

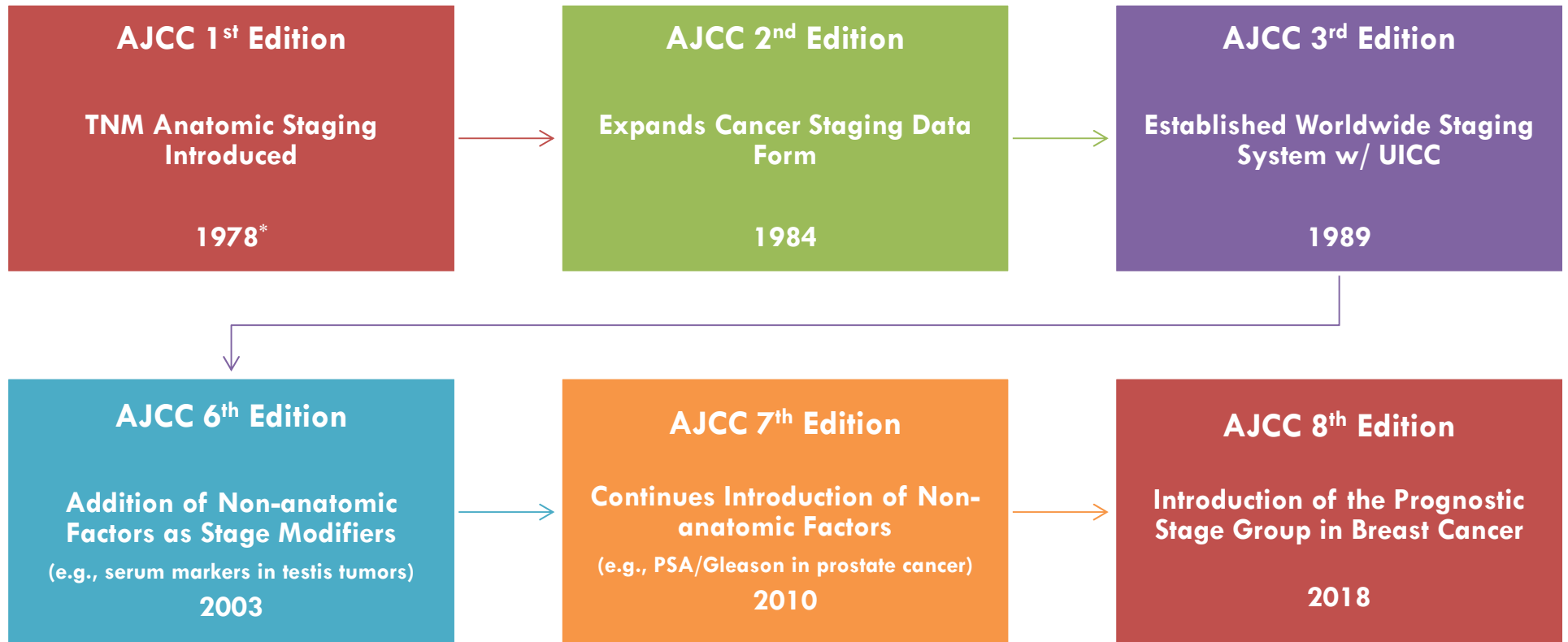
A New Era of Defining Breast Cancer:
The 8th Edition of the American Joint
Commission on Cancer Staging Manual

What is the Purpose of Cancer Staging?

- Classification and staging allows the physician to stratify patients and:
 - Facilitate development of a common language of cancer
 - Permit standardized collection of essential data
 - Enable development of management guidelines based on prognosis
 - Provide high quality clinical care

Evolution of AJCC Cancer Staging Manual

From Anatomic Staging Towards Personalized Risk Assessment



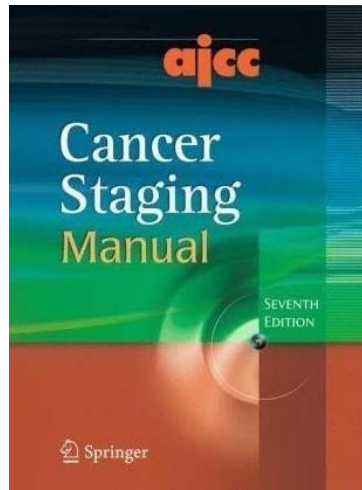
“The concept of molecular classification of cancer at a clinically relevant level is now accepted as an imminent reality...”

- Dr. Mahul Amin (AJCC 8th Edition Editor-in-Chief)

*Year each edition went into effect

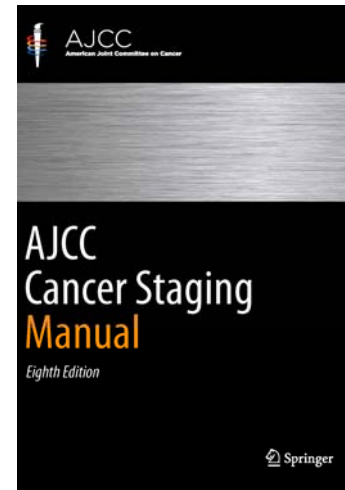
Significant Changes to the AJCC 8th Edition

7th Edition



- 3-year Project
- 57 Chapters
- 16 Task Forces
- 266 individuals from
 - 5 continents
 - 11 countries

