# AJCC Staging Guidelines for Breast Cancer and the Implications for Treatment

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# Introduction

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- The American Joint Committee on Cancer (AJCC) staging system:
  - Is universally used and has largely displaced other staging classifications for most, although not all, cancers
  - Previous editions relied on anatomic methods of staging alone
    - Used population-based survival data to predict clinical outcomes
  - The 8th edition incorporated prognostic biomarkers to more accurately predict clinical outcomes and treatment response

# Introduction

**Our goal today is to:**

- **Discuss objectives of staging and AJCC staging history**
- **Review studies that served as an impetus for change**
- **Discuss changes to AJCC 8th edition breast chapter**
- **Discuss rationale for changes and data supporting these changes**
- **Discuss practical implications**

# Objectives of Staging

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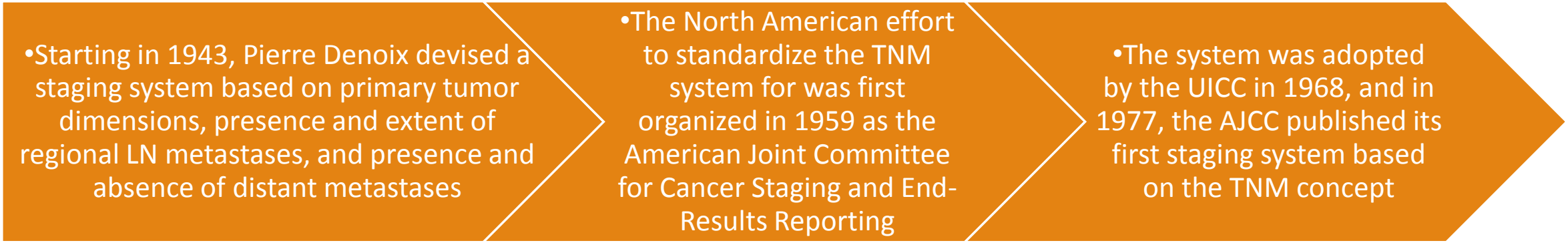
- Staging classifications were developed to:
  - Better understand the clinical behavior of specific malignancies
  - Determine prognosis and improve individual patient care
  - Enable physicians and their patients to compare outcomes of similar groups of patient
  - Permit current investigators in the field to communicate with one another using a standardized language that reflects disease burden and tumor biology

# AJCC Staging History

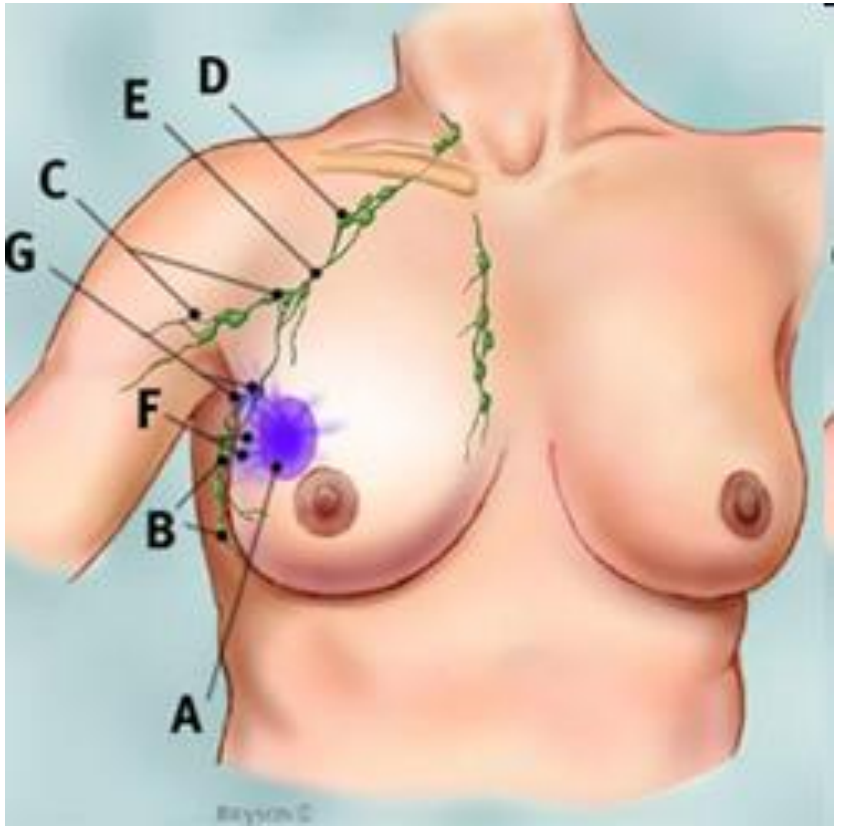
# AJCC Staging History




Denoix PF, 1954. Manual for Staging of Cancer, 1977.

# AJCC Staging History

- The TNM system was developed in the absence of effective systemic therapy and based on limited understanding of tumor biology
- Old system relied on Halstedian view of spread
  - Based on the paradigm of progression of the tumor to regional nodes and thence to distant sites
- Given this, the initial TNM system was generated to reflect the risk of distant recurrence and death subsequent to local therapy
  - Local therapy at the time was almost universally radical mastectomy and postoperative radiation to the chest wall



# Progress in Knowledge/Systemic Therapy ➡ Need for Revised Staging

- Following initiation of TNM system, progress has:
  - Challenged the Halstedian view of tumor progression with the understanding of the potential for distant systemic spread of all invasive cancers irrespective of node involvement

The Fisher model suggests that breast cancer is a systemic disease at diagnosis

- At time of diagnosis, the disease:

  (a) is disseminated already to other sites that will become apparent at a later date

  OR

  (a) will never disseminate.

