Pathologic Assessment After Neoadjuvant Therapy

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Disclosures

Nuvera Biosciences, Inc. Co-founder and scientific advisor

Can you imagine a primary endpoint for clinical trials that is defined by absence of disease, but relies on preferences of local sites to identify and sample the correct area within each resection specimen?
Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration


Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group

Elisa Provenzano1, Vincenzo Bossi1, Giuseppe Cugilano1, David Cameron5, Sariel Baldu, Carmen Remus1, Galen MacGregor2, Paul Franklin1, Judy Hogdams1, Giuseppe Cugilano1, Michael Musgrove1, Lauri Ensminger1, Fred Fritzen1, Thomsen1,11, and W. Fraser Symmans2 on behalf of the Residual Disease Characterization Working Group of the Breast International Group-North American Breast Cancer Group (BIG-NABCG) collaboration

Summary of Recommendations

Mandate of this working group committee is limited to recommendations for clinical trials

Provide the following information:
1. pCR (ypT0 ypN0 and ypT0/is ypN0) versus residual disease,
2. ypT and ypN Stage using the current AJCC/UICC staging system, &
3. Residual cancer burden (RCB)

A single standardized approach to macroscopic and microscopic pathologic examination makes it easy to reliably provide all 3 results!

Different definitions of pCR in major neoadjuvant breast cancer trials

pCR = no invasive cancer in breast and lymph nodes


Guidance for Industry
Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2014
Center for Medical

E. Recommendation for Pathology Standard Operating Procedure


Federal Register 2014; 79 (194): 60476–77

AJCC Stage of Tumor and Neoadjuvant Treatment
7th edition, 2010

• Introduced the following specific recommendations:

• Clinical T Stage should be based on the clinical or imaging measurement that is thought to be most accurate

• Postneoadjuvant therapy T Stage should be based on clinical or imaging (ypT) or pathologic findings (pT)

• Estimate the size of tumors that are unapparent by clinical modalities or gross pathologic examination by carefully mapping the relative positions of the tissue sections and determining which contain tumor

• Pathologic (posttreatment) size should be estimated based on the best combination of gross and microscopic histological findings
Defining The Size Of The Residual Invasive Cancer

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- Introduced the following specific recommendations:
  - Clinical T Stage should be based on the clinical or imaging measurement that is thought to be most accurate
  - Postneoadjuvant therapy T Stage should be based on clinical or imaging (ypT) or pathologic findings (pT)
  - Estimate the size of tumors that are unapparent by clinical modalities or gross pathologic examination by carefully mapping the relative positions of the tissue sections and determining which contain tumor
  - Pathologic (posttreatment) size should be estimated based on the best combination of gross and microscopic histological findings
  - The posttreatment ypT will be defined as the largest continuous focus of invasive cancer as defined histopathologically with a subscript to indicate the presence of multiple tumor foci. Note: definition of posttreatment ypT remains controversial and an area in transition

AJCC Stage of Nodes and Neoadjuvant Treatment
7th edition, 2010

- Introduced the following specific recommendations:
  - Add subscript to clinical N Stage to indicate whether N was derived from clinical examination, FNA, core biopsy, or sentinel node biopsy
  - Posttreatment nodal metastases ≤ 0.2 mm are classified as ypN0(i+)
    - No patients' outcomes data to support this recommendation
  - Prone to subjectivity when residual metastasis consists of scattered remaining cells in fibrotic/treatment changes
Clinical Stage + ER Status + Grade + Pathologic Stage (CPS-EG)

<table>
<thead>
<tr>
<th>Pre-Rx Stage (c)</th>
<th>Pre-Rx Pathobiology</th>
<th>Post-Rx Stage (yp)</th>
</tr>
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<tbody>
<tr>
<td>c Stage</td>
<td>ER Status</td>
<td>N Grade</td>
</tr>
<tr>
<td>I - IIA</td>
<td>0 Positive</td>
<td>0</td>
</tr>
<tr>
<td>IIIB - IIIA</td>
<td>1 Negative</td>
<td>1</td>
</tr>
<tr>
<td>IIIB - IIIC</td>
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</table>


Prognosis (DFS) of CPS-EG Groups In MDACC T/FAC Cohorts: Development (n=932) and Validation (n=969)


Residual Cancer Burden (RCB)

