Evaluation of Pathologic Response in Breast Cancer Treated with Primary Systemic Therapy

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Indications of NAC

• Management of locally advanced invasive breast ca including inflammatory BC
• ‘Down-staging’ of large inoperable cancers: reduced tumor size in order to avoid mastectomy
• Routine management of high risk BC: test the in vivo chemo sensitivity of the tumor cells
Contents

• pathologic complete response
• different patterns of tumor response in different molecular subtypes
• grading of partial response
• response in the lymph nodes
• evaluation of the axilla before and after treatment
• practical approach to sampling of the post-neoadjuvant surgical specimen
• detailed method for calculating the residual cancer burden (RCB) score
Pathologic Assessment of Specimen that received Neoadjuvant Therapy

• Pathologic complete response (pCR)
  – Absence of residual invasive carcinoma in the breast and lymph nodes at the time of surgery
  – Excellent prognostic indicator
  – validated and evaluable primary endpoint for neoadjuvant trials
pCR and EFS

FDA Meta analysis (Cortazar et al, Lancet 2014)
- >11K patients from 12 NAC trials
- Median follow-up for EFS: 5.4 years
Methods to Determine Response to NAC

- Clinical examination
- Imaging methods (mammographs, US, MRI)
- Histopathologic evaluation
Clinical Response of NAC

- 60-80% patients with locally advanced breast carcinoma show measurable clinical response
- Imprecise
Methods to Determine Response to NAC

• Clinical/imaging methods
  – False negative 40-60%
    → underestimation of disease burden (minimal residual disease with pervasive lymphovascular neoplastic embolization)
  – False positive (residual fibrosis only) 20-30%
    → overtreatment (less conservative surgical procedure)

• Histopathologic evaluation is gold standard
Pre treatment Evaluation

invasive lobular carcinoma (low Ki67, ER/PR+)

vs

high grade TNBC (high Ki67)
Pathologic Assessment of Specimen that received Neoadjuvant Therapy

• Correlation between pCR and outcomes: HER2+ & TNBC
• pCR (Cortazar et al. Lancet. 2014):
  – 9.6% of hormonal receptor (HR)+HER2-
  – 22.7% of HR+/HER2+
  – 39% of HR-/HER2+
  – 33.6% of TNBCs
• Residual cancer burden in the breast and nodes is associated with increased regional recurrence and decreased survival
• Accurate assessment of pCR or residual cancer burden is crucial
Response Rates by Subtype

A. Luminal A

B. Luminal B non-Her2

C. Luminal B Her2+

D. HER2+

E. TNBC

Von Minckwitz et al, JCO 2012
Patterns of Tumor Response

• Concentric shrinking

• Scattered pattern
Residual Tumor Growth Pattern

Size unchanged
Cellularity decreased

Size changed/unchanged
Cellularity decreased/heterogeneous

Size changed/unchanged
Cellularity decreased/heterogeneous
“scatter pattern”

Size decreased
Cellularity similar
“concentric shrinking”
Correlations between molecular subtypes and pathologic response patterns of residual non pCR cancer after NAC

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Cancer cellularity</th>
<th>In situ component</th>
<th>Nuclear/histologic grade</th>
<th>Residual LN metastasis</th>
<th>TIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+</td>
<td>No change</td>
<td>Decreased</td>
<td>Less frequent</td>
<td>Low/intermediate</td>
<td>Frequent</td>
</tr>
<tr>
<td>HER2+</td>
<td>Decreased</td>
<td>Same</td>
<td>Frequent</td>
<td>High</td>
<td>Less</td>
</tr>
<tr>
<td>TNBC</td>
<td>Decreased</td>
<td>Same</td>
<td>Less</td>
<td>High</td>
<td>Less</td>
</tr>
</tbody>
</table>

