed almost 4 years.

• Small tumor emboli trapped w/in the dermal and subdermal lymphatics between the site of the primary and the regional lymph node drainage basin.
In-transit Recurrence
In-transit Recurrence

- Risk Factors
  - Age > 50
  - Lower extremity location of the primary
  - Tumor thickness
  - Ulceration
  - Positive SN status

- 56% of patients who develop in-transit recurrence go on to develop distant metastases
  - Distant metastases are more likely to occur in patients with large in-situ (>2cm), subcutaneous in-transits, SN (+), and short disease-free interval.

Treatment of In-transit Melanoma

- Surgical excision (for small no. of lesions)
- Intra-lesional BCG injection
- CO2 laser ablation
- External beam radiation therapy
- Isolated limb perfusion
- Systemic therapy
Regional Nodal Recurrence

- Incidence: 1.2 - 4.6%
  - SN(+): 0 - 8% over 3 years
  - SN(-): 1 - 4% over 3 years

Zogakis TG et al. *Arch of Surg.* 140:865-71, 2005
Nodal Recurrence
Reasons for Regional Nodal Recurrence

• SN(-)
  – Inaccurate intra-operative identification of the SN
  – Inaccurate pathological diagnosis
  – Intra-lymphatic disease that spreads to the regional nodes

• SN(+) followed by CLND
  – Disease in the nodal basin not fully removed by CLND.
  – Intra-lymphatic disease that spreads to the regional nodes.
Regional Nodal Recurrence

• Pts with nodal recurrence are at increased risk for developing distant metastases.
  – Imaging should be performed

• Close follow-up is important
  – Clinical exam
  – Imaging
Treatment of Nodal Recurrence

• Surgical Resection

• Radiation Therapy

• Systemic Therapy
  – CMTX
  – Biochemotherapy
  – Vaccine Therapy
Distant Recurrence

- Cutaneous
- Distant lymph nodes
- Lung, Pleura, Mediastinum
- Brain and spinal cord
- Gastrointestinal tract
- Liver
- Bone
Treatment of Distant Metastases

• Surgical Resection
  – Improves survival and relieves symptoms

• Systemic Therapy
Kaplan-Meier Survival Estimates of SN (-) Melanoma Patients Based on Sites of First Recurrence

% Survival

Distant

Local / In-transit

Nodal

P=0.0005

Months After the First Recurrence

Kaplan-Meier Survival Estimates of SN (+) Melanoma Patients Based on Sites of First Recurrence

- Local / In-transit
- Distant
- Nodal

P = 0.04

Months After the First Recurrence

% Survival
Time Course to Recurrence

• Variable.
  – Depends on biology

• Currently, there is no way to accurately predict who will recur.

• Close follow-up is important.
Questions?