Updates to the 8th Edition
AJCC Staging System for Breast Cancer

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Disclosures

• I served on the expert panel that revised the AJCC staging system for breast cancer
Acknowledgments

• MD Anderson
  – Mariana Chavez-MacGregor, MD
  – Kelly Hunt, MD
  – Sharon Giordano, MD, MPH
  – Gabriel Hortobagyi, MD
  – Min Yi, MD

• Dana Farber/Brigham
  – Tari King, MD
  – Anna Weiss, MD

• California Cancer Registry
  – Daphne Lichtensztajn, MS
  – Christina Clarke, PhD, MPH

• AJCC expert panel
  – James Connolly, MD
  – Carl D’Orsi, MD
  – Stephen Edge, MD
  – Armando Giuliano, MD
  – Gabriel Hortobagyi, MD
  – Hope Rugo, MD
  – Lawrence Solin, MD
  – Donald Weaver, MD
  – David Winchester, MD
Goals of Staging

- Determine extent of disease
- Help determine a treatment plan
  - Management guidelines developed based on prognosis
- Inform prognosis
- Facilitate communication between providers (common language)
- Permit standardized collection of essential data
Evolution of AJCC Staging Manual:
From Anatomic Staging Towards Personalized Risk Assessment

AJCC 1st Edition
TNM Anatomic Staging Introduced
1978*

AJCC 2nd Edition
Expands Cancer Staging Data Form
1984

AJCC 3rd Edition
Established Worldwide Staging System w/ UICC
1989

AJCC 6th Edition
Addition of Non-anatomic Factors as Stage Modifiers (e.g., serum markers in testis tumors)
2003

AJCC 7th Edition
Continues Introduction of Non-anatomic Factors (e.g., PSA/Gleason in prostate cancer)
2010

AJCC 8th Edition
Introduction of the Prognostic Stage Group in Breast Cancer
2018

* Year edition went into effect

“The concept of molecular classification of cancer at a clinically relevant level is now accepted as an imminent reality…”
- Dr. Mahul Amin (AJCC 8th Edition Editor-in-Chief)

7th Edition AJCC Staging System

- TNM stage:
  - T: primary tumor
  - N: regional (ipsilateral) lymph nodes
  - M: distant metastasis
AJCC Staging System

- T stage:
AJCC Staging System

- Clinical N stage:
AJCC Staging System

• Pathologic N stage:

- Isolated Tumor Cell
- Micrometastasis
- Macrometastasis
AJCC Staging System

- **ITC**
  - Small clusters of cells not > 0.2mm
  - A cluster of < 200 cells in a single histologic cross-section
  - May be detected by H&E or IHC

**AJCC Staging System**

- **Pathologic N stage***:

<table>
<thead>
<tr>
<th>pNx</th>
<th>Regional LN cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No regional LN metastasis</td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>Malignant cells in LN no &gt;0.2mm (detected by H&amp;E or IHC)</td>
</tr>
<tr>
<td>pN1mi</td>
<td>Micrometastases (&gt;0.2mm and/or more than 200 cells, but none &gt;2.0mm)</td>
</tr>
<tr>
<td>pN1</td>
<td>Metastases in 1-3 axillary LN, at least one &gt; 2.0mm</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastases in 4-9 axillary LN, or in clinically detected IM LNs in absence of axillary LN metastases</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastases in ≥ 10 axillary LN; or in ipsilateral infraclavicular or supraclavicular LN; or ipsilateral IM nodes in presence of + axillary LN(s)</td>
</tr>
</tbody>
</table>

*abbreviated table; AJCC staging manual provides more detailed classification i.e. differentiating pN1a from pN1b
AJCC Staging System

• M stage:
  - M0  no clinical or radiographic evidence of distant metastases
  - M1  Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven > 0.2mm
7th Edition AJCC Staging System

• Clinical stage: Based on findings of history, physical examination, and any imaging studies that are done