- Lymph nodes are not an intermediate site for dissemination, but merely an indicator of whether or not a particular cancer is likely systemic

Van Poznak C et al, 2015.

# Progress in Knowledge/Systemic Therapy ➡ Need for Revised Staging

- Following initiation of TNM system, progress has:
  - Demonstrated the value of adjuvant systemic therapy
- These changes have led to:
  - More limited surgical management
  - Reduction in the extent of axillary staging
  - Dramatic improvements in the delivery and safety of radiation treatment
  - Recognition that early systemic therapy reduces the chance of recurrence and mortality
  - Increasing implementation of preoperative (neoadjuvant) systemic therapies for larger operable tumors and locally advanced breast cancer
  - Better understanding of biologic markers of prognosis and prediction or response to selective categories of systemic therapy (such as those targeting cancer cells positive for ER and HER2 amplification)

Van Poznak C et al, 2015.

# Progress in Knowledge/Systemic Therapy → Need for Revised Staging

- Following initi
  - Demonstrate
- These change
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  - Reduction in
  - Dramatic imp
  - Recognition t
  - Increasing im operable tum
  - Better under categories of amplification

**Enhanced knowledge of the importance of biologic factors (such as grade, hormone receptor expression, HER2 overexpression/amplification, and genomic panels) has led to significant changes in diagnostic and therapeutic approaches**

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r ER and HER2

Van Poznak C et al, 2015.

# Impetus for Change

# Impetus for Change – MDACC Study

Novel Staging System for Predicting Disease-Specific Survival in Patients With Breast Cancer Treated With Surgery As the First Intervention: Time to Modify the Current American Joint Committee on Cancer Staging System

*Min Yi, Elizabeth A. Mittendorf, Janice N. Cormier, Thomas A. Buchholz, Karl Bilimoria, Aysegul A. Sahin, Gabriel N. Hortobagyi, Ana Maria Gonzalez-Angulo, Sheng Luo, Aman U. Buzdar, Jaime R. Crow, Henry M. Kuerer, and Kelly K. Hunt*

- 3728 invasive breast cancer patients treated at MDACC between 1/1997 and 12/2006 were identified with no known distant metastases and no receipt of neoadjuvant chemotherapy
  - All patients had known biomarkers and minimum two-year follow up
- Calculated disease-specific survival (DSS) from diagnosis to death due to breast cancer
- Utilized pathologic stage to derive prognostic model for DSS
- Uni- and multivariate models identified factors associated with DSS
  - ER, PR, grade, LVI
- This was validated with 26,711 patients from the SEER database

Min Y et al, 2011.

# Impetus for Change – MDACC Study

- Limitations of initial MDACC study: predated use of trastuzumab for HER2-amplified patients
- Recognizing this, the MDACC group updated the model using a cohort of 3327 patients, including 306 patients with HER2 amplified breast cancer, treated at MDACC between 1/2007 and 12/2013
- With this update, a multivariate analysis was again performed to identify factors associated with DSS
- The staging system that included pathologic stage, grade, ER and HER2 had the highest C-index and lowest AIC
  - The Harrell concordance index (C index) is used to quantify models' predictive performance
  - The Akaike information criterion (AIC) is used to compare model fits
- These results were validated using a cohort of 67,944 patients identified from the California Cancer Registry diagnosed between 2005 and 2010 with a first primary non-metastatic breast cancer who underwent surgery as initial intervention with known grade, ER, and HER2 status

**TABLE 6. The University of Texas MD Anderson Cancer Center Univariate and Multivariate Analyses for Clinicopathologic Factors Associated With Disease-Specific Survival**

| | | UNIVARIATE ANALYSIS | | MULTIVARIATE ANALYSIS | | |
|---|---|---|---|---|---|---|
| FACTOR | 5-YEAR DSS, % | HR | *P* | HR | *P* | BIOSCORE POINTS ASSIGNED |
| Pathologic stage | | | | | | |
| IA/IB | 99.1 | Referent | | Referent | | 0 |
| IIA | 98.0 | 2.8 | .002 | 2.3 | .01 | 1 |
| IIB | 95.6 | 4.8 | < .0001 | 4.0 | < .0001 | 2 |
| IIIA | 95.4 | 6.8 | < .0001 | 7.2 | < .0001 | 3 |
| IIIC | 79.5 | 26.6 | < .0001 | 19.9 | < .0001 | 4 |
| ER status | | | | | | |
| Positive | 98.8 | Referent | | Referent | | 0 |
| Negative | 92.9 | 4.9 | < .0001 | 2.5 | .001 | 1 |
| PR status | | | | | | |
| Positive | 98.8 | Referent | | Referent | | |
| Negative | 95.2 | 4.0 | < .0001 | | NS | |
| HER2 status | | | | | | |
| Positive | 97.5 | Referent | | Referent | | 0 |
| Negative | 98.0 | 0.8 | .5 | 2.2 | .04 | 1 |
| Nuclear grade | | | | | | |
| 1 | 99.8 | Referent | | Referent | | 0 |
| 2 | 98.9 | 5.0 | .1 | 4.0 | .2 | 0 |
| 3 | 95.3 | 25.0 | .001 | 13.0 | .01 | 1 |

Abbreviations: DSS, disease-specific survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NS, nonsignificant; PR, progesterone receptor. Source: Personal communication, E.A. Mittendorf (unpublished data).

