Updates in Assessment of The Breast After Neoadjuvant Treatment

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AJCC, 8th Edition
• **Pathologic Prognostic Stage** is not applicable for patients who receive neoadjuvant therapy.
• Pathologic staging includes all data used for clinical staging, plus data from surgical resection.
• Information recorded should include:
  – Clinical Prognostic Stage.
  – The category information for either clinical (ycT and ycN) response to therapy if surgery is not performed, or pathologic (ypT and ypN) if surgery is performed.
  – Degree of response (complete, partial, none).
AJCC

- Post-treatment size should be estimated based on the best combination of imaging, gross, and microscopic histological findings.
- The ypT is determined by measuring the largest single focus of residual invasive tumor, with a modifier (m) indicating multiple foci of residual tumor.
- This measurement does not include areas of fibrosis within the tumor bed.
- When the only residual cancer intravascular or intralymphatic (LVI), the ypT0 category is assigned, but it is not classified as complete pathologic response.

A formal system (i.e. RCB, Miller-Payne, Chevalier, ...) may be offered in the report. Otherwise, description of the distance over which tumor foci extend, the number of tumor foci present, or the number of tumor slides/blocks in which tumor appears might be offered.
AJCC

• The ypN categories are the same as those used for pN.
• Only the largest contiguous focus of residual tumor is used for classification (treatment associated fibrosis is not included).

• *Inclusion of additional information such as distance over which tumor foci extend and the number of tumor foci present, may assist the clinician in estimating the extent of residual disease.*
Treatment Response Categories

AJCC

**No response (NR).**
No apparent change in either the T or N categories compared to clinical (pretreatment) assignment, or an increase in the T or N category at the time of pathologic evaluation.

**Partial response (cPR and pPR).**
A decrease in either or both T or N category compared to clinical (pretreatment) assignment, and with no increase in either T or N.

**Complete response (cCR and pCR).**
Clinical response is based on history, physical exam and available imaging studies.
Response category should be appended to the y stage description.

For example:

- ypTisypN0cM0CR
- ypT1ypN0cM0PR
- ypT2ypN-1cM0NR
The following questions about treatment effect are *required* if it is known that the patient had pre-surgical therapy.

**Treatment Effect in the Breast:**
- No definite response to therapy in the invasive carcinoma.
- Probable or definite response to therapy in the invasive carcinoma.
- No residual invasive carcinoma is present in the breast after therapy.
CAP

Treatment Effect in the Lymph Nodes:
- No definite response to therapy in metastatic carcinoma
- Probable or definite response to therapy in metastatic carcinoma
- No lymph node metastases;
  - Fibrous scarring, possibly related to prior metastases with pathologic complete response
- No prominent fibrous scarring in the nodes
RCB

Uses size and cellularity of the tumor bed including the percentage of residual DCIS together with tumor burden in lymph nodes, in a statistically complex algorithm, resulting in:

**RCB index/score**: A continuous parameter of response.

**RCB class**:
- RCB-0  No residual disease
- RCB-I  Minimal residual disease
- RCB-II  Moderate residual disease
- RCB-III Extensive residual disease
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: [ ] (mm) X [ ] (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)

[ ] Reset  [ ] Calculate

Residual Cancer Burden: [ ]
Residual Cancer Burden Class: [ ]
Prognosis

• Both RCB index and class have been shown to be prognostic in breast cancers of different phenotype (HR+/HER-2-, HER-2+/HR+/HR-, and triple negative).

• However, from the clinician’s point of view, the jury is still out on whether assessment of exact prognosis by RCB is required in all patients (i.e. added clinical value).

• Today, the impact of such information on clinical management might be limited. But this might change if new post-neoadjuvant treatment strategies become available, requiring a more refined assessment of response.

• For now, pCR remains the clinical trial standard to assess the effect of a given neoadjuvant chemotherapy-based treatment.
Residual Proliferative Cancer Burden (RPCB)

- PRCB has been claimed to provide significant prognostic information for patients with residual disease following neoadjuvant chemotherapy (more prognostic than either RCB or Ki67 alone).
- The same study group concluded that “prediction may be further improved by addition of post-treatment grade and ER, and warrants further investigation for estimating post-neoadjuvant risk of recurrence”.
- The expert Panel of the AJCC 8th edition did not consider Ki67 labeling index sufficiently reliable as a single marker of proliferation, because of lack of reproducibility (especially between different laboratories), as well as lack of agreement on an optimum cutoff point.
Logic Behind Moving Toward Newer Models

- Over the past decade, there have been fundamental changes in our understanding of the biology of breast cancer.
- We now think of breast cancer as a group of diseases that originate in breast epithelium but have different prognoses, patterns of recurrence, and dissemination after primary multidisciplinary treatments and have different sensitivities to available therapies.
- Biologic factors - such as grade, hormone receptor expression, HER-2 overexpression/amplification, and genomic panels - have become as or more important than the anatomic extent of disease to define prognosis, and select the optimum combination of therapies for each patient.
- Pathological Prognostic Stage is not applicable for patients who receive neoadjuvant therapy....
Logic Behind Moving Toward Newer Models

• Results from the group studying the impact of prognostic factors on staging using the National Cancer Data Base (NCDB) where used to establish Clinical and Pathological Prognostic Stage groups for the 8th edition of AJCC.

• Because of the relatively small number of patients who had received neoadjuvant chemotherapy, and the exponential increase in the number of variables generated with the degree of response, meaningful stage assignments for this group of patients could not be generated.

• The information collected by the 8th edition AJCC requirements, is considered to be critical to generate useful data for future staging modifications.
Newer Staging Models
CPS+EG System

• CPS+EG (Clinical-pathologic scoring system plus ER status and Grade) was the first staging system to incorporate tumor biology with staging.