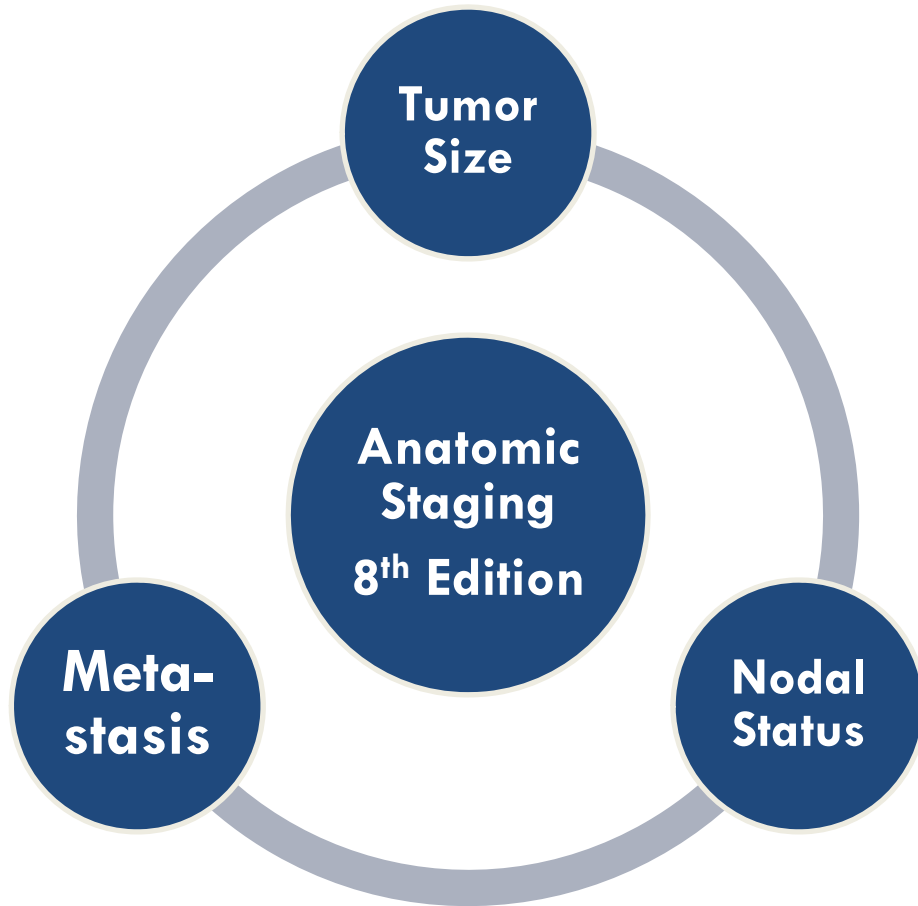
8th Edition



- 3-year Project
- 83 Chapters
 - Including 12 new chapters/staging systems
- 18 Expert Panels + 7 Cores
- 430 individuals from
 - 6 continents
 - 22 countries
 - 184 institutions

Breast Anatomic Staging

1st to 8th Edition AJCC Staging Manual*



*Effective January 2018, anatomic staging for breast cancer may only be used in countries without routine access to pathology services

Breast Anatomic Staging Table (8th Edition)

| When T is... | And N is... | And M is... | Then the stage group is... |
|--------------|-------------|-------------|----------------------------|
| Tis | N0 | M0 | 0 |
| T1 | N0 | M0 | IA |
| T0 | N1mi | M0 | IB |
| T1 | N1mi | M0 | IB |
| T0 | N1 | M0 | IIA |
| T1 | N1 | M0 | IIA |
| T2 | N0 | M0 | IIA |
| T2 | N1 | M0 | IIB |
| T3 | N0 | M0 | IIB |
| T0 | N2 | M0 | IIIA |
| T1 | N2 | M0 | IIIA |
| T2 | N2 | M0 | IIIA |
| T3 | N1 | M0 | IIIA |
| T3 | N2 | M0 | IIIA |
| T4 | N0 | M0 | IIIB |
| T4 | N1 | M0 | IIIB |
| T4 | N2 | M0 | IIIB |
| Any T | N3 | M0 | IIIC |
| Any T | Any N | M1 | IV |

Prognostic Group Staging

New Breast Cancer Staging System in 8th Edition AJCC Staging Manual

| Traditional TNM Factors | | | Expanded Non-Anatomic Factors Tumor Grade, HER2, ER, PR status | | | | = | 8 th Edition Prognostic Stage Group |
|-------------------------|--------------|--------------|---|-----------------------|---------------------|---------------------|----------------------------------|---|
| 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... | |
| T1 | N0 | M0 | 1 | Positive | Any | Any | IA | |
| T1 | N0 | M0 | 1 | Negative | Positive | Negative | IB | |
| T2 | N0 | M0 | 1,2 | Negative | Positive | Positive | IB | |
| T1 | N0 | M0 | 1-3 | Negative | Negative | Negative | IIA | |
| T2 | N0 | M0 | 3 | Negative | Positive | Positive | IIA | |
| T3 | N0 | M0 | 1 | Negative | Positive | Negative | IIIA | |

More than 140 staging permutations are in the latest edition

Development of AJCC 8th Edition Breast Cancer Prognostic Stage Group

MD Anderson

(MDACC)

- 3,728 patients with no known distant metastases
- Utilized pathologic stage to derive prognostic model for disease-specific survival (DSS)
- Validated in 26,711 patients from SEER

National Cancer Database

(NCDB)

- 238,265 patients
- Survival calculations performed on 7th edition anatomic stage group, tumor grade, HER2, ER, and PR
- Findings consistent with MDACC
- Prognostic subgroups assigned to stage according to calculated mean survival

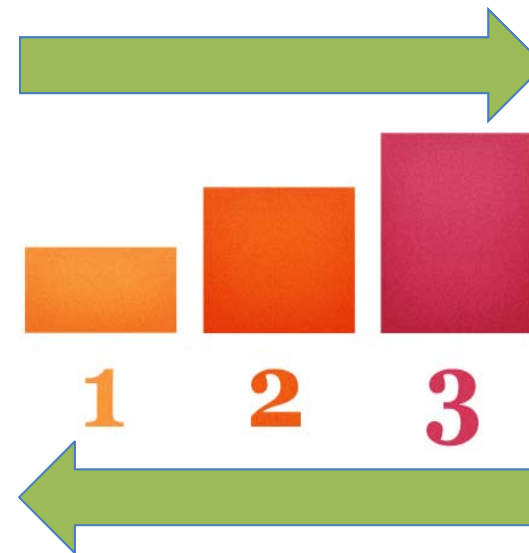
Biomarkers improved stratification of DSS by stage

Impact of New 8th Edition Staging Manual in Early Stage Breast Cancer

“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 8th Edition Cancer Staging Manual, page 616