A score of 0-4 was assigned to each factor based on its hazard ratio and an overall staging score, the Bioscore, was calculated by summing the scores for the individual independent predictors of disease-specific survival

## TABLE 7. Five-Year Disease-Specific Survival Outcomes by Bioscore for The University of Texas MD Anderson Cancer Center Cohort (N = 3327)

| BIOSCORE: POINTS ASSIGNED | DSS (95% CI), % |
|---|---|
| 0, n = 36 | 100 |
| 1, n = 1204 | 99.4 (98.8-99.8) |
| 2, n = 919 | 99.2 (98.0-99.7) |
| 3, n = 667 | 97.2 (95.2-98.4) |
| 4, n = 339 | 94.2 (90.1-96.7) |
| 5, n = 129 | 92.0 (84.5-96.0) |
| 6, n = 23 | 77.3 (53.6-89.9) |
| 7, n = 10 | 33.3 (6.3-64.6) |

Abbreviations: 95% CI, 95% confidence interval; DSS, disease-specific survival. Source: Personal communication, Mittendorf EA (unpublished data).

# Impetus for Change – MDACC Study

- The analyses performed on these large databases from MDACC assumed proper multidisciplinary treatment with appropriate adjuvant chemotherapy and hormonal therapy
- The data confirmed the prognostic significant of biologic factors to include grade, ER and HER2 status and led to the development of a risk profile that can be used to further refine the prognostic information provided by the pathological stage

**Table 48.4** Determination of the risk profile. MD Anderson Analysis

| Factor | 0 points | 1 point |
|---|---|---|
| Grade | Grade 1/2 | Grade 3 |
| ER status | ER positive | ER negative |
| HER2 status | HER2 positive | HER2 negative |

# Impetus for Change – MDACC Study

**Limitations:**

- **Relatively small cohort at a single institution**
- **Represents a complex departure from traditional TNM anatomic staging**

**Given these limitations, the AJCC expert panel felt that validation in a larger cohort would be required before the risk profile could be considered for incorporation into AJCC staging; however, its data strongly support the incorporation of biomarkers into the TNM staging system**

# Impetus for Change – NCDB Study

- Second piece of data used to formulate the 8th edition was led by Dr. David J. Winchester and colleagues, who studied the impact of prognostic factors on staging using patients in the National Cancer Database (NCDB) with complete set of variables (TNM, tumor grade, ER, PR and HER2 status)
- Survival calculation performed based on: 7th edition stage group, grade, HER2, ER and PR
- Prognostic subgroups were assigned to a respective stage according to the calculated mean survival

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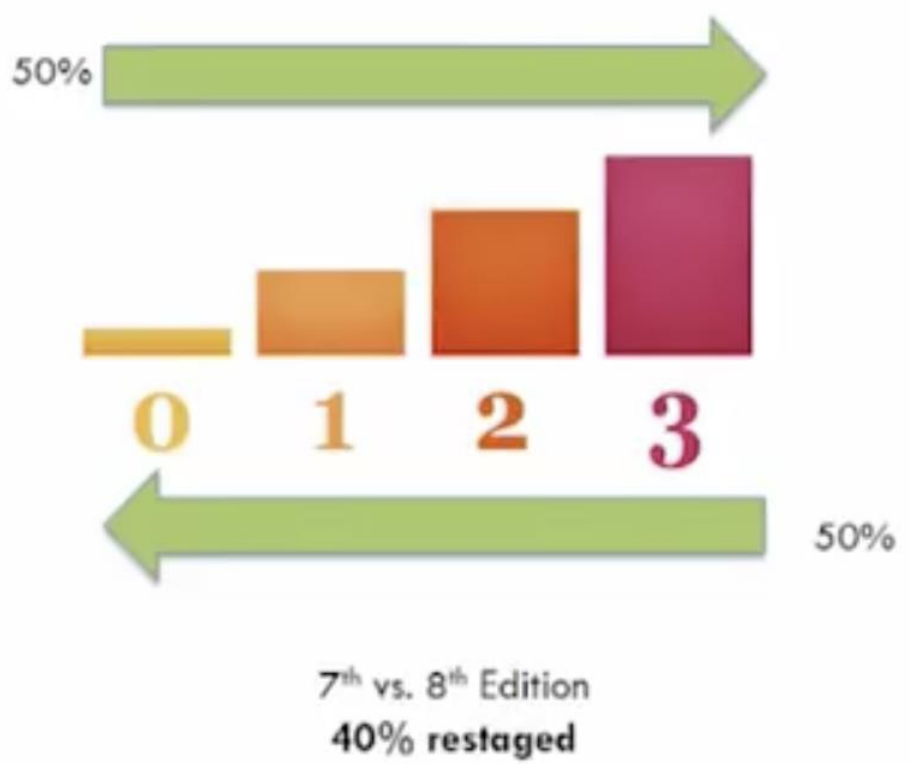
**NCDB Study findings were consistent with the point score developed in the MDACC model**

# Impetus for Change – NCDB Study

The inclusion of grade, HER2 and hormone receptor status resulted in stage reassignment for more than 35% of patients to a stage group higher or lower than would otherwise be assigned using 7th edition anatomic stage



# AJCC 8th Edition

# AJCC 8th Edition

- Effective January 1, 2018
  - Outside of the United States, the Union for International Cancer Control (UICC) implemented the eighth edition changes as of January 1, 2017
- Includes:
  - Anatomic stage groups (defined by TNM categories)
  - Two prognostic stage groups (incorporating TNM, grade, HER2, ER and PR status):
    - Clinical prognostic stage group (for use in all patients)
    - Pathologic prognostic stage group (for use in patients who undergo surgical resection as their initial treatment)
      - The pathologic prognostic staging should not be used for patients who received neoadjuvant systemic therapy before surgery. Rather, the postneoadjuvant (ypT and ypN) staging system should be used for these patients).
        - Because there is no large enough databases of patients who have received neoadjuvant systemic therapy and have complete information about ypTNM and biomarkers, no prognostic staging system has been developed for this population