• Pathologic stage: Definitive stage determined after surgery by pathologic evaluation of the primary tumor and regional lymph nodes
### 7th Edition AJCC Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T0</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1/2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIIB</td>
<td>T4</td>
<td>N0-2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Hierarchical Clustering Reveals Clinically Relevant Gene Expression Profiles in Breast Cancer

Sorlie T, et al. PNAS, 2001;98:10869-10874
Clinical considerations

49 yo female undergoes BCT and SLN dissection

- pT2N0M0 invasive ductal carcinoma, **ER+, PR+, HER2**
- pT2N0M0 invasive ductal carcinoma, **ER+, PR+, HER2**
- pT2N0M0 invasive ductal carcinoma, **ER-, PR-, HER2**
- pT2N0M0 invasive ductal carcinoma, **ER-, PR-, HER2**

Same TNM, different prognosis
5-yr BCSS According to Subtype

<table>
<thead>
<tr>
<th>_subtype</th>
<th>HR+/HER2-</th>
<th>HR+/HER2+</th>
<th>HER2+/HR-</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage T2N0</td>
<td>96%</td>
<td>94%</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>47%</td>
<td>39%</td>
<td>24%</td>
<td>17%</td>
</tr>
</tbody>
</table>

AJCC Staging System - Limitations

- Patient survival shows wide variation within each stage
- Does not take into account biologic factors that have prognostic and predictive value
  - Grade, ER, PR, HER2
- Treatment recommendations and response to therapy are dictated by these factors
AJCC Staging System - Challenge

- Make the staging system “current” i.e. more relevant
- Incorporate biologic tumor markers to facilitate more precise determination of prognosis
Developing a Novel Staging System

- 3,728 patients with invasive BC treated at MD Anderson 1997-2006
  - Stage I-III
  - Surgery as first treatment strategy
  - Known ER, PR and grade

Six different staging systems assessed:

1. Pathologic Stage (PS)
2. PS and grade
3. PS, grade, and LVI
4. PS, grade, and ER
5. PS, grade, and combination of ER and PR

Methods

- DSS calculated from the time of surgery → death due to breast cancer
- Univariate association of each potential prognostic factor with DSS
- Variables determined to have a significant impact on DSS with:
  - HR 1.1 - 3 were assigned 1 point
  - HR 3.1 – 6 were assigned 2 points
- Overall staging score calculated by summing the scores for the individual independent DSS predictors
Incorporation of Biologic Factors into Novel Staging System


Pathologic Stage

PS + G E

Disease-Specific Survival (proportion)

Follow-Up Time (years)

C–index: 0.68
AIC: 2,038.4

P < .001

PS

1

2A

2B

3A

Disease-Specific Survival (proportion)

Follow-Up Time (years)

C–index: 0.80
AIC: 1,931.9

P < .001

PS + G E

0

1

2

3

4

Novel Staging System Incorporating Tumor Biology

• Restaging considering ER and grade along with path stage → ↑ discrimination with respect to DSS

• Strengths
  • Externally validated with SEER dataset (n=26,711); C-index 0.8
  • ER and grade are variables routinely assessed at standard pathologic examination
Novel Staging System Incorporating Tumor Biology

A

Proportion survival

B

Follow-up time (Years)

Follow-up time (Years)

PS+GE Stage

Number at risk

Number at risk

PS+GE

0 1 2 3 4

Stage

I IIA IIB IIIA

I IIA IIB IIIA

P<0.0001

P<0.0001

Novel Staging System Incorporating Tumor Biology

• Limitations
  • Model built using retrospectively collected data
  • Treatment not assigned
  • Validation performed using population-based dataset
    • Possibility of coding errors
    • Report > 95% accuracy
  • Predated routine use of trastuzumab
Bioscore

- Update of previous staging system incorporating tumor biology
- MD Anderson cohort
  - 2007-2013
  - N=3,327
  - Included 306 HER2+ patients treated with trastuzumab

