Changes in the AJCC 8th Edition to Breast Cancer Staging

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TNM System Origins

• Developed between 1943 and 1952 by French surgeon Pierre Denoix

The goal was a COMMON LANGUAGE

Pierre Denoix, MD.
L’Institut Gustave Roussy

• Used in 1959 to reflect the risk of distant recurrence and death after surgery
• At the time, limited understanding of the biology of breast cancer and no effective systemic therapy
• Primary objective was to provide standard nomenclature for prognosis after surgery
Since 1959

7 Editions of AJCC Cancer Staging Manual have refined the TNM staging

Other organ systems

- Advances in treatment and prognostic factors have lead to inclusion of factors other than TNM in the staging system.
- Histologic grade for sarcomas and prostate tumors
- Age and histology in thyroid tumors
- Serum markers in testes and gestational trophoblastic
Fundamental Changes

- Now think of breast cancer as a group of diseases.
- Different molecular characteristics (identified by IHC, gene expression profiling, proteomics, next generation sequencing).
- Different prognoses, sensitivity to treatment, pattern of recurrence, and dissemination after multidisciplinary treatments

AJCC Staging 8th Edition

- Need to incorporate biologic factors, such as tumor grade, proliferation rate, estrogen and progesterone receptor expression, human epidermal growth factor 2 (HER2) expression, and gene expression prognostic panels into the staging system.
- Should remain based on TNM anatomic factors

Adopted as of January 1, 2018

What are the changes?
Major Changes

• Changes in the TNM aspect of staging
• Addition of Grade and Biomarkers into Stage determination

The clinical utility of biologic factors such as grade, hormone receptor expression, HER2 overexpression and/or amplification, and genomic panels has become at least as important as the anatomic extent of disease to predict survival.

These factors enable accurate determination of prognosis and selection of systemic therapy and increasingly are affecting locoregional management.
To address the importance of tumor biology, in addition to defining AJCC anatomic stage groups, the breast expert panel has defined biologic factor-based prognostic stage groups for the eighth edition that take into consideration tumor grade; HER2, ER, and PR status; and multigene panel (such as Oncotype DX) status.

TNM classifications remain the basis for the eighth edition stage groups.

Tumor grade, hormone receptor status, and HER2 status are important additional determinants of outcome.

Now incorporated into parallel prognostic stage groups that recognize intrinsic tumor biology.

But first some definitions

- **Anatomic Stage**
  - Based solely on TNM
  - Intended for use worldwide where biomarkers are NOT available

- **Clinical Prognostic Stage**
  - Used for ALL patients based on history, exam, imaging, biopsies.
  - Incorporates TNM, Grade, Biomarker Data

- **Pathologic Prognostic Stage**
  - Used to assign stage in patients with surgery as initial treatment before systemic or radiation therapy
  - Incorporates all clinical, biomarker, and anatomic markers
Clinical vs Pathologic Prognostic Staging

- Clinical staging (c) is determined using information prior to surgery or neoadjuvant therapy
- Pathologic staging (p) includes information defined at surgery (except neoadjuvant)

Essential to maintain purely Anatomic Stage for areas where no access to biomarkers

We’ve known these biomarkers affect stage for a while, why just now?

Lack of level I evidence available to support the impact of biologic factors on prognosis.
- No prospective trials, no “no-treatment” arm.
- Large data sets with complete data and adequate follow-up not available
- Recent analyses of large retrospective studies
3728 patients who were treated between 1997 and 2006
-Developed a staging system that incorporated grade, ER and PR status with pathologic stage
-Validated with 26,711 patients from the SEER

3327 patients with invasive breast cancer treated with surgery as a first intervention at MD Anderson between 2007 and 2013
306 patients with HER2-positive breast cancer that were treated with trastuzumab.

Led to the formation of the Risk Score to link to TNM staging

**Table 4.2** Determination of the risk profile, MD Anderson Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>0 points</th>
<th>1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Grade 1/2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>ER status</td>
<td>ER positive</td>
<td>ER negative</td>
</tr>
<tr>
<td>HER2 status</td>
<td>HER2 positive</td>
<td>HER2 negative</td>
</tr>
</tbody>
</table>

MD Anderson Cohort 3327 patients and validated with 43,938 patients in the California Cancer Registry
Risk score:
1 point if estrogen receptor negative
1 point if HER2 negative
1 point for grade 3 disease
Reference group was stage 1 risk 0.

Additional Study- National Cancer Database

- 238,265 patients with invasive breast cancer treated from 2010 to 2011 with a complete set of variables that included the AJCC 7th edition stage group, tumor grade, ER, PR, and HER2 status. (Similar to point system)
- These combinations of T, N, and M category with grade, ER, PR, and HER2 status assigned one of nine stage groups (0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV) (to maintain consistency with previous breast cancer staging groups).