# AJCC 8th Edition

- It is important to recognize that the Clinical and Pathological Prognostic Staging systems reflect the prognosis in patients offered treatment appropriate for the clinical extent and biomarker status of the case
  - Lower stage disease reflects favorable biology, effective therapy or both
  - Lower stage does not denote the need for less treatment

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*For example, a woman with a T3, N1, Grade 2, HER2-positive, ER and PR-positive cancer is staged as Prognostic Stage IB. However to achieve the excellent prognosis this reflects, the patient should receive systemic therapy appropriate for a larger HER2-positive caner – systemic chemotherapy coupled with anti-HER2 therapy, followed by endocrine therapy*

# AJCC 8th Edition

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  - Lower stage disease reflects favorable biology, effective therapy or both
  - Lower stage does not denote the need for less treatment

**It is important that clinicians recognize that this new breast cancer staging system assigns stage group based on overall prognosis with treatment, and not simply on the anatomic extent of cancer**

# Factors Included in AJCC 8th Edition

- **Anatomic Factors**: Tumor, Node, Metastases
- **Clinical Prognostic Factors**: Grade, HER2, ER, PR
  - The expert panel felt that, when possible, evaluation of these four biomarkers should adhere to guidelines of the American Society of Clinical Oncology and the College of American Pathology
- **Pathological Prognostic Factors**: Multigene genomic profile assays
  - The results of a multigene assay should be incorporated into the prognostic staging for patients with hormone receptor-positive, HER2-negative, node-negative tumors that are <5 cm

# Factors Not Included in AJCC 8th Edition

- The AJCC expert panel also identified several other factors that may also yield prognostic information, but are not formally included in the staging system:
  - **Ki-67:** Ki-67 is a nuclear protein associated with cellular proliferation assessed by immunohistochemistry, although a uniform methodology is lacking
  - **Multigene expression assays other than RS:** RS was the only multigene expression panel supported by level I evidence
    - Other multigene expression panels, however, including Mammaprint, EndoPredict, PAM50 Risk of Recurrence (ROR), and the Breast Cancer Index are supported by level II evidence and may be incorporated into future editions of the TNM staging system when high-level data are available
  - **Risk assessment models:** The AJCC evaluated 30 prognostication tools for breast cancer and found that two tools, Adjuvant! Online and PREDICT-Plus, met all of the predefined inclusion criteria and none of the exclusion criteria
    - These tools, which were externally validated and have acceptable levels of predictive accuracy, provide estimates of outcomes among women treated for early breast cancer and indicate the relative benefit of adjuvant treatments

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- The AJCC expert panel also identified several other factors that may also yield prognostic information, but are not formally included in the staging system:
  - **Circulating tumor cells (CTCs):** CTCs are cancer cells that separate from solid tumors and enter the blood stream
    - The US FDA has approved the CellSearch assay for detection of CTCs in metastatic breast cancer, in which they are a poor prognostic indicator
    - Although the use of this assay in primary breast cancer has been explored, an expert panel from ASCO concluded that there are insufficient data to support its use in this setting
  - **Disseminated tumor cells (DTCs):** DTCs in the bone marrow provide prognostic information regarding the likelihood of relapse at the time of initial tumor resection
    - Although DTCs may provide prognostic information and are included as an additional factor for clinical care in the eighth edition AJCC manual, an ASCO expert panel on tumor markers in breast cancer concluded that the available data were insufficient to recommend their use in clinical decision-making

# Multigene Genomic Assay Incorporation

# Multigene Panels in Breast Cancer

- These commercially available panels have been shown to reproducibly identify patients with better and worse prognosis after initial treatment with curative intent
- Important considerations when including multigene panels in staging:
  - These panels have been used in the determination of prognosis in existing tumor collections, mostly tumor banks; although some used patients samples from prospective clinical trials
  - Most panels were developed for hormone receptor positive, HER2 negative tumors, although MammaPrint was developed in an unselected group of patients with breast cancer
  - Most of the clinical validation has taken place in patient groups with LN negative breast cancer, although information based on LN-positive breast cancer is starting to appear in the peer-reviewed literature

# Multigene Genomic Profile Assay Incorporation

- The panel decided to assign Pathological Prognostic Stage Group IA for those patients with T1 or T2 (< 5 cm), N0, M0 cancers that are ER positive and HER2 negative, and have an Oncotype DX recurrence score of less than 11
  - This decision was based on the published information from a prospective clinical trial indicating that for a specific group of patients (ER+, LN-, RS <11), the prognosis was excellent and comparable to patients with T1a-T1b N0 breast cancer with similar characteristics
    - In addition, two additional prospective studies and a population- based analysis (SEER database) provided similarly excellent outcomes for this group of patients

| When T is… | When N is… | When M is… | And G is… | And HER2 status is… | And ER status is… | And PR status is… | The Prognostic Stage Group is… |
|---|---|---|---|---|---|---|---|
| MultiGene Panel – Oncotype DX Recurrence Score Results Less Than 11 | | | | | | | |
| T1-T2 | N0 | M0 | 1-3 | Negative | Positive | Any | IA |

Sparano JA et al, 2015. Stemmer S et al, 2015. Gluz O et al, 2015. Petkov VI et al, 2016.