AJCC 7th vs. 8th Edition



40% of Early Stage Breast Cancer Patients Restaged

8th Edition: Patients Now Considered Stage IIIA

Some T1N1 and Node-negative Patients Are Now Included

| What the T is... And N is... | And M is... | And G is.. | And HER2 status is... | And ER status is... | And PR status is... | The Prognostic Stage Group Is... | |
|------------------------------|-------------|------------|-----------------------|---------------------|---------------------|----------------------------------|---------|
| T0-1 | N1 | M0 | 2 | Negative | Negative | Negative | IIIA*** |
| T0-1 | N1 | M0 | 3 | Negative | Positive | Negative | IIIA |
| T0-1 | N1 | M0 | 3 | Negative | Negative | Any | IIIA |
| T2 | N0 | M0 | 2 | Negative | Negative | Negative | IIIA*** |
| T2 | N0 | M0 | 3 | Negative | Positive | Negative | IIIA*** |
| T2 | N0 | M0 | 3 | Negative | Negative | Any | IIIA*** |
| T2 | N1 | M0 | 1 | Negative | Positive | Negative | IIIA |
| T2 | N1 | M0 | 2 | Positive | Negative | Negative | IIIA |
| T2 | N1 | M0 | 2 | Negative | Positive | Negative | IIIA |
| T2 | N1 | M0 | 3 | Positive | Positive | Negative | IIIA |
| T2 | N1 | M0 | 3 | Positive | Negative | Negative | IIIA |
| T3 | N0 | M0 | 1 | Negative | Positive | Negative | IIIA |
| T3 | N0 | M0 | 2 | Positive | Negative | Negative | IIIA |
| T3 | N0 | M0 | 2 | Negative | Positive | Negative | IIIA |
| T3 | N0 | M0 | 3 | Positive | Positive | Negative | IIIA |
| T3 | N0 | M0 | 3 | Positive | Negative | Negative | IIIA |
| T0-2 | N2 | M0 | 1 | Positive | Positive | Negative | IIIA |
| T0-2 | N2 | M0 | 1 | Positive | Negative | Any | IIIA |
| T0-2 | N2 | M0 | 1 | Negative | Positive | Negative | IIIA |
| T0-2 | N2 | M0 | 1 | Negative | Negative | Positive | IIIA |
| T0-2 | N2 | M0 | 2 | Positive | Positive | Negative | IIIA |
| T0-2 | N2 | M0 | 2 | Positive | Negative | Any | IIIA |
| T3 | N1-2 | M0 | 1 | Positive | Positive | Negative | IIIA |
| T3 | N1-2 | M0 | 1 | Positive | Negative | Any | IIIA |
| T3 | N1-2 | M0 | 1 | Negative | Positive | Negative | IIIA |
| T3 | N1-2 | M0 | 1 | Negative | Negative | Positive | IIIA |
| T3 | N1-2 | M0 | 2 | Positive | Positive | Negative | IIIA |
| T3 | N1-2 | M0 | 2 | Positive | Negative | Any | IIIA |
| T4 | N0-2 | M0 | 1 | Negative | Positive | Positive | IIIA |
| Any | N3 | M0 | 1 | Negative | Positive | Positive | IIIA*** |

Inclusion of Oncotype DX Breast Recurrence Score[®] into AJCC 8th Edition Staging Manual

“...the Expert Panel determined that it was appropriate to incorporate multigene molecular profiling **to incorporate the Oncotype DX score into staging** for the subgroup of patients defined by Arm A of the TAILORx study (including Oncotype DX Recurrence Score[®] less than or equal to 10).” (Emphasis added.)

| 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 |

**If Available

Some Prognostic Group Stage IB to IIIA Patients Will Downstage to Stage IA with a Recurrence Score[®] Value <11

In T1-2 patients with ER+, HER2-, lymph-node negative disease, an Oncotype DX Breast Recurrence Score[®] result <11 will downstage patients to Prognostic Stage Group 1A