Bioscore – Model Building

- 2 staging systems assessed
  - Using path stage as backbone
    - PS
    - PS and grade
    - PS, grade, and ER
    - PS, grade, ER and HER2
  - Using T and N stage by summing the scores for T and N stage in the model
    - TN
    - TN and grade
    - TN, grade, and ER
    - TN, grade, ER and HER2
Bioscore – Model Building

• Score of 0-4 assigned to each factor by considering magnitude of hazard ratio
  • Binary variables, groups with significant impact on DSS assigned 1 point
  • Ordinal variables
    • HR 1.1-3 assigned 1 point
    • HR 3.1-6 assigned 2 points
    • HR 6.1-10 assigned 3 points
    • HR>10 assigned 4 points

Bioscore – Model Building

- Model performance quantified using Harrell’s concordance index (C-index)
  - Can range from perfect concordance (1.0) to perfect discordance (0.0)
- Akaike’s information criteria (AIC) also calculated
  - Takes into account how well model fits data
  - Takes into account complexity of the model
  - ↓ risk of overfitting
- Winner = highest C-index and lowest AIC value

AJCC stage + grade + ER + HER2

Disease-specific survival

- C-index: 0.81
- AIC: 987.8

T + N + grade + ER + HER2

Disease-specific survival

- C-index: 0.813
- AIC: 994.9

Bioscore Validation

- 67,944 BC patients stage I-III diagnosed 2005-2010 in the CCR
- Known grade, ER status, and HER2 status.
- Surgery as first treatment modality

More Models: Risk Score

- 43,938 patients with primary BC stage I-IV diagnosed 2005-2008 in the CCR
- Cox model identified grade, ER and HER2 as the most important prognostic factors in addition to stage
- Risk score point based system
  - One point for:
    - Grade 3
    - ER-negative
    - Her2-negative to complement the staging system
- 5-year BCSS and 5-y OS calculated

Risk Score – BCSS Stage I-III

Chavez-MacGregor, et al. The Oncologist 2017 Jun 7 [Epub ahead of print]
Risk Score – BCSS Stage IV

Chavez-MacGregor, et al. The Oncologist 2017 Jun 7 [Epub ahead of print]
Risk Score Hazard Ratios
Risk Score

- Most favorable outcomes were seen in HR+ tumors followed closely by HER2+ tumors with the worst outcomes observed in TNBC.
- Risk score system separated patients into 4 risk groups within each stage category (all P<0.05).
- Our simple risk score system incorporates biological factors into the staging system providing accurate prognostic information.

Chavez-MacGregor, et al. The Oncologist 2017 Jun 7 [Epub ahead of print]
• Recognizing limitations of 7th ed staging system, the AJCC expert panel revised the staging system and incorporated a **prognostic stage** to take into account biologic factors
  – Grade
  – Hormone receptor status
  – HER2
Grade

• Defined by histologic grading system of Scarff, Bloom, and Richardson, as updated and standardized by the Nottingham group

• Determined by evaluating
  – Glandular (Acinar)/Tubular differentiation
  – Nuclear pleomorphism
  – Mitotic rate

• Reported as overall grade
  – 1: well differentiated
  – 2: moderately differentiated
  – 3: poorly differentiated
Grade

Grade 1

Grade 2

Grade 3

Nottingham Breast Cancer Grade

<table>
<thead>
<tr>
<th>Total Feature Score</th>
<th>Tumor Grade</th>
<th>Appearance of Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-5</td>
<td>Grade 1 Tumor</td>
<td>Well-differentiated (appear normal, growing slowly, not aggressive)</td>
</tr>
<tr>
<td>6-7</td>
<td>Grade 2 Tumor</td>
<td>Moderately-differentiated (semi-normal, growing moderately fast)</td>
</tr>
<tr>
<td>8-9</td>
<td>Grade 3 Tumor</td>
<td>Poorly-differentiated (abnormal, growing quickly, aggressive)</td>
</tr>
</tbody>
</table>
Estrogen receptor