# Multigene Genomic Profile Assay Incorporation

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  - This decision was based on the published information from a prospective clinical trial indicating that for excellent outcomes for this group of patients

**Notably, at the time of incorporation of Oncotype DX into the 8th edition, only outcomes for the low recurrence score group were reported**

| When T is… | When N is… | When M is… | And G is… | And HER2 status is… | And ER status is… | And PR status is… | The Prognostic Stage Group is… |
|---|---|---|---|---|---|---|---|
| MultiGene Panel – Oncotype DX Recurrence Score Results Less Than 11 | | | | | | | |
| T1-T2 | N0 | M0 | 1-3 | Negative | Positive | Any | IA |

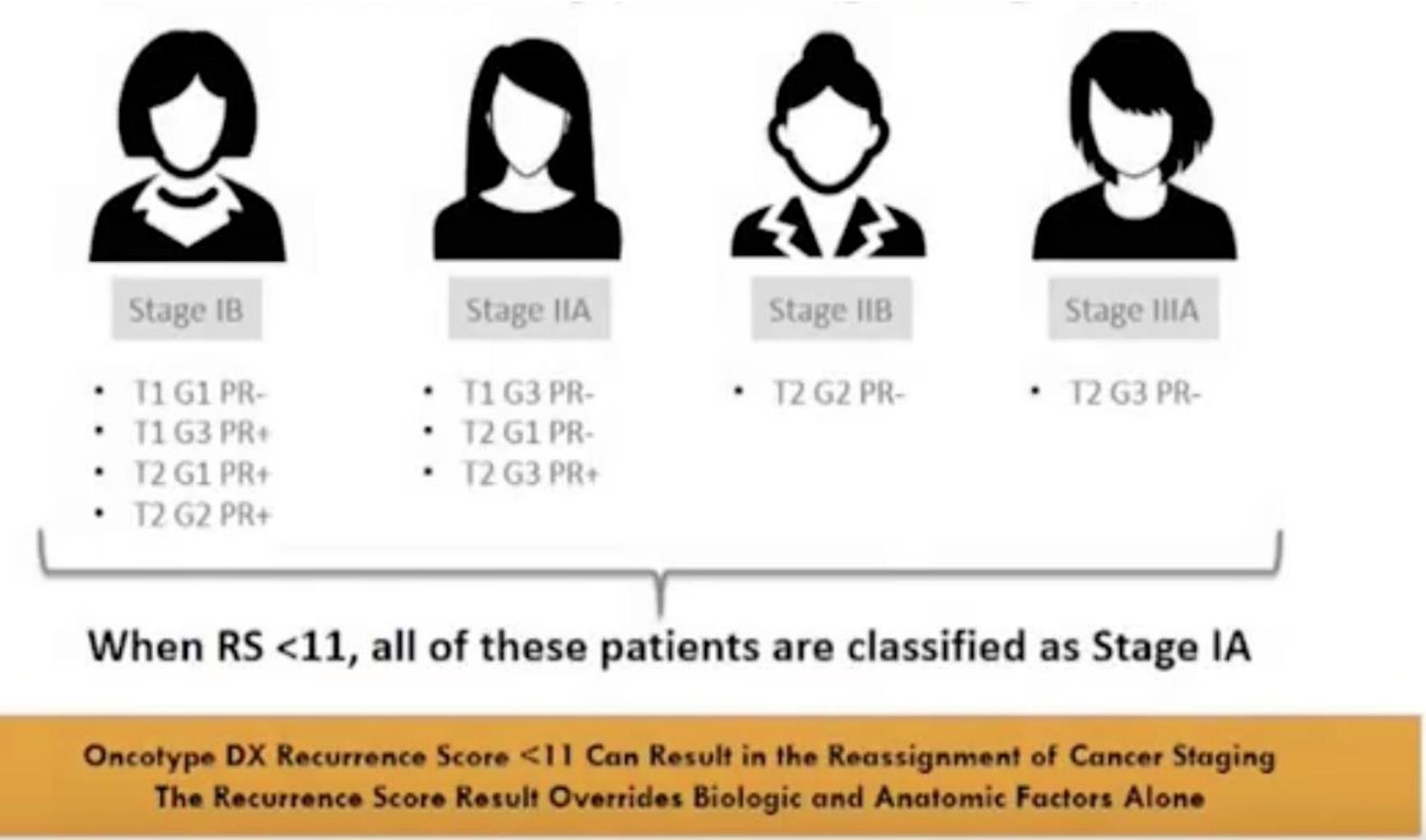
Sparano JA et al, 2015. Stemmer S et al, 2015. Gluz O et al, 2015. Petkov VI et al, 2016.

# Multigene Genomic Profile Assay Incorporation

- The panel decided not to include the specific results of other genomic profile or multigene assays to assign Pathologic Prognostic Stage in the staging table
  - This reflects the more limited Level I evidence for other profiles, and the difficulty in specifying exactly how they should be included in the tables

| Multigene Panel | Details of Change | Level of Evidence |
|---|---|---|
| Inclusion of Multigene Panels (when available) as Stage Modifiers – 21 Gene Recurrence Score (Oncotype Dx®) | For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 21-gene (Oncotype Dx®) recurrence score less than 11, regardless of T size, places the tumor into the same prognostic category as T1a–T1b N0 M0 and **staged using the AJCC Prognostic Stage table as Stage I.** | I |
| Inclusion of Multigene Panels (when available) as Stage Modifiers – Mammaprint® | For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Mammaprint® low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b N0 M0. | II |
| Inclusion of Multigene Panels (when available) as Stage Modifiers – EndoPredict® | For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 12-gene (EndoPredict) low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b N0 M0. | II |
| Inclusion of Multigene Panels (when available) as Stage Modifiers – PAM 50® (Prosigna) | For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a PAM50 risk of recurrence (ROR) score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b N0 M0. | II |
| Inclusion of Multigene Panels (when available) as Stage Modifiers – Breast Cancer Index | For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Breast Cancer Index in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0. | II |