Stage IB

- T1 G1 PR-
- T1 G3 PR+
- T2 G1 PR+
- T2 G2 PR+



Stage IIA

- T1 G3 PR-
- T2 G1 PR-
- T2 G3 PR+



Stage IIB

- T2 G2 PR-



Stage IIIA

- T2 G3 PR-

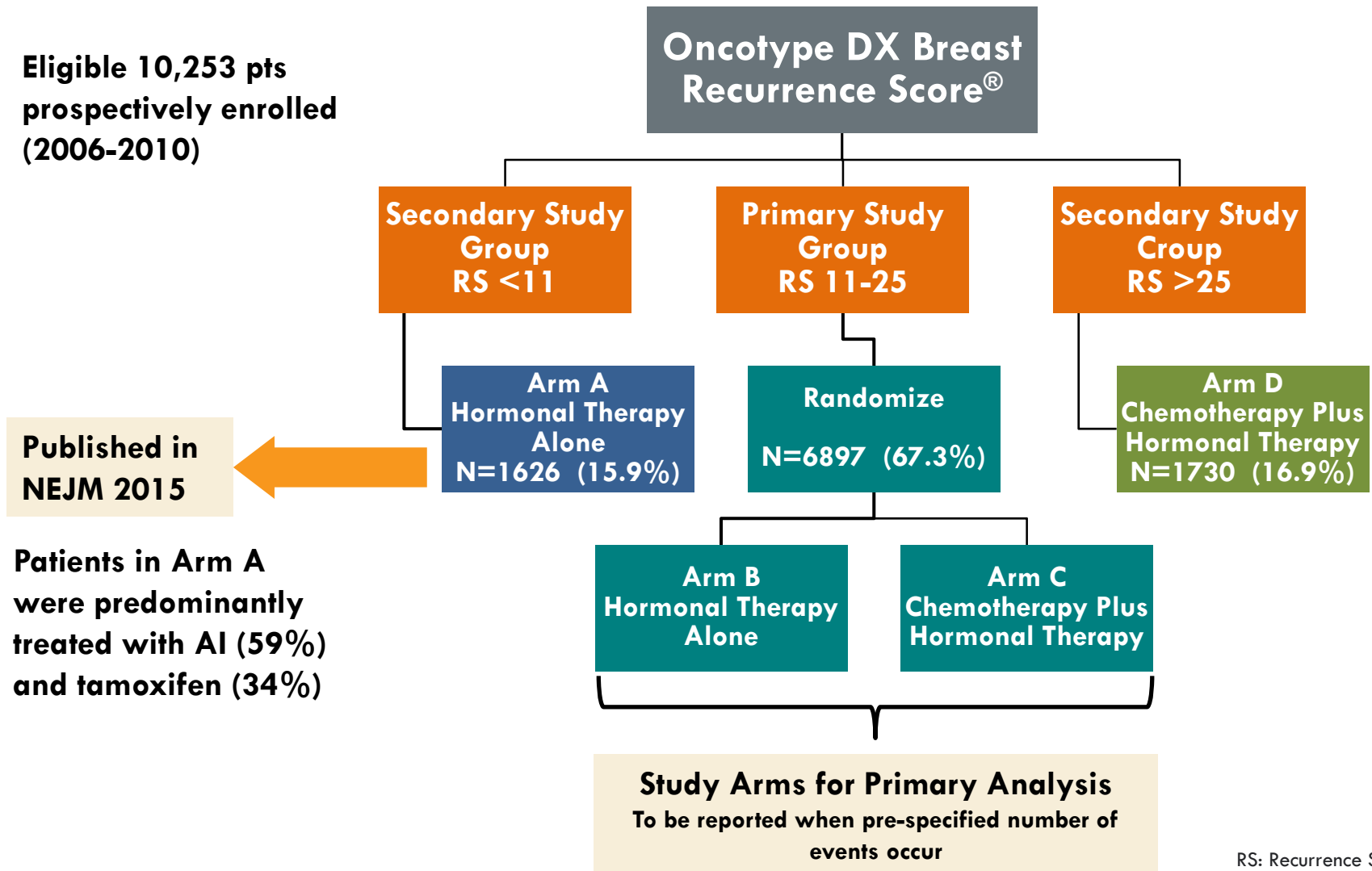
When Oncotype DX Breast Recurrence Score result is <11, all of these patients are classified as Stage IA

Identification of a Patient Population that Does Not Benefit from Adjuvant Chemotherapy:
Outcomes from Large Population-based Genomic Studies

Basis for inclusion in AJCC 8th Edition staging

TAILORx: A Clinical Trial Assigning Individualized Options for Treatment (Rx)

Eligible 10,253 pts prospectively enrolled (2006-2010)

