THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

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

Elizabeth A. Mittendorf, MD, PhD
Professor
Department of
Breast Surgical Oncology

Disclosures

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

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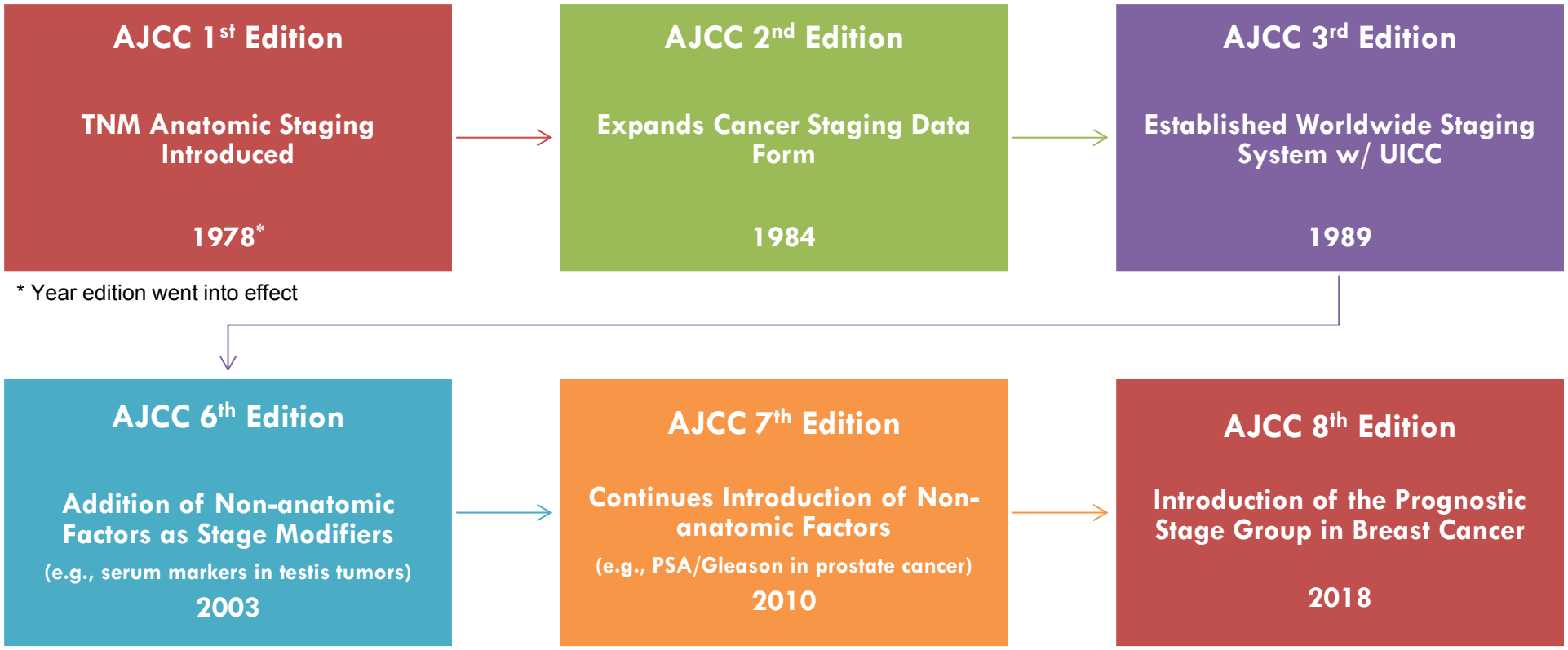
Goals of Staging

- 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



"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)

