Pathologic Assessment Of The Breast And Axilla After Preoperative Therapy

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Pathologic Complete Response (pCR)

Proof of no residual invasive cancer requires:
- Identification of the tumor bed location
- Adequate sampling for microscopic study
Pathologic Complete Response: NSABP-B27

pCR in the breast

Nodal status in pCR patients

Bear et al JCO 2006 24:2019-27
Pathologic AJCC Stage After Preoperative Chemotherapy: UNC

N = 132

Carey et al JNCI 2005 97:1137-42
Residual Ductal Carcinoma *in situ* Alone: MDACC

N = 2302

pCR with DCIS only in:
- 3% of overall MDACC experience
- 7% of recent T/FAC study

*Mazouni et al JCO, in press*
Nodal Micrometastasis After Preoperative Chemotherapy: NSABP-B18

Any nodal disease after neoadjuvant chemotherapy is relevant

<table>
<thead>
<tr>
<th>Postoperative Chemotherapy</th>
<th>Preoperative Chemotherapy</th>
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</table>

Metastasis < 2 mm in:
10% of postoperative chemotherapy patients
17% of preoperative chemotherapy patients

4% of recent MDACC T/FAC study

Fisher et al Cancer 2002 95:681-95
Pathologic Complete Response

No residual invasive cancer & node-negative

Residual *in situ* disease only
- Current prognostic data are limited
- Prognosis similar to pCR (few studies)
- Relevant for local control

Residual nodal micrometastasis
- Prognosis is the same as node-positive
The Extent Of Residual Cancer Is Variable
Histopathological Response Is Also Variable

Core Biopsy → Resection

A. 2.0 cm
B. 1.8 cm
C. 1.7 cm
D. 1.5 cm
Reduction in Tumor Cellularity: “Miller and Payne”

Histopathology scoring system to assess response
Compares cancer cellularity of the core biopsy (before treatment) with the resected tumor (after treatment)

Grade 1: No reduction
Grade 2: Minor loss (≤ 30%)
Grade 3: Some loss (30% - 90%)
Grade 4: Marked loss (> 90%)
Grade 5: No residual invasive cancer

170 patients Tumor ≥ 4 cm
Rx: CVAP 4 - 6 cycles

Grade 1: 15%
Grade 2: 24%
Grade 3: 27%
Grade 4: 20%
Grade 5: 14%

Ogston et al The Breast 2003 12:320-7
Reduction in tumor cellularity is related to residual tumor size

T/FAC, n = 108

The greatest cellularity reduction occurs in residual tumors ≤ 1 cm

Reduction in cellularity is variable in all T-stage groups

Rajan et al Cancer 2004 100:1365-73
### Honkoop Classification

<table>
<thead>
<tr>
<th>pCR</th>
<th>No cancer in breast or axillary nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Residual Disease</td>
<td>Only microscopic RD in breast or axillary nodes</td>
</tr>
<tr>
<td>Macroscopic Residual Disease</td>
<td>Macroscopic RD in breast or axillary nodes</td>
</tr>
</tbody>
</table>

### Chevallier Classification

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>No cancer in breast or axillary nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Only <em>in situ</em> carcinoma remains, nodes are negative</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Invasive carcinoma with stromal fibrosis</td>
</tr>
<tr>
<td>Grade 4</td>
<td>No or few modifications of stromal fibrosis</td>
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</tbody>
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### Sataloff Classification

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Axillary Nodes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>T-A</td>
</tr>
<tr>
<td></td>
<td>Total or near-total therapeutic effect</td>
</tr>
<tr>
<td>N-A</td>
<td>N-B</td>
</tr>
<tr>
<td>N-</td>
<td>N+</td>
</tr>
<tr>
<td>Evidence of therapeutic effect</td>
<td>No evidence of therapeutic effect</td>
</tr>
</tbody>
</table>
Relevant Prognostic Variables In The Post-treatment Pathologic Specimen

• Primary Tumor
  – Size
  – Cellularity
  – Invasive vs. *in situ*
  – Margins

• Axillary Lymph Nodes
  – Number of positive nodes
  – Size of metastases
  – Extranodal extension
Irregular hypoechoic mass in 1 o'clock position of right breast