# Oncotype DX Incorporation



# Validation of AJCC 8th Edition

# Validation of 8th Edition

- 3327 patients with stage I to IIIC breast cancer treated with surgery as an initial intervention were identified in a prospective institutional database from MD Anderson Cancer Center
  - Years of treatment 2007-2013
  - Median follow-up of 5 years
- Calculated disease-specific survival (DSS), C index was used to quantify models' predictive performance, and the AIC was used to compare model fits
- Compared with the AJCC anatomic stage, the prognostic stage upstaged 29.5% of patients and downstaged 28.1%
- The prognostic stage (C index, 0.8357 and AIC, 816.8) provided more accurate stratification with respect to disease-specific survival than the anatomic stage (C index, 0.737 and AIC, 1039.8) ($P < .001$ for the C index)

Weiss A et al. 2018.

# Validation of 8th Edition

- 54,727 patients with stage I to IIIC breast cancer treated with surgery as an initial intervention were identified in a prospective institutional database from the California Cancer Registry
  - Years of treatment 2005-2009
  - Median follow-up of 7 years
- Calculated disease-specific survival (DSS), C index was used to quantify models' predictive performance, and the AIC was used to compare model fits
- The prognostic stage upstaged 31.0% of patients and downstaged 20.6%
- The prognostic stage (C index, 0.8426 and AIC, 80 661.68) performed better than the anatomic stage (C index, 0.8097 and AIC, 81 577.89) ($P < .001$ for the C index)

Weiss A et al. 2018.

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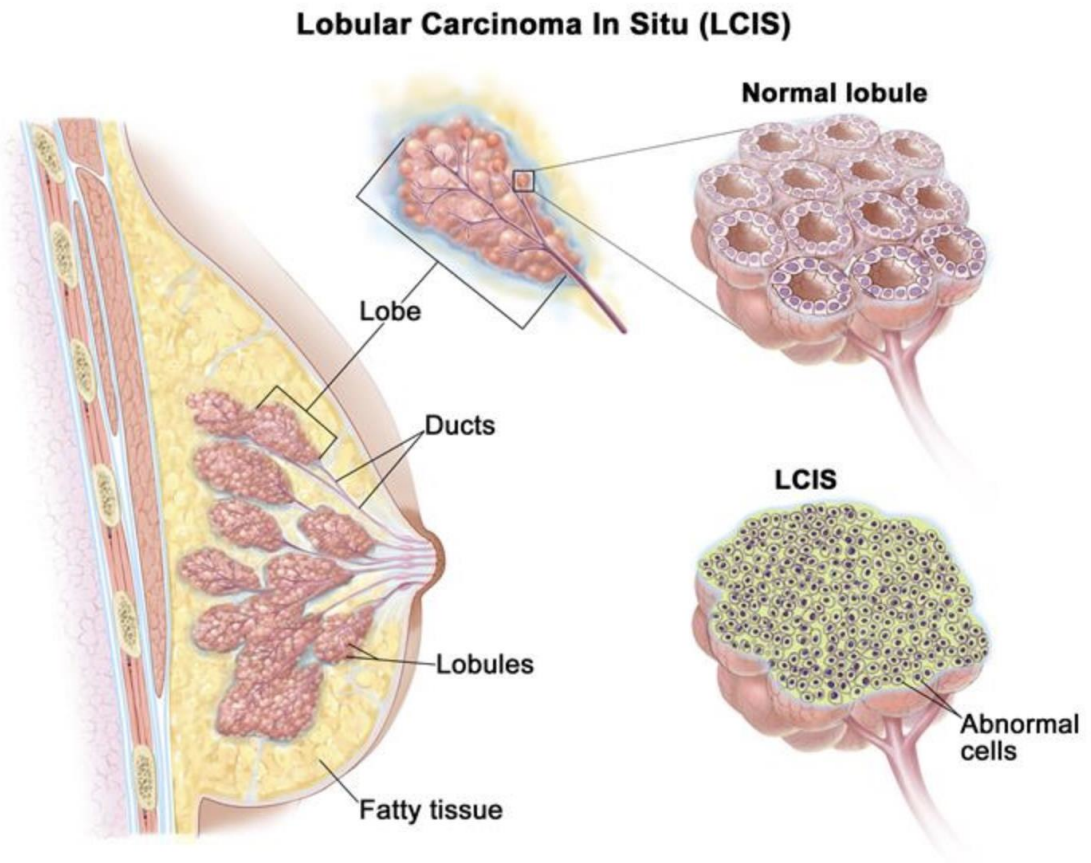
**The prognostic stage provided more accurate prognostic information than the anatomic stage alone in both a single-institution cohort and a large population database, thereby supporting its use in breast cancer staging**

Weiss A et al. 2018.