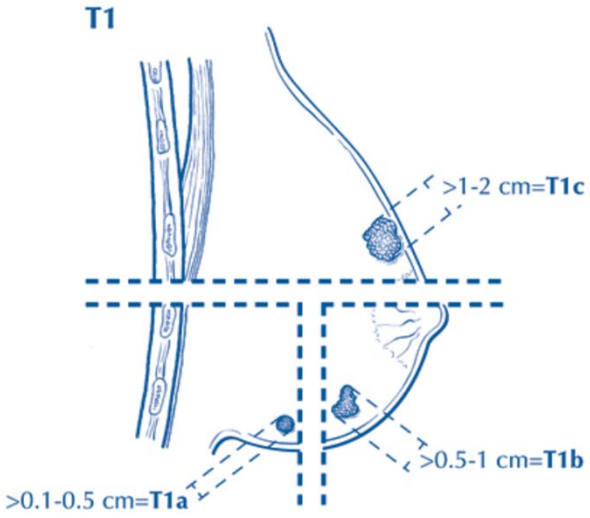
Amin M et al. *CA Cancer J Clin* 2017;67:93-99

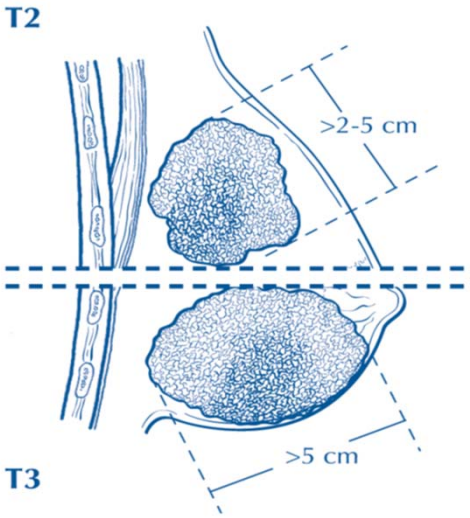
7th Edition AJCC Staging System

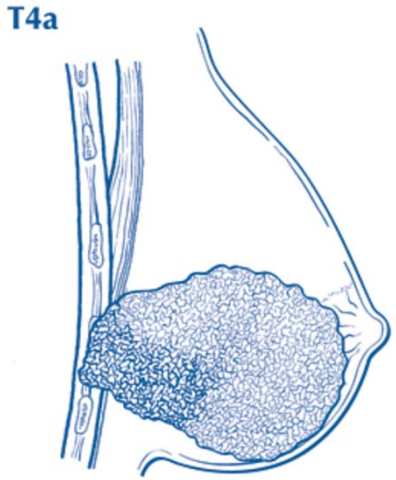
- TNM stage:
  - T: primary tumor
  - N: regional (ipsilateral) lymph nodes
  - M: distant metastasis

AJCC Staging System

- T stage:

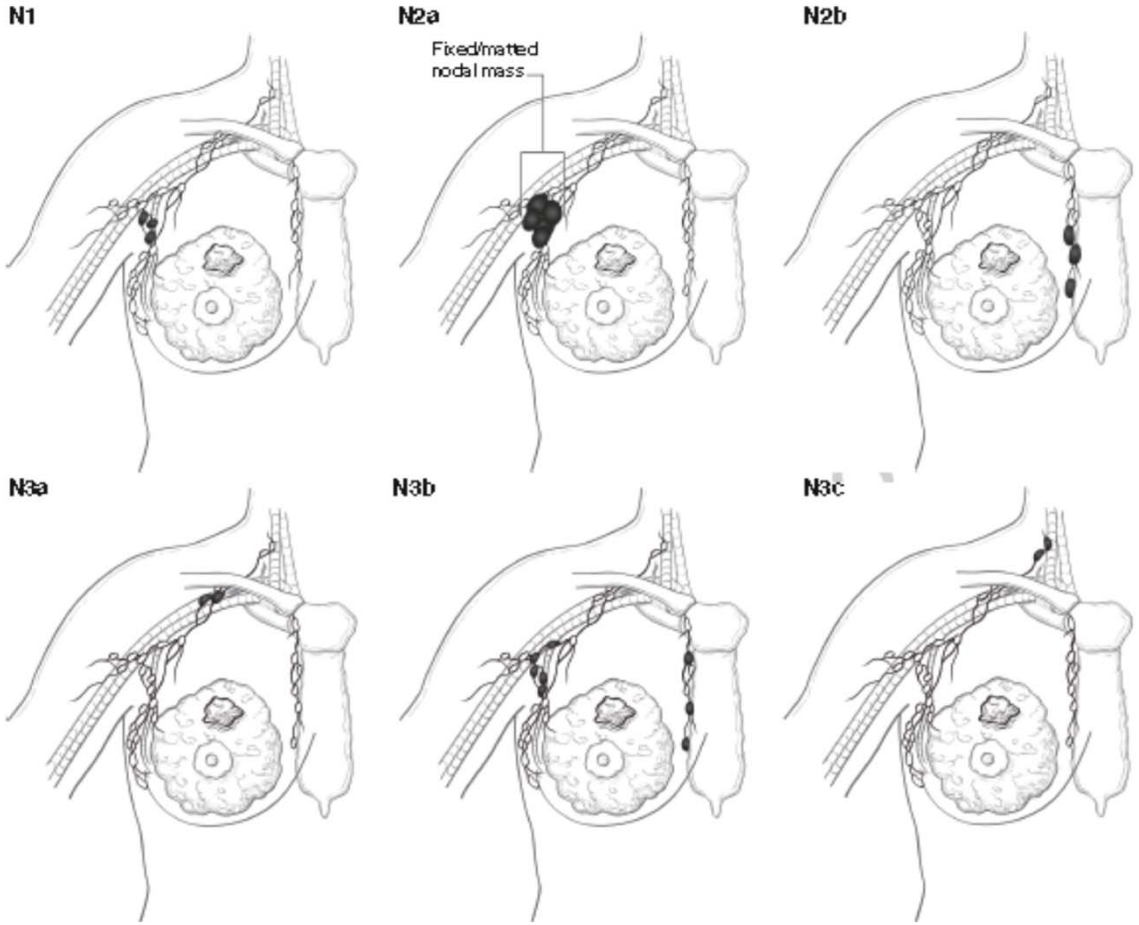






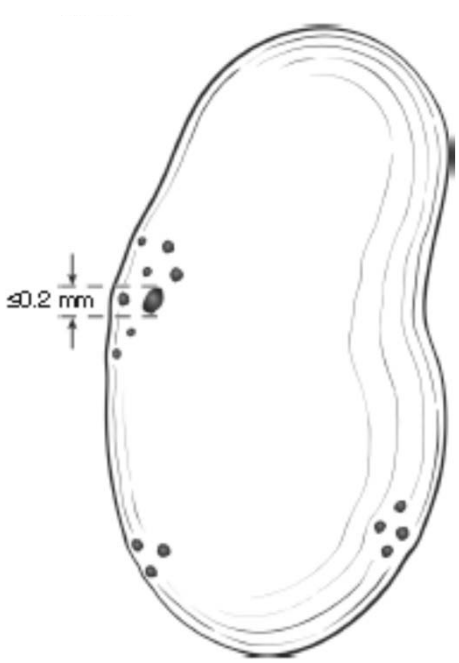
AJCC Staging System

- Clinical N stage:

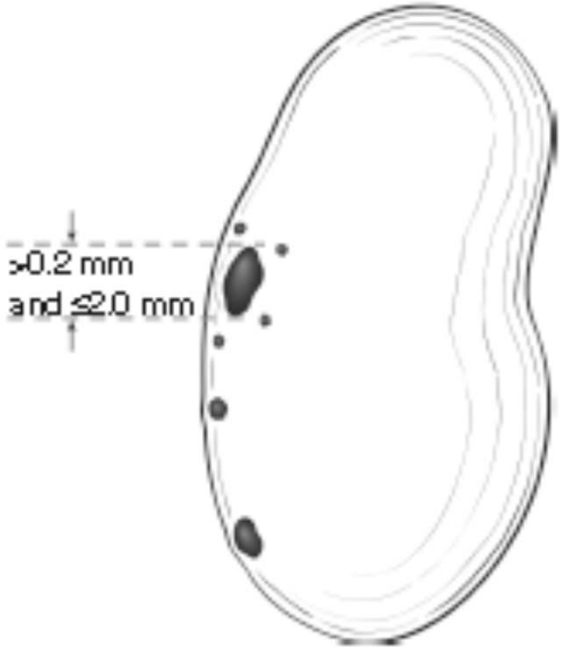


AJCC Staging System

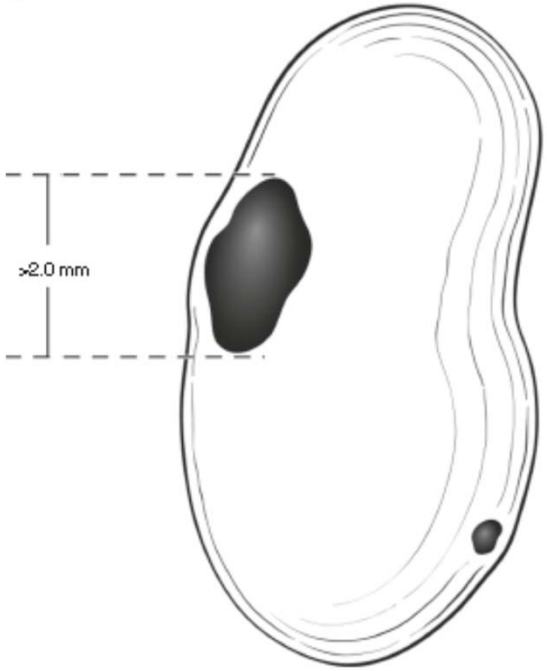
- Pathologic N stage:



Isolated Tumor Cell



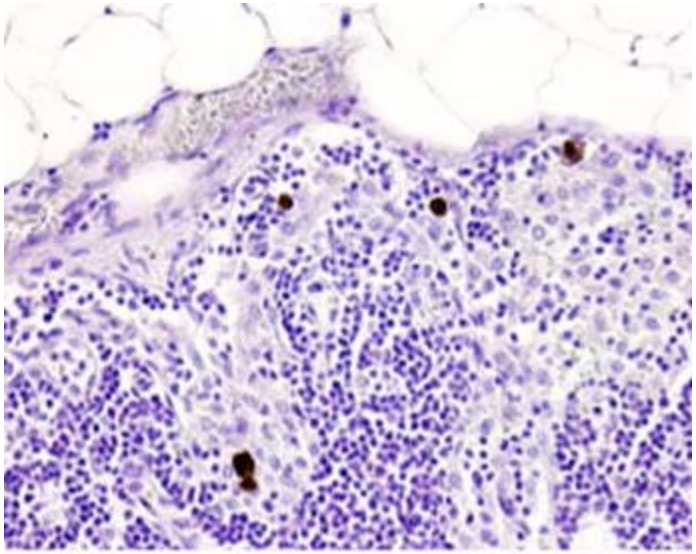
Micrometastasis

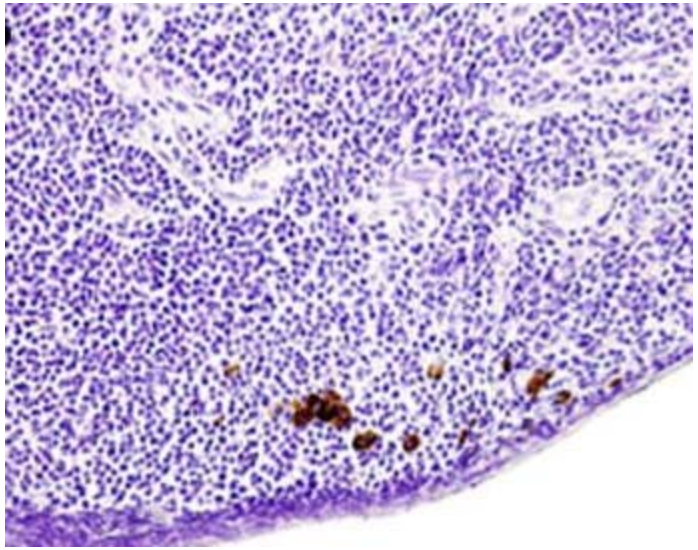


Macrometastasis

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





Mittendorf EA et al. *Ann Surg Oncol* 2008;15:3369-3377

AJCC Staging System

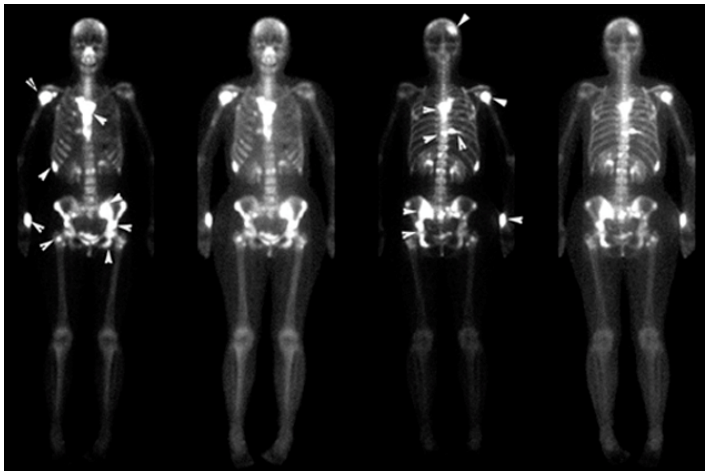
- Pathologic N stage*:

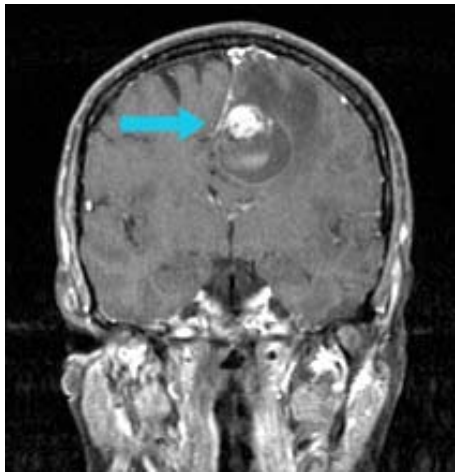
pNx	Regional LN cannot be assessed
pN0	No regional LN metastasis
pN0(i+)	Malignant cells in LN no >0.2mm (detected by H&E or IHC)
pN1mi	Micrometastases (>0.2mm and/or more than 200 cells, but none >2.0mm)
pN1	Metastases in 1-3 axillary LN, at least one > 2.0mm
pN2	Metastases in 4-9 axillary LN, or in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

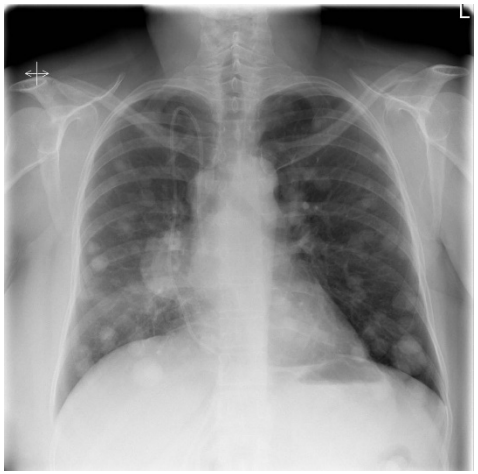
*abbreviated table; AJCC staging manual provides more detailed classification i.e. differentiating pN1a from pN1b