DRFS Following Neoadjuvant T/FAC Chemotherapy (N=241)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Primary tumor bed size (d1d2)</td>
<td>1.34 (1.54-1.48)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fraction of invasive cancer (finv)</td>
<td>1.20 (0.94-1.56)</td>
<td>0.099</td>
</tr>
<tr>
<td>Number of positive lymph nodes (LN)</td>
<td>1.15 (1.04-1.15)</td>
<td>0.002</td>
</tr>
<tr>
<td>Size of largest metastasis (dmet)</td>
<td>1.57 (1.09-1.31)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Symmans et al JCO 2007;25:4414-22
Example: Pathologist’s Preparatory Notes
52 year old with triple-negative right breast cancer (T2, N0)

Imaging
Tumor in right breast, 11-12 o’clock position, 8 cm from nipple
2.7 cm mass + minute satellites, overall 3.4 cm greatest dimension
Metal clip placed in tumor at time of diagnostic core biopsy
Ultrasound of regional nodal basins did not show any abnormal LNs

Pathology From Biopsy
IDC grade 3, HR- / HER2- (TNBC)

Treatment & Response
Weekly paclitaxel x 12 then 3-weekly FAC x 4 (T/FAC)
Residual architectural distortion, but no mass
Radioactive seed placed in tumor on morning of surgery
For segmental mastectomy and sentinel node biopsy procedure

The clip and the seed are in the specimen
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: 
  - Overall Cancer Cellularity (as percentage of area): 14 (mm) X 17 (mm)
  - Percentage of Cancer That Is In situ Disease: 50 (%)

(2) Lymph Nodes
- Number of Positive Lymph Nodes: 0
- Diameter of Largest Metastasis: 5 (mm)

Residual Cancer Burden: 1.665
Residual Cancer Burden Class: RCB-0

Google terms: residual cancer burden breast

www.mdanderson.org/breastcancer_RCB
Prognosis According To RCB Categories (RFS)

Developmental Cohort T/FAC

<table>
<thead>
<tr>
<th>Class</th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>pCR</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>RCB-I</td>
<td>40</td>
<td>18</td>
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<tr>
<td>RCB-II</td>
<td>105</td>
<td>48</td>
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<tr>
<td>RCB-III</td>
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<td>11</td>
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Validation Cohort T/FAC

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<tr>
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<tr>
<td>RCB-II</td>
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<tr>
<td>RCB-III</td>
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Validation Cohort FAC

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<tr>
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<tr>
<td>RCB-II</td>
<td>60</td>
<td>46</td>
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<tr>
<td>RCB-III</td>
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<td>24</td>
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RCB Categories: Combined T/FAC Cohorts (RFS)

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<td>pCR</td>
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<td>34</td>
</tr>
<tr>
<td>RCB-I</td>
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<td>14</td>
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<tr>
<td>RCB-II</td>
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<td>34</td>
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<tr>
<td>RCB-III</td>
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<td>26</td>
<td>10</td>
</tr>
<tr>
<td>RCB-I</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>RCB-II</td>
<td>30</td>
<td>17</td>
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<tr>
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<td>17</td>
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Inter-Pathologist Reproducibility For RCB

100 cases of residual disease (invasive, metastatic, or in situ)

Results from 5 pathologists
4 had no prior training or experience with RCB, but read
manuscript and materials on the RCB website
Followed the patients for 7 more years to a median follow up of 12 years

RCB Index Score
- Overall concordance correlation coefficient: 0.93 (95% CI 0.91 to 0.95)
- Overall accuracy: 0.99

RCB Categories (pCR, RCB-I, RCB-II, RCB-III)
- Kappa coefficient for overall agreement: 0.58 (95% CI 0.54 to 0.63)

Peintinger et al. Modern Pathology 2015;28:913-20
Inter-Pathologist Concordance of Predicted DRFS

Predicted DRFS From RCB Index Score

Example: Comparison In A Randomized Trial
I-SPY2 Trial: Addition of Veliparib and Carboplatin to Weekly Paclitaxel

Response Endpoint
pCR OR = 4.56, p = 0.013
pCR/RCB-I OR = 8.19, p = 0.0005

Liu MC, et al. SABCS, 2015, abstract P3-07-49
Summary

- Record pretreatment cStage from clinical records
- Record pretreatment phenotype and grade
- pCR
  - pCR in breast and nodes
  - Report presence and extent of in situ residual disease
- Require standardized procedures to evaluate the gross specimen, record a map of the tissue sections related to the gross & imaging findings, and relate the histopathologic findings to that map
  - Multidisciplinary teamwork from surgeons, radiologists, and pathologists
- Then it becomes very easy to interpret and report
  - ypT Stage defined by largest continuous extent of invasive cancer
  - RCB from the dimensions and cellularity of primary tumor bed
  - Multifocality

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