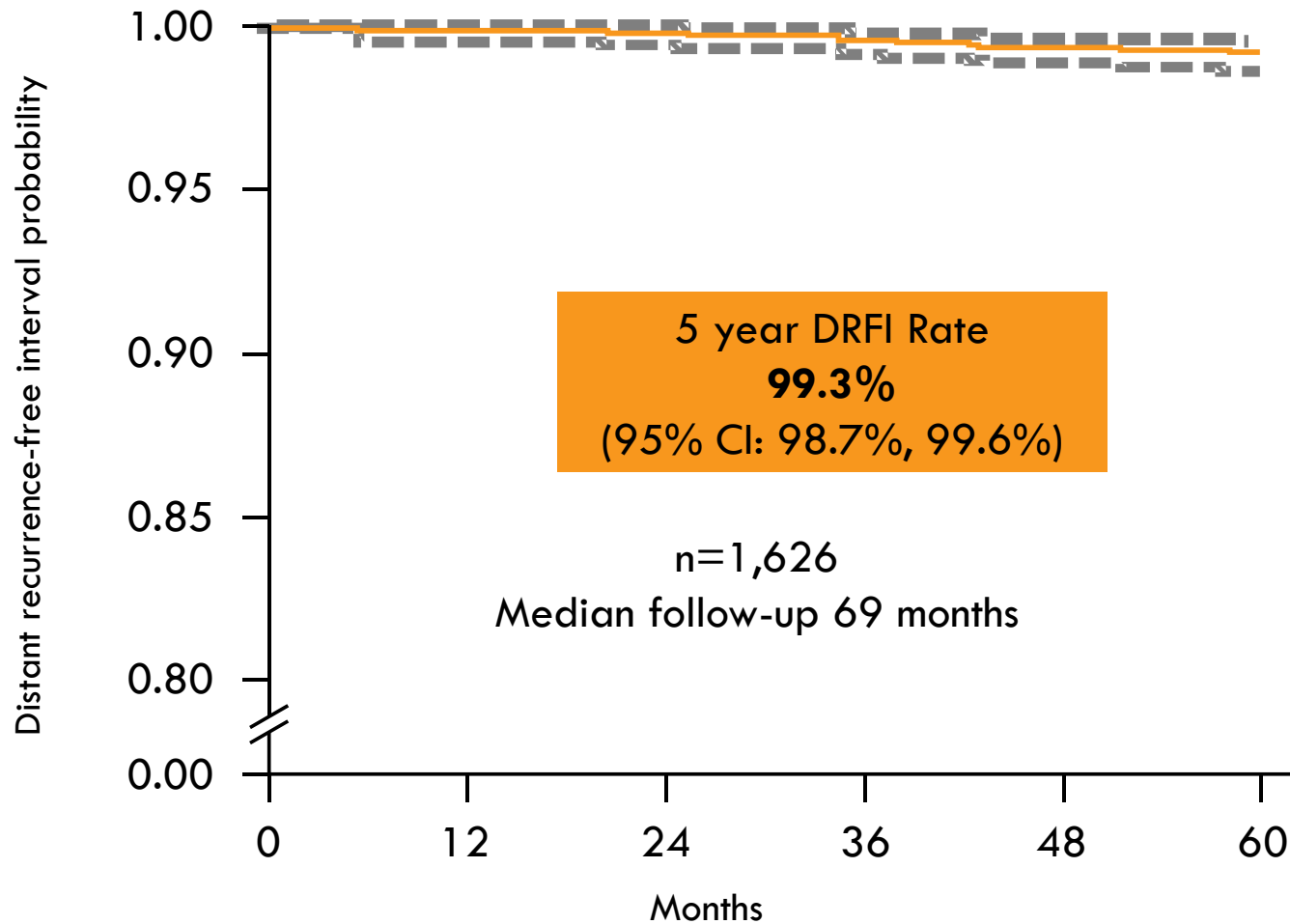


Most Patient Characteristics and Surgical Treatment Between Arms Were Similar

| | Arm A (Recurrence Score [®] result <11) | Arm B/C (Recurrence Score [®] result 11-25) |
|------------------------|---|---|
| No. eligible patients | 1626 | 6897 |
| Median age - yrs | 58 | 55 |
| Post-menopausal | 70% | 64% |
| Median tumor size - cm | 1.5 | 1.5 |
| Histologic grade | | |
| Low | 34% | 29% |
| Intermediate | 59% | 57% |
| High | 7% | 14% |
| ER expression | >99% | >99% |
| PgR expression | 98% | 92% |
| Surgery | | |
| Lumpectomy | 68% | 72% |
| Mastectomy | 32% | 28% |

Differences between arms were clinically modest and would not allow a clinician to distinguish between patients having a low or mid-range Recurrence Score result

Patients with Recurrence Score[®] Results <11 Have Less than 1% Risk of Distant Recurrence at 5 Years



Grade Did Not Impact the 5-year Distant Recurrence Risk or Overall Survival

Event rates by central grade

| | DRFI, % (95% CI) | OS, % (95% CI) |
|--------------------|-------------------------|-----------------------|
| All grades | 99.3 (98.7-99.6) | 98.0 (97.1-98.6) |
| Low grade | 99.8 (98.3-100) | 98.7 (97.0-99.4) |
| Intermediate grade | 99.0 (98.0-99.5) | 97.9 (96.8-98.7) |
| High grade | 100 (NC-NC) | 97.3 (91.9-99.1) |

HR, hazard ratio; NC, not calculated; DRFI, distant recurrence-free interval; OS, overall survival.

Patient Case Study:
*Downstaging with the Oncotype DX Breast
Recurrence Score[®] Result*

CASE STUDY

NODE
[-]

AGE
59

PATIENT 59-years-old

TUMOR SIZE 3.5 cm

MENOPAUSAL Postmenopausal

TUMOR TYPE Invasive Carcinoma

ER STATUS (IHC) Positive

PR STATUS (IHC) Positive

HER2/NEU STATUS Negative

HISTOLOGIC GRADE 3

LYMPH NODE STATUS Negative (3 SNs)

SUBMITTED BY

Anthony Lucci, MD
University of Texas,
MD Anderson
Cancer Center
Houston, TX

Note: This patient is Stage IIA per the 8th Edition Prognostic Staging criteria (using only TNM, ER/PR, HER2, and tumor grade)

CASE STUDY

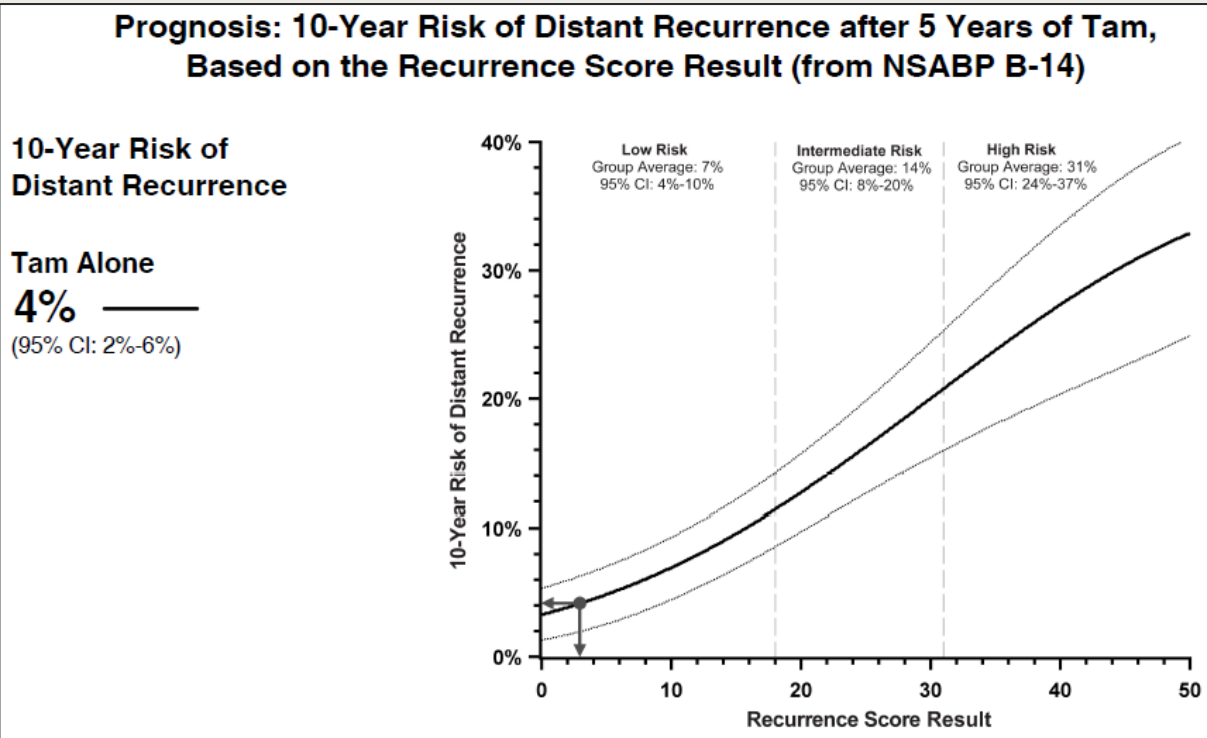
CLINICAL EXPERIENCE

Prognosis for Node Negative, ER-Positive Patients

In the clinical validation study¹, after 5 years of tamoxifen therapy patients with a Recurrence Score of 3 had an Average Rate of Distant Recurrence at 10 years of 4% (95% CI: 2%-6%).