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





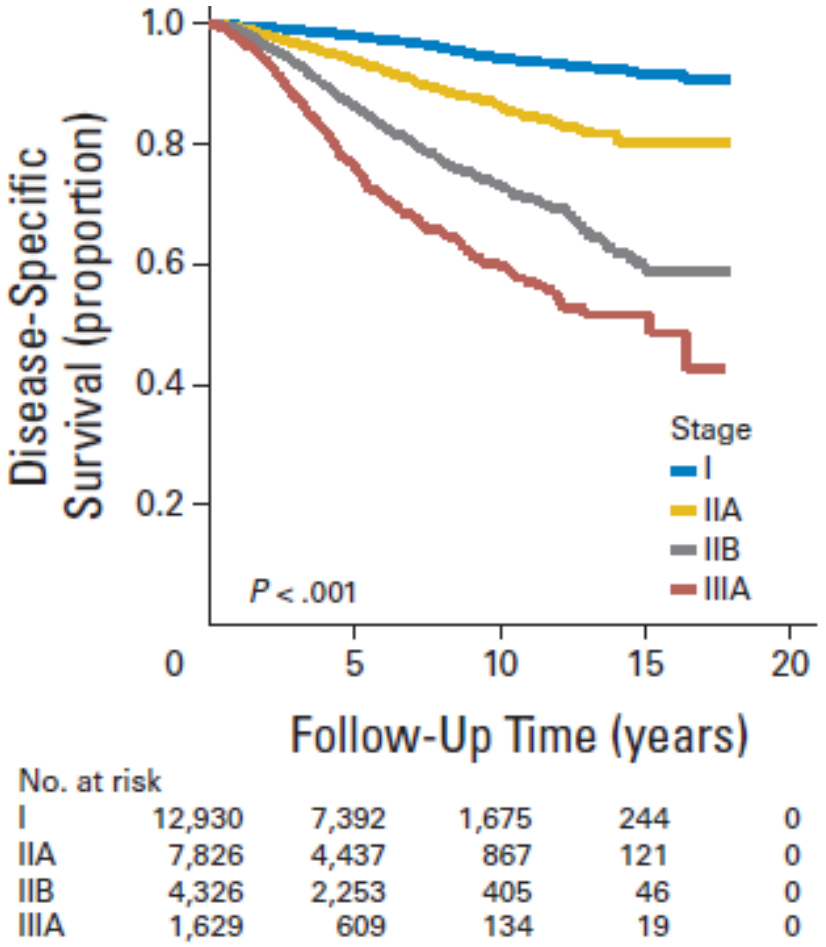


7th Edition AJCC Staging System

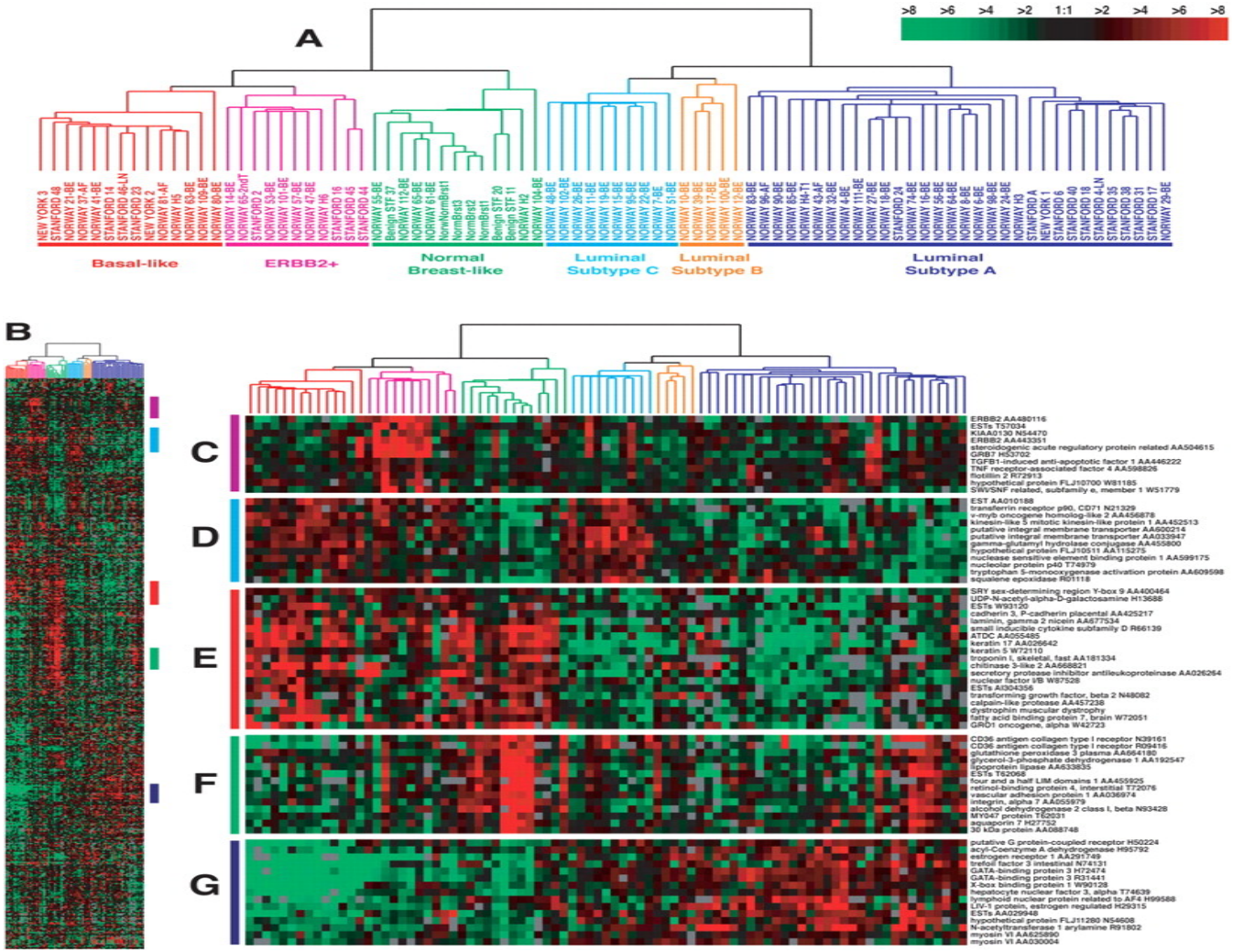
- Clinical stage: Based on findings of history, physical examination, and any imaging studies that are done
- Pathologic stage: Definitive stage determined after surgery by pathologic evaluation of the primary tumor and regional lymph nodes