NCDB Findings

- Survival calculation performed for each prognostic subgroup based on 7th edition stage, grade, HER2, ER, and PR.
- Patients with triple negative tumors (all grades) have survival comparable to cancers of one stage higher that than those that express HER2, ER, or PR.
- Grade 3 tumors, that were HER2- and positive for either ER or PR had survival comparable to that of patients with disease one stage higher than those with tumors of a lower grade.
Two Analyses Performed

- Clinical Prognostic Stage
  - 334,243 patients from 2010-12 with 41.7 months follow up
  - All patients regardless of therapy

- Anatomic Prognostic Stage
  - Restricted to patients who received surgery as initial therapy (had pathologic info)
  - 305,519 patients from 2010-12 with 42.3 months follow up

Neoadjuvant?

- Evaluated Neoadjuvant patients
- Smaller numbers (44,189)
- Increased number of variables with treatment
- Meaningful stage assignments could not be generated at that time

NCDB data lead to formation of Clinical and Anatomic Prognostic Stages

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Clinical Prognostic Stage

Used for ALL patients with available markers

Pathologic Prognostic Stage

Applies to patients treated with surgery as initial treatment (based on resection).

Lead to stage reassignment for 35% of patients higher or lower than from anatomic stage alone

Data captured approximately 70% of breast cancers diagnosed in the US.
NCDB Analyses

• Relatively short follow-up but robust data
• Reflect modern treatment
• Survival at short term follow-up correlates highly with that of longer-term follow-up
• Excellent correlation with the MD Anderson analyses*

Excellent correlation with the MD Anderson analyses*

• Why is the AJCC not using the MD Anderson Bioscore?
• Bioscore incorporates the pathologic stage as determined by T, N, and M categories, it does not strictly maintain the traditional pathologic stage.
• Bioscore translates the pathologic stage to a point score then adds additional points to reflect the biologic characteristics.
• AJCC Expert Panel wanted maintenance of TNM Anatomic Stage
  • Countries without access to biomarkers or treatment
  • Common terminology for clinicians regardless of the country where they practice
  • Link to past for clinical trials

Addition of Multigene Assays

• Test for levels of expression of a large number of genes in the tumor at the RNA level
• Oncotype DX, Mammaprint, Endo- Predict, PAM50, and Breast Cancer Index.
Oncotype Dx incorporated into staging

• In August 2016, it was felt that the only multigene panel for which there was level one evidence was Oncotype Dx based on the first publication of results from the TAILORx study.

Supports the use of the 21-gene assay to spare the use of chemotherapy in patients who otherwise would be recommended to receive it on the basis of clinicopathologic features

Recurrence Score < 11

The major impact of a multi-gene panel in the eighth edition prognostic stage grouping is the downstaging of biologically low-risk T2 N0 from stage II to stage I for tumors with a low Oncotype DX recurrence score.

No upstaging based on a high recurrence score at this time
ONLY for T1/T2 ER+, HER2-, Node Negative disease

What about the other multigene assays?

• "It is not clear that any of these profile assays is superior to the others"
• "Despite inclusion of one multigene panel...no one or another of the genomic profiles should or should not be used in defining prognosis and making treatment decisions"
• "It is likely that additional evidence will become available in the near- to mid-term"

Expect Updates

Validation of the new Staging

Validation Study of the American Joint Committee on Cancer Eighth Edition Prognostic Stage Compared With the Anatomic Stage in Breast Cancer

The University of Texas MD Anderson Cancer Center (n = 3327, years of treatment 2007-2013, median follow-up of 5 years)
California Cancer Registry (n = 54,727, years of treatment 2005-2009, median follow-up of 7 years)

In both cohorts, the prognostic stage was significantly more accurate than the anatomic stage.
Revisions...already

- A percentage of patients could not be assigned a prognostic stage
  - Staging for patients with pN1mi disease and T2 or T3 tumors (~3%)
    - T2, T3, and T4 tumors with nodal micrometastases (N1mi) are now staged using the N1 category
  - Future revisions to the AJCC breast cancer staging system should further evaluate the pN1mi designation.
  - Data suggest T1 N1mi behave more like pN0 so Stage IB designation may not be appropriate

Revisions...already

- Additional data available regarding the use of multigene molecular profiling.
  - MINDACT trial was published to provide Level I evidence for MammaPrint
  - 8th edition has still not adopted MammaPrint in the staging.
  - Could not calculate clinical risk of recurrence similar to MINDACT trial as they were based on survival estimates from Adjuvant! Online.
  - There will be forthcoming updates

The Bottom Line

The application of the prognostic stages is more complicated but it more accurately predicts outcome
What Changed in the AJCC 8th Edition Breast Cancer Staging?

What Will Change in the AJCC 8th Edition Breast Cancer Staging?

There will be revisions as more data are available.