Pathologic Response to NAC

• Less than complete response (partial response) is difficult to classify
• There are different classification systems
• Different staging systems yield different estimates of future risk
The definition of pCR

definitions of pCR in major neoadjuvant breast cancer clinical trials

Modern pathol. 2015
The definition of pCR

Survival curves showing impact of different definitions of pCR on survival: Residual disease in the LN indicates a worse prognosis, even pCR in the breast pCR±DCIS (EFF vs OS), reduction in cellularity, RDBN

Modern pathol. 2015
Residual tumor evaluation (NAC)

- **NSABP-B18**: simple dichotomy
- **Miller-Payne grading**: linear histologic response in breast only
- **Sataloff tumor and nodes**: breast and lymph nodes
- **Chevallier classification**: 4-step algorithm to grade response in breast and lymph nodes
- **Residual disease in breast and nodes (RDBN)**: to more complex algorithms, including a formula
- **Residual cancer burden (RCB)**: Web calculator
- **Residual Proliferative Cancer Burden**: combines Residual Cancer Burden with posttreatment Ki67 index
- **clinical-pathologic stage + estrogen receptor status and grade staging system (CPS+EG)**
- **AJCC**

Corben AD et al. APLM 2013
Recommendations from an international working group

• Residual Cancer Burden (RCB)
  – an online tool for the quantification of residual disease
  – simple to apply, reproducible
  – clinically validated with long-term FU data
  – the preferred method for quantifying residual disease in neoadjuvant clinical trials in breast cancer
Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

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

2. Lymph Nodes
   - Number of Positive Lymph Nodes: 
     - \(\Box\)
   - Diameter of Largest Metastasis: 
     - \(\Box\) (mm)

The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after neoadjuvant treatment:

The website is www.mdanderson.org/breastcancer_RCB.
Residual Cancer Burden (RCB)

- Residual cancer burden score
  - Largest area and cellularity of residual invasive cancer of the breast
  - Number of involved lymph nodes and the largest nodal metastasis size

- RCB0 = pCR, RCB I = minimal residual disease
- RCB II and III = moderate and extensive residual disease
What is the primary tumor bed?
Pathologic assessment After NAC

- Residual tumor size:

- Cellularity: comparison of cellularity with the pretreatment biopsy: Miller–Payne, Pinder, Sinn, and Sataloff system
Miller Payne System

Variable cellularity changes in residual tumors

Residual Cancer Burden (RCB)

(1) Primary Tumor Bed
- Primary Tumor Bed Area: \[ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ (mm) \times \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ (mm) \]
- Overall Cancer Cellularity (as percentage of area): \[ \_ \_ \_ \_ (\%) \]
- Percentage of Cancer That Is in situ Disease: \[ \_ \_ \_ \_ (\%) \]

(2) Lymph Nodes
- Number of Positive Lymph Nodes: \[ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \]
- Diameter of Largest Metastasis: \[ \_ \_ \_ \_ (mm) \]

Residual Cancer Burden:
[Blank]
Residual Cancer Burden Class:
[Blank]
Tumor cellularity (RCB)

Guide for Measuring Cancer Cellularity (pdf)
Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration

1. Size
   (A) Two dimensions of largest cross section of entire area involved by (possibly scattered) residual invasive tumor foci (=largest distance between invasive tumor cell foci) and
   (B) Extent of largest contiguous focus of invasive carcinoma as recommended by AJCC 7th edition [23]

   ![Diagram of tumor bed with annotations](image1)

   In the opinion of the working group, the largest dimension in (A) (longest blue arrow), together with tumor cellularity, is likely a better indicator of response than measurement (B) [19, 24]. The report should clearly state how the size was determined and which dimension was used for staging, especially in cases with scattered residual disease, where there is possible interobserver variability due to differences in guidelines regarding how size should be measured. (A) is needed to calculate the Residual Cancer Burden (RCB) score.

2. Cellularity
   - Qualitative statement
   - Largest cross section of residual tumor bed represented in blocks: ... (e.g. ‘G through F’)
   - Compare with pretreatment cellularity if available (Miller-Payne or Pinder Systems)

3. Tumor bed
   - Identified or not
   - Presence of tumor bed at margin

4. Lymph node metastasis
   - Size of largest metastasis

   Assessment of average cancer cellularity across the largest cross section of the residual tumor bed (that contains residual cancer) is needed to calculate the Residual Cancer Burden (RCB) score.