# Other Changes to AJCC 8th Edition

# Other Changes to AJCC 8th Edition: LCIS

- Given lobular carcinoma in situ (LCIS) is a benign entity, it was removed from the list of malignant tumors
  - LCIS is treated as a benign entity with an associated risk for developing carcinoma in the future but not as a malignancy capable of metastases



# Other Changes to 8th Edition: T Stage

- Standard procedures for defining the dimension of the primary tumor were addressed:
  - Rounding the size of very small tumors was discouraged
    - The general rules for rounding to the nearest millimeter do not apply for tumors between 1.0 and 1.5 mm, so that these cancers are not classified as microinvasive (T1mi) carcinomas
      - Clarifies that tumors between 1.0 and 1.5 mm should be rounded up to 2.0 mm (pT1a)
  - T size in the presence of multiple tumor foci was clarified
    - It is confirmed that the maximum invasive tumor size (T) is a reasonable estimate of tumor volume
      - Small, microscopic satellite foci of tumor around the primary tumor do not appreciably alter tumor volume and are not added to the maximum tumor size.
      - This new edition specifically continues using only the maximum dimension of the largest tumor for clinical (cT) and pathological (pT) T classification; the size of multiple tumors is not added.
  - A clear definition of satellite tumor nodules in the skin was included
    - A clear definition is added that satellite tumor nodules in the skin must be separate from the primary tumor and macroscopically identified to categorize as T4b
      - Skin and dermal tumor satellite nodules identified only on microscopic examination and in the absence of epidermal ulceration or skin edema (clinical peau d'orange) do not qualify as T4b (such tumors should be categorized based on tumor size)

# Other Changes to 8th Edition: N Stage

- Clarifications to the N category were also added:
  - Measurement of nodal metastases was clearly defined
    - The largest contiguous tumor deposit is used for pN; adjacent satellite tumor deposits are not added
  - cNX was further defined
    - The expert panel affirmed that cNX is not a valid category unless the lymph node basin has been removed and cannot be examined by imaging or clinical examination
      - A cN0 category is to be assigned when any evaluation of the lymph nodes is possible and the physical examination or imaging examination is negative.

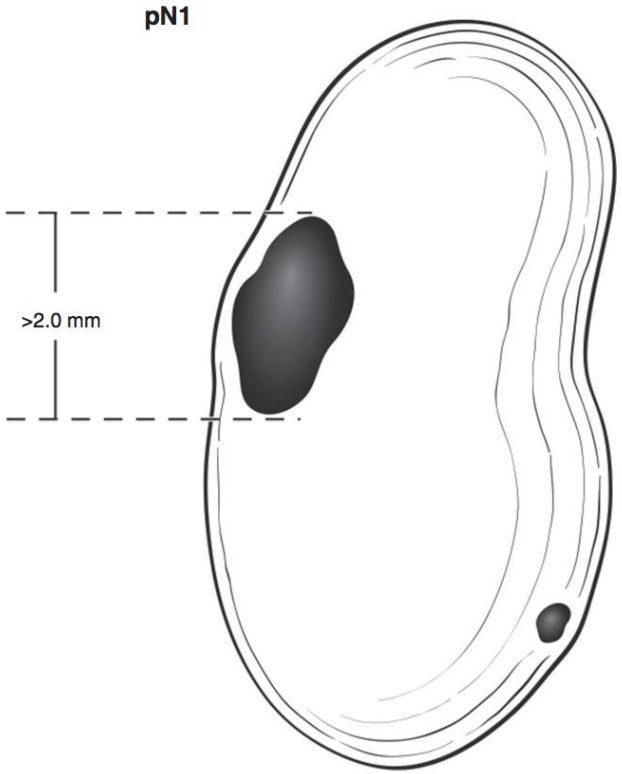
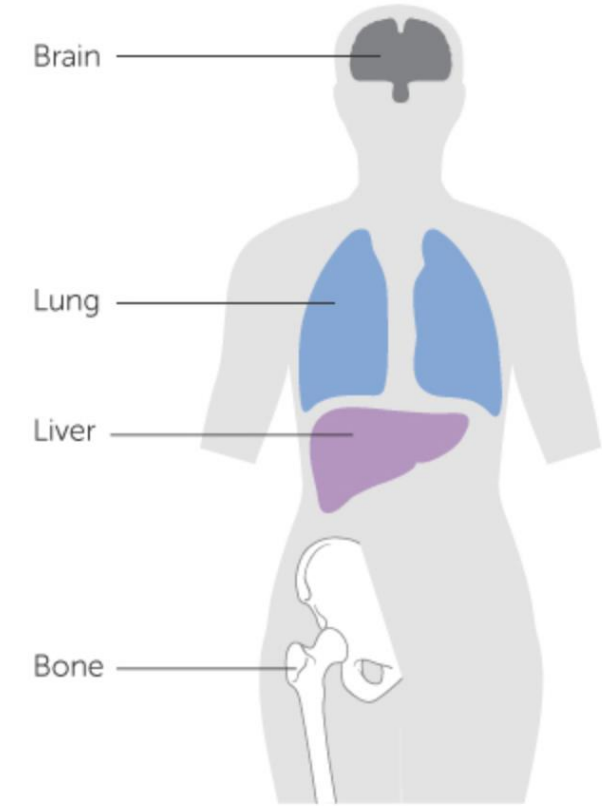



**Fig. 48.7** Macrometastasis; pN1. At least one contiguous tumor deposit must be larger than 2.0 mm

# Other Changes to 8th Edition: M Stage

- The designation pM0 was determined to be invalid, whereas cM1 and pM1 were reaffirmed
  - The expert panel affirmed that pM0 is not a valid category
    - All cases should be categorized as either cM0 or cM1; however, if cM1 is subsequently microscopically confirmed, pM1 is used



# Other Changes to 8th Edition: Postneoadjuvant Stage

- The postneoadjuvant systemic therapy classification was further elaborated:
  - Determination of ypT size was clarified to exclude surrounding fibrosis
    - The expert panel clarified that the postneoadjuvant therapy pathological T category (ypT) is based on the largest focus of residual tumor, if present
  - Determination of the dimensions of residual nodal metastases was restated
    - The expert panel clarified that the largest focus of residual tumor in the lymph nodes, if present, is used for ypN categorization
      - Treatment-related fibrosis adjacent to residual lymph node tumor deposits is not included in the ypN dimension and classification.
  - The definition of pathologic complete remission was revisited, and clarification was made of pathologic complete remission in the presence of M1 disease
    - If a cancer is categorized M1 (clinical or pathological) prior to therapy, the cancer is categorized as M1 after neoadjuvant therapy, regardless of the observed response to therapy.