RESULTS
Recurrence
Score

3



Incorporating a Recurrence Score[®] of 3, this patient is now Prognostic Stage Group IA

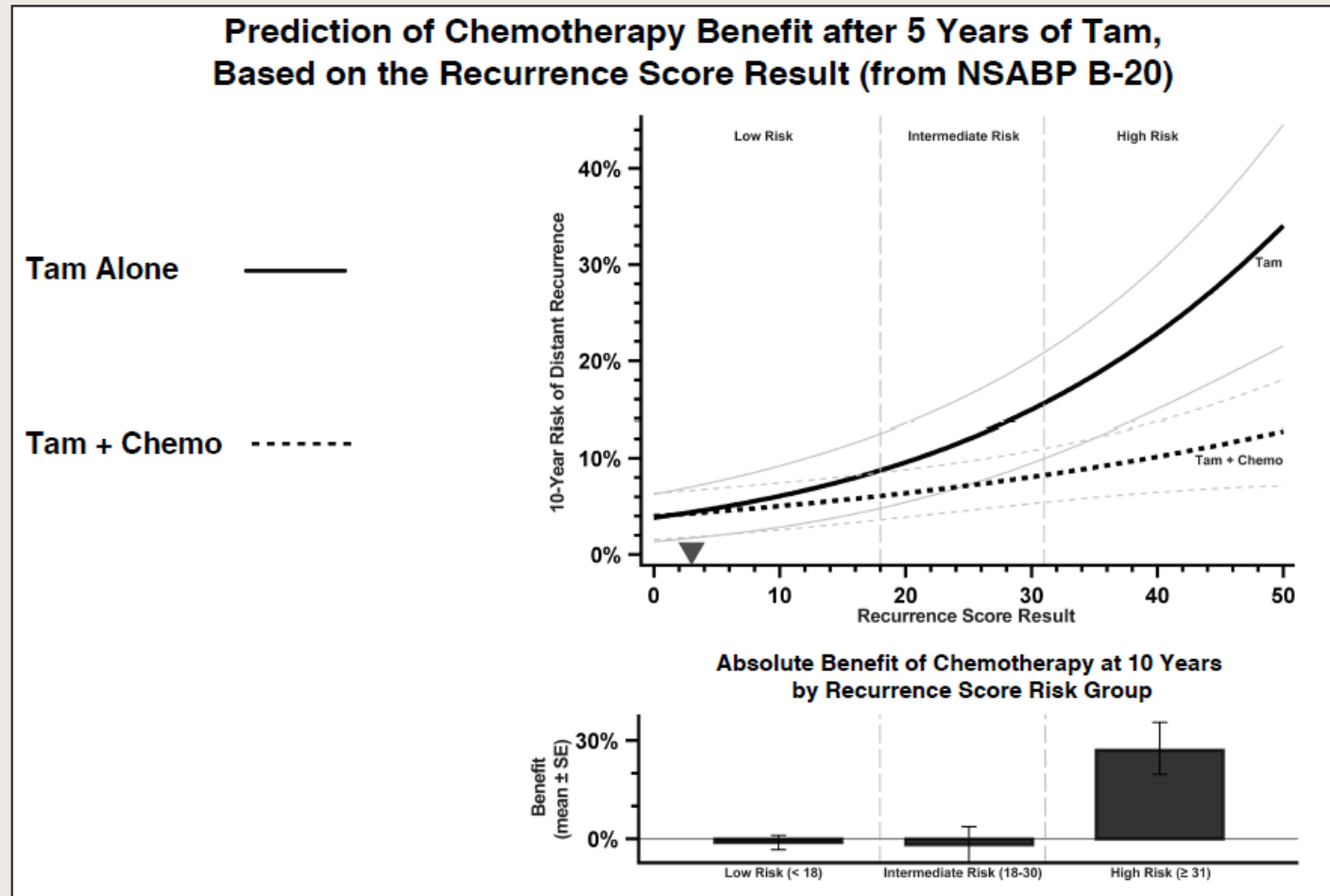
CASE STUDY

CLINICAL EXPERIENCE:

Prediction of Chemotherapy Benefit for Node Negative, ER-Positive Patients

RESULTS
Recurrence
Score

3



**Incorporating a Recurrence Score[®] of 3, this patient is now
Prognostic Stage Group IA**

What Does the Staging Criteria Say About
Other Genomic Assays?

AJCC 8th Edition: Levels of Evidence Now Added

“Based on the best available evidence at this time, it was appropriate to incorporate the Oncotype DX[®] score into staging for the subgroup of patients defined by TAILORx Arm A, Recurrence Score[®] ≤ 10”

- AJCC 8th Edition Cancer Staging Manual, page 614

| 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 – PAM50[®] (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 |

The Oncotype DX[®] Assay Is the Only Multigene Assay Incorporated in Major Guidelines for Prediction of Adjuvant Chemotherapy Benefit

NCCN Guidelines[®]

- 0.5 cm, node negative, N1mi
- May be considered for select node-positive (1-3 LN) patients

Quantifies risk of recurrence as a continuous variable and predicts responsiveness to both tamoxifen and chemotherapy¹

ASCO[®] Guidelines

Node negative

Predicts the risk of recurrence and may be used to identify patients likely to benefit from tamoxifen or chemotherapy²

St. Gallen Consensus

Node negative, node positive

Provides not only prognostic but also predictive information regarding the utility of cytotoxic therapy in addition to endocrine therapy³

NICE

Node negative

Recommended as an option for guidance of chemotherapy decisions in patients at intermediate risk* of distant recurrence⁴

