Sentinel Lymph Nodes in Breast Cancer: Histology, reporting, and clinical implications

D. Page, Feb.’06

tumor burden, and Relevance to other Px Measures
Sentinel Lymph Node

First node in regional nodal basin that drains a primary tumor and reflects the tumor status of the entire nodal basin

Surgical aspects per Dr. Morrow
Gold Standard, before sentinel methodology accepted

- Axillary lymph node dissection (although minimal cases missed)
- Histopathologic study of nodes
- report # of positive nodes/ # nodes present
Sentinel Lymph Node

- Gross examination
- Frozen section
- Touch prep
- Immunohistochemistry
- PCR [not indicated, high false +]

- Stage 0 – increase
- Stage 1 - increase
- Stage 2 node negative – stable
- Stage 3, 4 – stable
- Stage 2, node positive - increase of as much as 30%, most minimal involvement
Metastasis in SLN

<table>
<thead>
<tr>
<th></th>
<th>SLND</th>
<th>ALND</th>
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<tbody>
<tr>
<td>no. patients</td>
<td>162</td>
<td>134</td>
</tr>
<tr>
<td>% positive</td>
<td>42%</td>
<td>29%</td>
</tr>
<tr>
<td>% &lt;2mm</td>
<td>38%</td>
<td>10%</td>
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Giuliano, Ann Surg 1995
“IHC metastases do not appear to adversely affect prognosis”
“IHC should not be routinely performed” on SLN,
“nor should treatment decisions be made” [recall that average size is T1c, and grades are mostly low.]

CO$T CON$IDERATION
Don Weaver, MD

- In order to detect single cells:
  - Section at 10 micron (0.01 mm) intervals
  - One paraffin block (2 mm) results in 200 slides
- $12 per slide = $4800 per case
- Newly diagnosed breast cancer in US = $900 million annually
- 77 million slides
Significance of isolated tumor cells and Cell Clusters (ITCs)?
Patterns: missed & detected micrometastases

Don Weaver

pN0(i+)
pN1mi
pN0(i-)
pN0(i-)
Patterns of missed micrometastases for various strategies

Don Weaver

Three levels
200 micron intervals

Four levels through block
500 micron (0.5 mm) intervals

Two levels
1.0 mm interval

Multiple levels through block
200 micron intervals
Pathologists’ charge

Minimal epithelial cells need to be examined and analyzed without the assumption that they represent relevant node involvement by cancer

Quantitatively and Qualitatively
False Positive Nodal Involvement

- CK staining of dendritic macrophages, and plasmablasts as well as degenerating cell debris
- Benign inclusions
- Viable fragments of papillomas
- Benign transport: usually fragments of hyperplasia as seen in the displaced clusters in granulation tissue of biopsy site or papilloma(s)
- Artifactual keratinocytes in plane above node
Benign Transport

- 15 cases from breast consult files
- Node dissection 15 days after biopsy
- 7 of 15 with DCIS
- Cluster (<100μm) of epithelial cells in subcapsular sinus accompanied by hemosiderin-laden macrophages, giant cells, and altered RBC’s

NI. Glands at Bx. Site
CLUSTER OF 3 DEGENERATING CELLS IN SINUS WITH SURROUNDING MACROPHAGE REACTION.
AJCC Cancer Staging 2002

• Micromets distinguished from ITC

• Identifiers added to indicate SLN and IHC

• Major classification of lymph node status designated according to number of involved axillary nodes
AJCC/UICC Cancer Staging
6th edition

Isolated tumor cells (ITCs)
defined as single tumor cells or small clusters
not greater than 0.2 mm

pN0 (it)

Modified by Singletary, et al, Cancer; 2003
ITC = Isolated tumor cells and cell clusters
AJCC Cancer Staging 2003

• Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)

pN1mi
Dense small cell groups, probably significant = < 2mm.
Individual Tumor Cells and Clusters, = ITC
Some more “real” than others. Still small
Normal glandular inclusions in capsule
Benign Inclusion, in capsule substance
Nodal Inclusion, nl. polarized cells
ITC or Benign transport
Lymph Node Sinusoid, Nl. Gland & giant cell
CK, B9 transport & squamous metaplasia

Sinusoid
Individual tumor cells and clusters
Benign papilloma “inclusion” in node
Benign transport, subcapsular sinus
Anucleate squames in subcapsular sinus
Occult Cells in Lymph Nodes

Does the finding change the prognosis from that already indicated by other information?

Implication of minimal cells in other nodes not = survival prediction

But may indicate other nodes with tumor
further axillary involvement was significantly associated with the type and size of SLN metastases, the number of affected SLNs, and the occurrence of peritumoral vascular invasion. A predictive model was able to identify subgroups of patients at significantly different risk for further axillary involvement. CONCLUSIONS: Patients with the most favorable combination of predictive factors still have no less than 13% risk for nonsentinel lymph node metastases and should be offered completion ALND outside of clinical trials of SLN biopsy without back-up axillary dissection.
Pinder et al, Br.J.Cancer;2005

- Metastatic deposits were classified as macrometastasis (>2.0 mm), micrometastasis (0.2-2.0 mm) or isolated tumour cells (ITC, <0.2 mm). Of the 216 patients, 56 (26%) had metastasis as identified by H&E. IHC detected metastatic deposits in a further nine patients (4%), of whom four (2%) had micrometastasis and five (2%) had ITC only. Those with micrometastases were all, on review, visible on the H&E sections. IHC detects few SLNs, of which were either micrometastasis or ITC. Until the prognostic significance of these deposits has been determined, IHC may be of limited value in the histopathological examination of SLNs
The Milan Studies involve complete analysis of each node.

There are varieties of epithelial presence other than benign transport in lymph nodes. There are also instances of cytokeration staining of other than epithelial cells, particularly of dendritic macrophages.
Micrometastasis $\leq 2$ mm

Recorded: N1

Prognostically: N0

AJCC Staging Manual 5th edition
## Minimal Occult Metastasis

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<tr>
<th>author</th>
<th>method</th>
<th>survival impact</th>
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<tbody>
<tr>
<td>De Mascarell</td>
<td>IHC</td>
<td>none</td>
</tr>
<tr>
<td>Cote</td>
<td>IHC</td>
<td>none overall, post menopausal only</td>
</tr>
</tbody>
</table>
AJCC reporting and CAP Guidelines:
7,9,13,14
Pathology and prediction10-12
1-6,8,15-24

2. Chagpar A, Middleton LP, Sahin AA, et al.: Clinical outcome of patients with lymph node-negative breast carcinoma who have sentinel lymph node micrometastases detected by immunohistochemistry. Cancer 2005, 103:1581-6