• The system has been validated for assessing prognosis after neoadjuvant chemotherapy using *pre-treatment clinical stage, post-treatment pathologic stage, ER status and grade.*

• Scoring points are assigned for each factor, and are added to determine a CPS+FG score, which facilitates more refined stratification by disease-specific survival than either *clinical* stage or *pathologic* stage.
<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Score</th>
<th>Pathologic stage</th>
<th>Score</th>
<th>Tumor Marker</th>
<th>Score</th>
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<tbody>
<tr>
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<td>Stage 0</td>
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<td>Stage I</td>
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<td>Stage IIA</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Stage IIIA</td>
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<td>Stage IIB</td>
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<td>Stage IIIA</td>
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<tr>
<td>Stage IIIC</td>
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<td>Stage IIIC</td>
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</tbody>
</table>
Problem:
The development of this system predated the routine use of trastuzumab in treating patients with ERBB-2 positive breast cancer.

Facts:
The addition of trastuzumab to chemotherapy in the neoadjuvant setting results in higher pCR rates.
Patients with ERBB-2 positive breast cancer achieving cPR have improved outcome over patients with less than a pCR.

Resolution:
Neo-Bioscore system
Neo-Bioscore

- Study was undertaken to update the CPS+EG staging system with a more contemporary cohort of patients to include those with $ERBB2$-positive disease receiving trastuzumab.
- Included 2377 patients with non-metastatic invasive breast cancer treated with neoadjuvant chemotherapy from January 2005 through December 2012 (None of these patients had been included in the development or validation of the CPS+EG staging system).
- All patients received an anthracycline- and/or taxane-based neoadjuvant chemotherapy regimen; trastuzumab was administered as part of the neoadjuvant regimen for patients with $ERBB2$-positive disease.
Neo-Bioscore

- Incorporated **ERBB2** status into the CPS+EG system and re-validated using the current definition of ER positivity (>1%).
- Positive ERBB-2 status is defined as 3+ staining by IHC, or gene amplification on FISH.
- The revised system defined 8 prognostic groups, resulting in significant improvement in 5-yr disease-specific survival (DSS) estimates (compared to AJCC).
- *In addition to meet the growing interest in treating patients with residual disease following neoadjuvant chemotherapy, the Neo-Bioscore could be used to identify high-risk patients for clinical trial participation or to stratify patients in such studies.*
Table 1. Point Assignments for the CPS+EG and Neo-Bioscore Staging Systems

<table>
<thead>
<tr>
<th>Cancer Stage</th>
<th>CPS+EG Points</th>
<th>Neo-Bioscore Points</th>
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<td>Clinical stage</td>
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<td>1</td>
</tr>
<tr>
<td>ERBB2 negative</td>
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</tr>
</tbody>
</table>

Abbreviations: CPS+EG, clinical-pathologic staging system incorporating ER-negative disease and nuclear grade 3 tumor pathology; ER, estrogen receptor.
Neoadjuvant Therapy Outcomes Calculator

This software calculates the anticipated 5-year distant metastasis-free survival and disease-specific survival for breast cancer patients following treatment with neoadjuvant chemotherapy. The scoring systems provide a novel means for evaluating prognosis in these patients by incorporating the pretreatment clinical stage and post-treatment pathologic stage (CPS score) as well as estrogen receptor status and tumor grade (CSP+EG score). Please note that this calculator is not applicable for patients presenting with distant metastatic (M1) disease or for patients who go on to develop M1 disease.

**Clinical Stage**

Clinical Staging for Breast Cancer

TNM Stage: Select Clinical Stage

**Pathologic Stage**

Pathologic Staging for Breast Cancer

TNM Stage: Select Pathologic Stage

**Estrogen Receptor Status**

Select Estrogen Receptor Status

**Nuclear Grade**

Select Nuclear Grade

[Calculate] [Clear]

**Clinical-Pathologic Scoring System**

- Total Score:
- 5-year Distant Metastasis Free Survival: 95% CI:
- 5-year Disease Specific Survival: 95% CI:

**Clinical-Pathologic Scoring System incorporating estrogen receptor status and nuclear grade**

- Total Score:
- 5-year Distant Metastasis Free Survival: 95% CI:
- 5-year Disease Specific Survival: 95% CI:
Incorporation of Treatment Response, Tumor Grade and Receptor Status Improves Staging Quality in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy

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Confirmatory Reports

• The National Cancer Data Base (NCDB) was searched for patients with invasive breast cancer who received neoadjuvant chemotherapy between 2006 and 2012.

• Analyses were based on 43,320 patients (12,002 of whom had evaluable Neo-Bioscore), to compare four staging systems (end point: overall survival):
  - Clinical AJCC
  - Pathologic AJCC
  - CPS-EG
  - Neo-Bioscore

• At 5 years, the integrated discrimination improvement index relative to the baseline of AJCC clinical stage was about 9% for Neo-Bioscore, 7% for CPS+EG score, and 2% for AJCC pathologic stage.
Promising...

• “In a heterogeneous national cohort of breast cancer patients treated with NAC therapy and surgery, both GPS+EG and neo-Bioscore demonstrated significant improvement over TNM staging”.

• “Neo-Bioscore provided superior staging discrimination to CPS+EG”.
Path to the Future
The staging system is adapting to reflect a better understanding of the heterogeneity of breast cancers and the implications of individual tumor factors on prognosis and treatment.

The unintended consequence may be an increasingly complex and perhaps more difficult-to-manage staging system, but the added clinical value outweighs the added complexity.

In the coming years, and potentially as soon as the next 2-3 years, additional data from the NCDB and other large group populations of patients with full prognostic factor information and increasingly longer follow-up will become available, resulting in evolution of a post-NAT prognostic staging system.
References

Thank you