5. Treatment effect
   - Presence of treatment effect in the breast
   - Number of lymph nodes with possible treatment effect

   The largest distance between tumor cell foci including intervening areas of fibrosis.

   Size of largest metastasis is needed to calculate the Residual Cancer Burden (RCB) score.
Gross Handling of Surgical Specimens After NAC

• One of the most critical steps
• the single greatest determinant for accurate definition of pCR or residual disease

• The specimen is evaluated in the context of pretreatment clinical and imaging findings
• The tumor bed/clip must be identified
Sampling of small lumpectomy specimens

• No gross residual mass lesion
  – No residual tumor
    • Tumor bed with clip identified
    • Tumor bed indistinct, but clip identified
  – Microscopic residual disease

• Obvious gross residual tumor
  – mass sampling $+\alpha$
    • Gross size confirmed
    • Microscopic residual disease beyond grossly visible tumor
Random sampling is a problem

Decreased cellularity!

No residual disease!
Systemic sampling is appropriate

Mapping of the specimen
Largest cross section of tumor bed is sampled
Axillary Evaluation Before NAC

- Routine axillary U/S with histological assessment of abnormal nodes by CNB or FNA
- Pre-treatment SLNB not advised unless positive result will influence decision to give chemotherapy
- Nodal response is an important prognostic factor independent of response in the breast
Evaluation of the axilla

- Nodal status after NAC is a strong predictor of outcome

von Minckwitz, et al, JCO 2012
Evaluation of the axilla

- Neo-Tango result
  - 6% residual axillary disease despite pCR in the breast

### Graphs

**Non-pCR**

<table>
<thead>
<tr>
<th>Nodal Status</th>
<th>N</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>884</td>
<td>119</td>
</tr>
<tr>
<td>1-3 positive</td>
<td>587</td>
<td>119</td>
</tr>
<tr>
<td>4-9 positive</td>
<td>308</td>
<td>116</td>
</tr>
<tr>
<td>10+ positive</td>
<td>102</td>
<td>56</td>
</tr>
</tbody>
</table>

**pCR**

<table>
<thead>
<tr>
<th>Nodal Status</th>
<th>N</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>342</td>
<td>18</td>
</tr>
<tr>
<td>1-3 positive</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>4-9 positive</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>10+ positive</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*JCO 2006*
Evaluation of the axilla

- 925 pts with proven node mets in 5 prospective NAC trials (22% axillary pCR)
- Residual primary tumor not predictive in pts with residual nodal disease.
- Residual primary tumor did not affect outcome of those with axillary pCR.
- No influence of size of metastasis: Prognosis still worse in even micromets

Hennessy, et al, JCO 2005
Evaluation of the axilla

- Metastasis size and number of involved lymph nodes independent predictors.
- ITC: positive node

Isolated Tumor Cells after NAC

• Deposit (<0.2mm) is ypTN0(i+): NOT regard as pCR (AJCC and WHO)
Evaluation of the axilla

• 8th AJCC:
  – Size of largest contiguous focus of residual tumor in the node
  – Any treatment associated fibrosis should not be included

• RCB:
  – The largest deposit including associated treatment related fibrosis
Residual lymphovascular invasion is documented and is not classified as pCR.
**AJCC 8th staging after NAC**

- ypT is based on largest single focus of residual invasive carcinoma
- Treatment-related fibrosis around residual tumor is NOT included in the ypT dimension (don’t measure tumor bed)
- Pathologic complete response (pCR) is defined as no residual invasive cancer – ypT0 N0 or ypTis N0
- microinvasion/only LVI in breast, ITC in LN≠pCR
- Cases categorized as M1 before neoadjuvant therapy stay that way (i.e. they remain Stage IV even if there is pCR)
THANK YOU