• Determined in FFPE sections by IHC
• Evaluating for nuclear staining
• Quantification may use the proportion of positive cells ± the intensity of immunoreactivity
• Reporting results:
  – Positive if immunoreactive tumor cells present (≥ 1%)*
  – Negative if <1% immunoreactive tumor cells present

* The percentage of immunoreactive cells may be determined by visual estimation or quantitation. Quantitation can be provided by reporting the percentage of positive cells or by a scoring system, such as the Allred score or H score

HER2

- Can test for HER2 protein expression (IHC assay) or HER2 gene expression (ISH assay)
<table>
<thead>
<tr>
<th>HER2 positive</th>
<th>IHC 3+ based on circumferential membrane staining that is complete, intense</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISH positive based on:</td>
</tr>
<tr>
<td></td>
<td>single-probe average HER2 copy number ≥6.0 signals/cell</td>
</tr>
<tr>
<td></td>
<td>dual-probe HER2/CEP17 ratio ≥2.0 with an ave HER2 copy number ≥4.0 signals/cell</td>
</tr>
<tr>
<td></td>
<td>dual-probe HER2/CEP17 ratio &lt;2.0 with an ave HER2 copy number &lt;6.0 signals/cell</td>
</tr>
<tr>
<td>HER2 equivocal</td>
<td>IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within &gt;10% of invasive tumor cells; or complete and circumferential membrane staining that is intense and within ≤10% of invasive tumors cells</td>
</tr>
<tr>
<td></td>
<td>ISH equivocal based on:</td>
</tr>
<tr>
<td></td>
<td>single-probe average HER2 copy number ≥4.0 and &lt;6.0 signals/cell</td>
</tr>
<tr>
<td></td>
<td>dual-probe HER2/CEP17 ratio &lt;2.0 with an ave HER2 copy number ≥4.0 and &lt;6.0 signals/cell</td>
</tr>
<tr>
<td>HER2 negative</td>
<td>IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within &gt;10% of the invasive tumors cells</td>
</tr>
<tr>
<td></td>
<td>IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cells</td>
</tr>
<tr>
<td></td>
<td>ISH negative based on:</td>
</tr>
<tr>
<td></td>
<td>single-probe average HER2 copy number &lt;4.0 signals/cell</td>
</tr>
<tr>
<td></td>
<td>dual-probe HER2/CEP17 ratio &lt;2.0 with an ave HER2 copy number &lt;4.0 signals/cell</td>
</tr>
<tr>
<td>HER2 indeterminate</td>
<td>Report as indeterminate if technical issues prevent tests from being reported as positive, negative or equivocal</td>
</tr>
<tr>
<td></td>
<td>Inadequate specimen handling</td>
</tr>
<tr>
<td></td>
<td>Artifacts that interfere with interpretation</td>
</tr>
<tr>
<td></td>
<td>Analysis testing failure</td>
</tr>
</tbody>
</table>

ER/PR/HER2

AJCC 8th Edition

• Anatomic stage group
  – T,N,M

• Prognostic stage group
  – Incorporates grade, ER, PR, HER2 status in addition to T,N,M
  – Inclusion of multigene panels as stage modifiers when available

AJCC 8th Edition

- Prognostic stage group
  - Developed using data from the National Cancer Data Base
  - Considers patients treated with surgery as initial intervention follow by adjuvant therapy
  - 238,265 patients 2010-2011 in whom complete TNM, grade, ER and HER2 data were available

- Analysis confirmed prognosis varied within TNM groupings based on tumor biology

- 152 prognostic groups

### AJCC 8th Edition

#### Traditional TNM Factors + Expanded Non-Anatomic Factors

<table>
<thead>
<tr>
<th>When T is...</th>
<th>When N is...</th>
<th>When M is...</th>
<th>And G is...</th>
<th>And HER2 Status is...</th>
<th>And ER Status is...</th>
<th>And PR Status is...</th>
<th>The Prognostic Stage Group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Positive</td>
<td>Any</td>
<td>Any</td>
<td>IA</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>IB</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>1-2</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>IB</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1-3</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>IIA</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>IIA</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>IIIA</td>
</tr>
</tbody>
</table>

“Compared to the [8th Edition] anatomic stage groups, the application of the prognostic stage groups assigns 41% of cases to a different group with either a better or worse prognosis.”