# Clinical Examples Illustrating the Impact of these Changes on Clinical Practice

# Clinical Examples Illustrating the Impact of these Changes on Clinical Practice

- 58 yo F with R breast lump measuring 3.5 x 4.0 cm with no palpable axillary LAD. Biopsy showed a grade 2 IDC, ER+, PR-, HER2-. The patient underwent breast conserving surgery, which confirmed an IDC, measuring 3.0 x 3.5 cm, with negative sentinel LN biopsy. Oncotype DX showed RS of 9.

  - **AJCC 7th edition:** Anatomic stage IIA (pT2N0M0)
  - **AJCC 8th edition:**
    - Clinical prognostic stage IIA
    - Pathologic prognostic stage IIA, however with the result of the Oncotype DX RS (genomic modifier), her tumor would be downstaged to IA

# Clinical Examples Illustrating the Impact of these Changes on Clinical Practice

- 63 yo F with L breast lump measuring 8.2 x 6.6 cm with one palpable axillary LN measuring 1.5 x 1.5 cm. Biopsy showed a grade 1 IDC, ER+, PR+, HER2+. Breast conserving surgery confirmed an IDC measuring 8.0 x 6.5 cm. Sentinel LN biopsy was positive.

  - **AJCC 7th edition:** Anatomic stage IIIA (pT3N1M0)
  - **AJCC 8th edition:**
    - Clinical prognostic stage IIA
    - Pathologic prognostic stage IB

# Clinical Examples Illustrating the Impact of these Changes on Clinical Practice

- 63 yo F with L breast lump measuring 8.2 x 6.6 cm with one palpable axillary LN measuring 1.5 x 1.5 cm. Biopsy showed a grade 1 IDC, ER+, PR+, HER2+. Breast conserving surgery confirmed an IDC measuring 8.0 x 6.5 cm. Sentinel LN biopsy was positive.

  - **AJCC 7th edition:** Anatomic stage IIIA (pT3N1M0)
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    - Clinical prognostic stage IIA
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**Remember, the change in prognosis is based on assumption that she is offered and received systemic therapy based on the T, N and biomarker status of her cancer**

# Clinical Examples Illustrating the Impact of these Changes on Clinical Practice

- 72 yo F with mammographic abnormality in the R breast, not detected by physical exam and without palpable axillary LN. Measuring 1.1 x 0.8 cm by imaging. Biopsy showed a grade 3 IDC, ER-, PR-, HER2-. Breast conserving surgery confirmed an IDC, measuring 1.0 x 0.7 cm. Sentinel LN biopsy was positive (0.4 cm). Axillary LN dissection was not performed.
  - **AJCC 7th edition:** Anatomic stage IIA (pT1N1M0)
  - **AJCC 8th edition:**
    - Clinical prognostic stage IB
    - Pathologic prognostic stage IIA
- If this same woman had been diagnosed with the exact same cancer but different biomarker profile, ER+, PR+, HER2+
  - **AJCC 7th edition:** Anatomic stage IIA (pT1N1M0)
  - **AJCC 8th edition:**
    - Clinical prognostic stage IA
    - Pathologic prognostic stage IA

<u>These differences would have major implications on the selection of optimal adjuvant therapy</u>

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**Notably, given outcomes of patients relate to utilization of appropriate therapy, survival calculations of patients treated more than a decade ago are likely not reflective of current therapy for many patients**

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- Even with the very large group of patients represented by the National Cancer Database, when distributed into 120 possible stage groups, the numbers decrease dramatically
- In addition, the median follow up of this large cohort was only 41.7 months
  - Although this provides a reliable preliminary analysis, longer follow up will be needed, particularly in view of the rather protracted nature of some breast cancer subtypes
    - This is particularly true for hormone receptor positive breast cancers, for which a 10 year follow up is barely acceptable, and recurrences continue to occur for more than 20 years

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  - Although this provides a reliable preliminary analysis, longer follow up will be needed, particularly in view of the rather protracted nature of some breast cancer subtypes
- Although the databases of patients whose tumors have been tested with the multigene panels is growing, the denominator is usually much smaller when, in addition to the results of genomic assays, complete clinic-pathologic information, biomarkers and appropriate follow up with outcomes is sought
  - The development of more sophisticated multigene panels in triple negative and HER2 enriched populations would be a welcome addition in the future

# Conclusions/Practical Implications

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- While more complex, the AJCC 8th edition incorporation of tumor biology and prognostic stage groups makes for a more accurate and clinically relevant staging system
  - It better groups patients with similar prognoses
  - It is now possible to identify a group of patients who have invasive breast cancer with a prognosis so favorable that they may forgo systemic chemotherapy

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- The ability to predict benefit from or resistance to specific treatments is of major clinical relevance
- Staging systems divide patient cohorts into distinct prognostic categories and allow more precise comparison of patient cohorts, clinical trial results, and therapeutic outcomes

# Questions?

# Thank You!

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