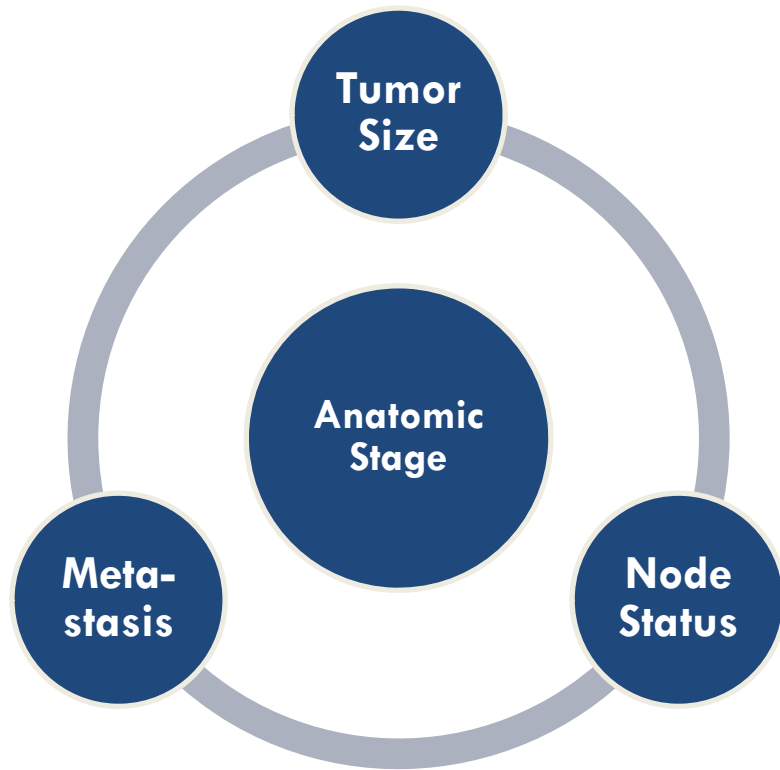
ASCO is a trademark of the American Society of Clinical Oncology. NCCN and NCCN Guidelines are trademarks of the National Comprehensive Cancer Network. The guidelines do not endorse products or therapies.

*Intermediate risk of distant recurrence is defined as Nottingham Prognostic Index score above 3.4 or being at intermediate risk by other decision-making tools or protocols

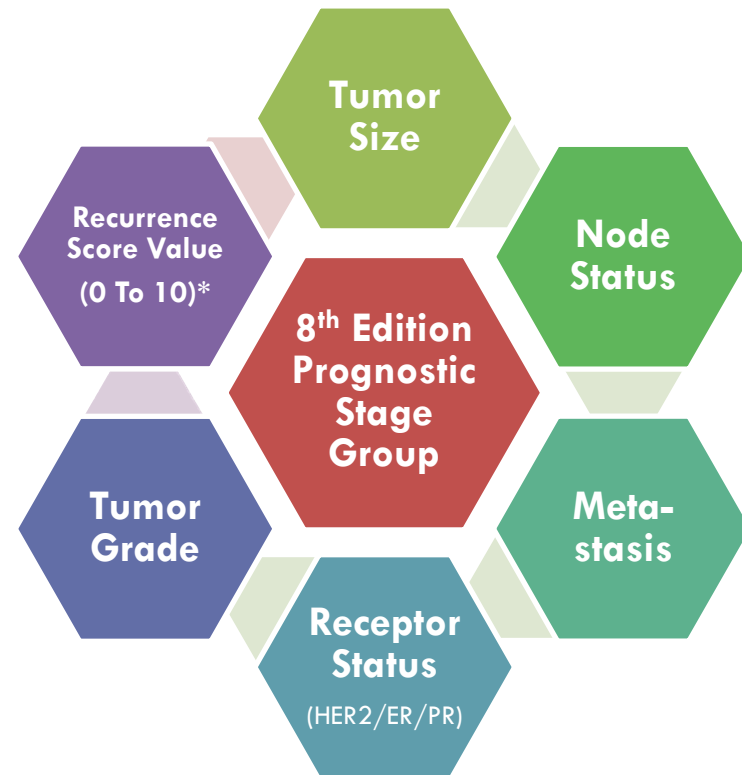
AJCC 8th Edition: Biology Trumps Anatomy

“...Biologic factors – such as grade, hormone receptor expression, HER2 overexpression / amplification, and genomic panels – have become as or more important than the anatomic extent of disease to define prognosis, select the optimal combination of systemic therapies, and increasingly, influence the selection of locoregional treatments.” (Emphasis added.)

-AJCC 8th Edition Cancer Staging Manual, page 592



1977 to 2017



2018 and Beyond

AJCC 8th Edition Updates

Important Points to Consider

- The 8th Edition published in October 2016 and will be effective January 1st, 2018
 - One year for community to incorporate updates into their systems (e.g., physicians, tumor registrars, EMR vendors, CAP, etc.)
 - CDC and NCI-SEER are the agencies that will train tumor registrars on the changes
- Physicians may use updated manual immediately for patient management
- Developed countries with routine and reliable access to pathology services are mandated to use the new Prognostic Stage Group table for cancer staging starting in 2018
 - Purely anatomic staging (TNM only) will remain to enable usage around the world
- New 8th edition will guide optimal therapy use
 - Allow for continued data collection and optimization of staging
 - Anticipate rolling updates rather than historical 6 to 8 year cycle of revisions

Conclusions

- **8th Edition Recognizes Biomarkers and Multigene Panels**
 - Refined risk discrimination in staging
 - More complex system which will go into effect in January 2018
- **Patients with ER+/HER2-, T1-2, N0, M0 disease and a Oncotype DX Breast Recurrence Score[®] Result of <11 can be downstaged regardless of tumor grade or PR status**
 - Level 1 evidence
 - Can safely avoid chemotherapy
 - Reduced morbidity by avoiding treatment with no benefit
 - Improved outcomes and quality of life

Thank you

Appendix

MD Anderson Study Parameters

- 3,728 patients with no known distant metastases
- Known biomarkers and minimum 2-year follow-up
- Validated in 26,711 pts from SEER registry
- 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: tumor grade, ER,PR, LVI

MD Anderson Study Limitations

- Limitation of initial MDACC study: predated use of trastuzumab for HER2-positive patients
- Updated model cohort 3,327 pts treated from 2007-2013
 - Including HER2-positive cohort (306 patients, 9%)
- Multi-variable analysis identified factors associated with DSS:
 - Grade
 - Her2 status
 - ER status
 - AJCC pathologic stage pathologic
- Validated in cohort of 67,944 patients from the California Cancer Registry