AJCC 7th vs. 8th Edition

40% of Early Stage Breast Cancer Patients Restaged

Expert panel determined it was appropriate to incorporate multigene molecular profiling based on the data reported from Arm A of the TAILORx study.

<table>
<thead>
<tr>
<th>When T is...</th>
<th>When N is...</th>
<th>When M is...</th>
<th>And G is...</th>
<th>And HER2 Status is...</th>
<th>And ER Status is...</th>
<th>And PR Status is...</th>
<th>The Prognostic Stage Group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-T2</td>
<td>N0</td>
<td>M0</td>
<td>1-3</td>
<td>Negative</td>
<td>Positive</td>
<td>Any</td>
<td>IA</td>
</tr>
</tbody>
</table>

MultiGene Panel** - Oncotype DX Recurrence Score Results Less Than 11
OS=98% if RS<11

Validation of the AJCC 8th Edition

- MD Anderson: 3,327 stage I-III BC patients treated 2007-2013
  - Compared to AJCC anatomic stage, the prognostic stage **upstaged 29.5%** of patients and **downstaged 28.1%**
  - The prognostic staging system provided more accurate stratification with respect to DSS than the anatomic stage
  - **Unable to assign prognostic stage in 451 (13.6%)**

Weiss A, Chavez-MacGregor M……Mittendorf EA. Manuscript under review
Validation of the AJCC 8th Edition

- CA Cancer Registry: 54,724 stage I-IV BC patients diagnosed 2005-2009
  - Compared to AJCC anatomic stage, the prognostic stage upstaged 31.0% of patients and downstaged 20.6%
  - The prognostic staging system provided more accurate stratification with respect to DSS than the anatomic stage
  - Unable to assign prognostic stage in 3,746 (6.8%)

Weiss A, Chavez-MacGregor M......Mittendorf EA. Manuscript under review
Validation of the AJCC 8th Edition

MD Anderson

CA Cancer Registry
• Added prognostic stage
• LCIS classified as a benign entity and removed from TNM staging
• Tumor grade defined by Nottingham histologic grade is required element for staging
AJCC 8\textsuperscript{th} Edition - Issues

- Complex - >150 prognostic stages
- Unable to assign prognostic stage in 7-14\% of cases
  - Uncategorized combinations of T,N,grade,ER,PR and HER2
  - pN1mic with T2 or T3 tumors
- Limited level I data for the many available genomic assays
- Prognostic stage CANNOT be used for patients receiving neoadjuvant chemotherapy
- How will the prognostic stage be used by busy clinicians?
- How will guidelines (i.e. NCTN) guidelines handle?
- What are the implications when communicating local regional management?
Expert panel has repeated analyses of NCDB database

- Accounts for all combinations of T,N,grade,ER,PR and HER2
- Further refines prognostic stage → clinical prognostic stage and pathologic prognostic stage
- Further discusses multiple genomic assays (i.e. MINDACT data discussed)
- Pending approval, will be available online
AJCC 8th Edition - Opportunities

- Education
- Dissemination
- IT platforms to facilitate use
- May refine clinical trial eligibility criteria
AJCC 8th Edition

1977 - 2017

- Tumor Size
- Anatomic Stage
- Node Status
- Metastasis

2018+

- Tumor Size
- 8th Edition Prognostic Stage Group
- Recurrence Score Value (0 To 10)*
- Tumor Grade
- Node Status
- Metastasis
- Receptor Status (HER2/ER/PR)
Acknowledgments

• MD Anderson
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