Tumor nidus 1.1 x 0.9 x 0.8 cm, but extends laterally for maximum dimension of 2.6 cm

No evidence for abnormal axillary, internal mammary, or infraclavicular adenopathy

Invasive ductal carcinoma

Low grade

ER 100%

PR 100%

FISH (HER2 / cep17) 1.14

Ki-67 10%
RIGHT BREAST, 1 O'CLOCK POSITION, SEGMENTAL MASTECTOMY:

RESIDUAL INVASIVE DUCTAL CARCINOMA MEASURES 0.8 X 0.6 CM AND CONTAINS APPROXIMATELY 20% CANCER CELLULARITY BY AREA, WITH 1% INTRADUCTAL COMPONENT.
SURROUNDING RESIDUAL FIBROUS TUMOR BED (2.7 X 1.0 CM) CONTAINING RARE SINGLE DUCTS WITH INTRADUCTAL CARCINOMA.
Margins of resection are free of tumor.

SENTINEL LYMPH NODE #1, RIGHT AXILLA, BIOPSY:
One lymph node, free of tumor (0/1).
Cytokeratin stain is negative.

NONSENSENL LYMHP NODE, RIGHT AXILLA, BIOPSY:
One lymph node, free of tumor (0/1).
Residual Cancer Burden Calculator

(1) Primary Tumor Bed
- Primary Tumor Bed Area: \(8\text{ (mm)} \times 6\text{ (mm)}\)
- Overall Cancer Cellularity (as percentage of area): \(20\%\)
- Percentage of Cancer That Is in situ Disease: \(1\%\)

(2) Lymph Nodes
- Number of Positive Lymph Nodes: \(0\)
- Diameter of Largest Metastasis: \(0\text{ (mm)}\)

Residual Cancer Burden: \(1.477\)
Residual Cancer Burden Class: RCB-II

Symmans et al ASCO 2006 #536
Residual Cancer Burden (RCB)

Primary Tumor Bed

\[ d_{prim} = \sqrt{d_1 d_2} \]

\( f_{inv} = \% \text{ area with invasive CA} \)

Lymph Nodes

\( d_{met} = \text{size largest metastasis} \)

\[ LN = \text{Number of Positive Nodes} \]

\[ RCB = 1.4 (d_{prim} \times f_{inv})^{0.17} + [4 (d_{met} \times (1 - 0.75^{LN}))]^{0.17} \]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Primary tumor bed size ((d_{prim}))</td>
<td>1.24 (1.04-1.48)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fraction of invasive cancer ((f_{inv}))</td>
<td>7.37 (2.16-25.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of positive lymph nodes ((LN))</td>
<td>1.11 (1.04-1.19)</td>
<td>0.002</td>
</tr>
<tr>
<td>Size of largest metastasis ((d_{met}))</td>
<td>1.17 (0.99-1.38)</td>
<td>0.06</td>
</tr>
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Symmans et al ASCO 2006 #536
Residual Cancer Burden Predicts Distant Relapse After T/FAC Chemotherapy

Symmans et al ASCO 2006 #536
Residual Cancer Burden (RCB) Classes Are Associated With DRFS After Chemotherapy

T/FAC (n = 241)

FAC alone (n = 141)
RCB Classes Stratify Residual Pathologic Stage After T/FAC Chemotherapy

Symmans et al ASCO 2006 #536
Effect of ER Status and Adjuvant Hormonal Therapy: Residual Cancer Burden After T/FAC Chemotherapy

Symmans et al ASCO 2006 #536
Conclusions

1. The definition of pCR should be limited to yT0 & yN0

2. The extent of residual disease clearly has prognostic relevance
   • Both the primary site and regional nodal basin
   • Consistent recommendations for pathologic assessment and reporting of residual disease are needed

3. AJCC Stage, “Miller-Payne”, and Residual Cancer Burden assessments improve the classification of residual disease
   • RCB-I identifies a group with prognosis similar to pCR
   • RCB-III provides a pathologic definition of resistance

4. Accurate and reliable classification of residual disease can assist us with
   • New trial designs for preoperative treatments
   • Development of diagnostic tests to select treatment based on predicted response