Pathological Stage, Grade, ER, and HER2 Used to Create Model for Disease Specific Survival (DSS) for AJCC 8th Edition

| Factor | 5-year DSS (%) | MVA DSS HR (p) | | Assigned Pts |
|-----------------|----------------|-------------------|----------|--------------|
| Path Stage I | 99.1 | ref | | 0 |
| Path Stage IIA | 98.0 | 2.3 | (.01) | 1 |
| Path Stage IIB | 95.6 | 4.0 | (<.0001) | 2 |
| Path Stage IIIA | 95.4 | 7.2 | (<.0001) | 3 |
| Path Stage IIIC | 79.5 | 19.9 | (<.0001) | 4 |
| Grade I | 99.8 | ref | | 0 |
| Grade II | 98.9 | 4.0 | (ns) | 0 |
| Grade III | 95.3 | 3.0 | (.01) | 1 |
| ER Positive | 98.8 | ref | | 0 |
| ER Negative | 92.9 | 2.5 | (.001) | 1 |
| HER2 Positive | 97.5 | ref | | 0 |
| HER2 Negative | 98.0 | 2.2 | (.04) | 1 |



Determination of Overall Survival and DSS from Risk Profile and AJCC TNM Pathological Staging

| Stage | Risk Profile | 5-year DSS (%) | 5-yr OS (%) |
|---------------------|--------------|----------------|-------------|
| Stage I (IA and IB) | 0 | 100 | 97 |
| | 1 | 99.4 | 96.7 |
| | 2 | 98.8 | 94.6 |
| | 3 | 96.6 | 93.8 |
| Stage IIA | 0 | 100 | 96.8 |
| | 1 | 99.4 | 97.1 |
| | 2 | 97.5 | 94.1 |
| | 3 | 91.0 | 88.2 |
| Stage IIB | 0 | 100 | 100 |
| | 1 | 96.9 | 94.6 |
| | 2 | 92.9 | 89.3 |
| | 3 | 91.5 | 91.5 |
| Stage IIIA | 0 | 100 | 100 |
| | 1 | 98.3 | 91.5 |
| | 2 | 92.2 | 90.3 |
| | 3 | 68.6 | 68.6 |

Use of NCDB to Determine Impact of Prognostic Factors on Staging

- 238,265 patients in NCDB
- Median follow-up of 38 months
- Survival calculations performed based on:
 - 7th Ed stage group
 - Grade
 - HER2
 - ER and PR
- Findings consistent with MD Anderson model
- Prognostic subgroups assigned to stage according to calculated mean survival

Prospective Outcome Studies

- TAILORx (US) 
 - Prospective trial outcomes of low Recurrence Score[®] (RS) values <11 managed with hormone therapy alone in N0 patients
- WSG-Plan B Trial (Germany) 
 - 5-year clinical trial outcomes in high risk N0 and N1-N2 patients; Recurrence Score values ≤ 11 assigned to HT alone
- Clalit Registry (Israel)
 - Outcome data from >2000 patients (N0 and N1) prospectively managed by physicians using Recurrence Score values
- SEER Registry (US)
 - Outcome data from >50,000 N0 and N1 patients prospectively managed by physicians using Recurrence Score values

Neither Age, Size nor Grade Impacted the 5-year Distant Recurrence Risk or Overall Survival

Distant recurrence

| | | DRFI, HR (95% CI) | P Value |
|-------------|--------------------|-------------------|---------|
| Age | ≤50 vs 51-60 years | 1.28 (0.12-4.22) | 0.27 |
| | ≤50 vs 61-75 years | 3.49 (0.42-29.16) | |
| Tumor size | >2 cm vs ≤2 cm | 1.55 (0.38-6.31) | 0.55 |
| Tumor grade | 2/3 vs 1 | 3.83 (0.48-30.69) | 0.14 |

Event rates by grade

| | DRFI, % (95% CI) | OS, % (95% CI) |
|--------------------|------------------|------------------|
| All grades | 99.3 (98.7-99.6) | 98.0 (97.1-98.6) |
| Low grade | 99.8 (98.3-100) | 98.7 (97.0-99.4) |
| Intermediate grade | 99.0 (98.0-99.5) | 97.9 (96.8-98.7) |
| High grade | 100 (NC-NC) | 97.3 (91.9-99.1) |

HR, hazard ratio; NC, not calculated; DRFI, distant recurrence-free interval; OS, overall survival.

Comparison of Genomic Breast Cancer Tests

| | | Genomic Health® Oncotype DX® | NanoString Prosigna® | Agendia® MammaPrint® | bioTheranostics Breast Cancer Index™ | Myriad EndoPredict® |
|---|---|---|------------------------------|-------------------------|--|------------------------|
| Validated for Prognosis ¹⁻⁶ | Node Negative and Node Positive | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Pre-Menopausal | ✓ | | ✓ | ✓ | ✓ |
| | Post-Menopausal | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Homogenous Populations | ✓ | ✓ | | ✓ | ✓ |
| Validated for Prediction of Chemotherapy Benefit ¹ | | ✓ | | | | |
| Inclusion in Major International Guidelines | NCCN® Algorithm ⁷ and NICE (UK) ⁸ | ✓ | | | | |
| | NCCN Discussion Section ⁷ | ✓ | ✓ | ✓ | | |
| | ASCO ⁹ | ✓ | ✓ | | | ✓ |
| | ESMO ¹⁰ , St. Gallen ¹¹ and AGO ¹² | ✓ | ✓ | ✓ | | ✓ |
| Prospective Outcomes Evidence | | >63,000 patients ¹³⁻²⁰ | | >7,000 ²¹⁻²⁴ | | |
| Inclusion in AJCC 8 th Edition Cancer Staging Manual for assignment of Prognostic Stage Group 1A ²⁵ | | ✓ | | | | |
| Additional Clinical Evidence | | DCIS, Neoadjuvant, Late Recurrence, Adjuvant Hormonal Therapy Benefit | Neoadjuvant, Late Recurrence | Neoadjuvant | Late Recurrence, Extended Hormonal Therapy Benefit | Late Recurrence |

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