7th Edition AJCC Staging System

Stage	T	N	M
IA	T1	N0	M0
IB	T0 T1	N1mi N1mi	M0 M0
IIA	T0 T1 T2	N1 N1 N0	M0 M0 M0
IIB	T2 T3	N1 N0	M0 M0
IIIA	T0 T1 T2 T3	N2 N2 N2 N1/2	M0 M0 M0 M0
IIIB	T4	N0-2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1



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

	HR+/HER2-	HR+/HER2+	HER2+/HR-	TNBC
Stage T2N0	96%	94%	92%	88%

	HR+/HER2-	HR+/HER2+	HER2+/HR-	TNBC
Stage IV	47%	39%	24%	17%

Chavez-MacGregor, et al. *The Oncologist* 2017 Jun 7 [Epub ahead of print]

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

Yi M et al. *J Clin Oncol* 2011;29:4654-4661

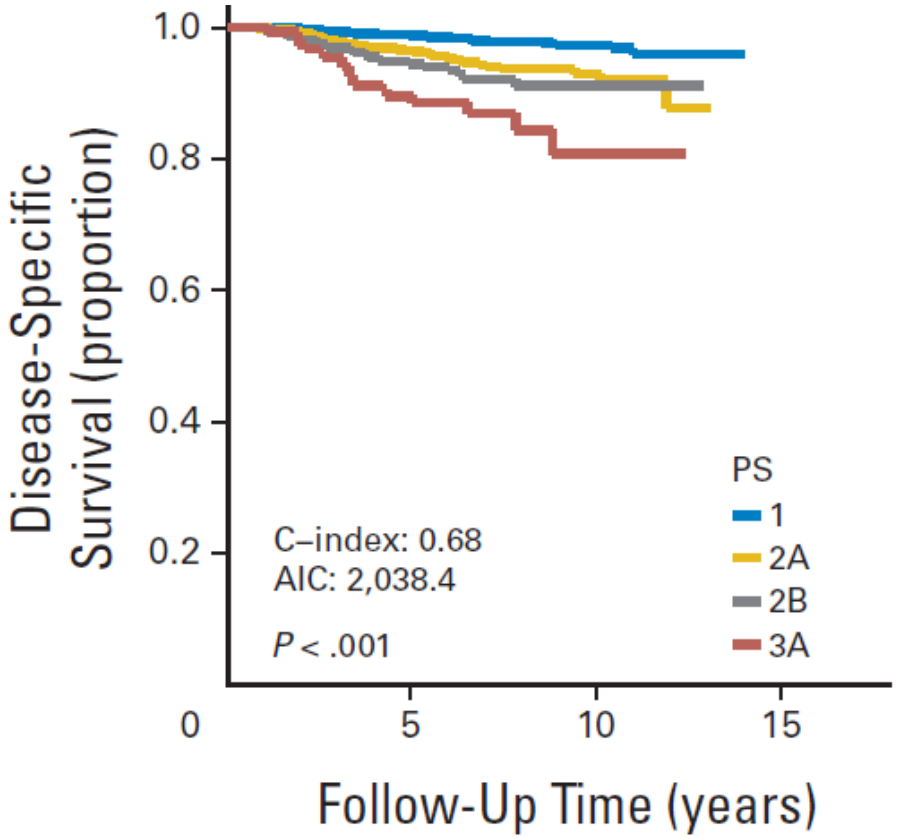
Methods

- 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

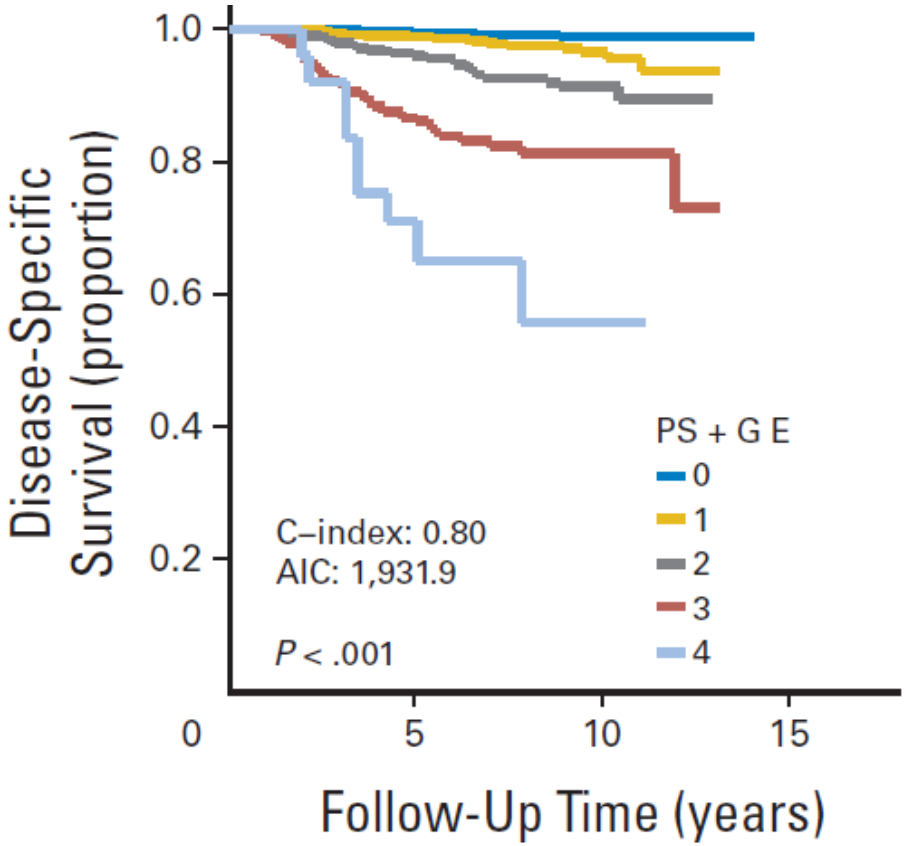
Yi M et al. *J Clin Oncol* 2011;29:4654-4661

Incorporation of Biologic Factors into Novel Staging System

Pathologic Stage



PS + G E



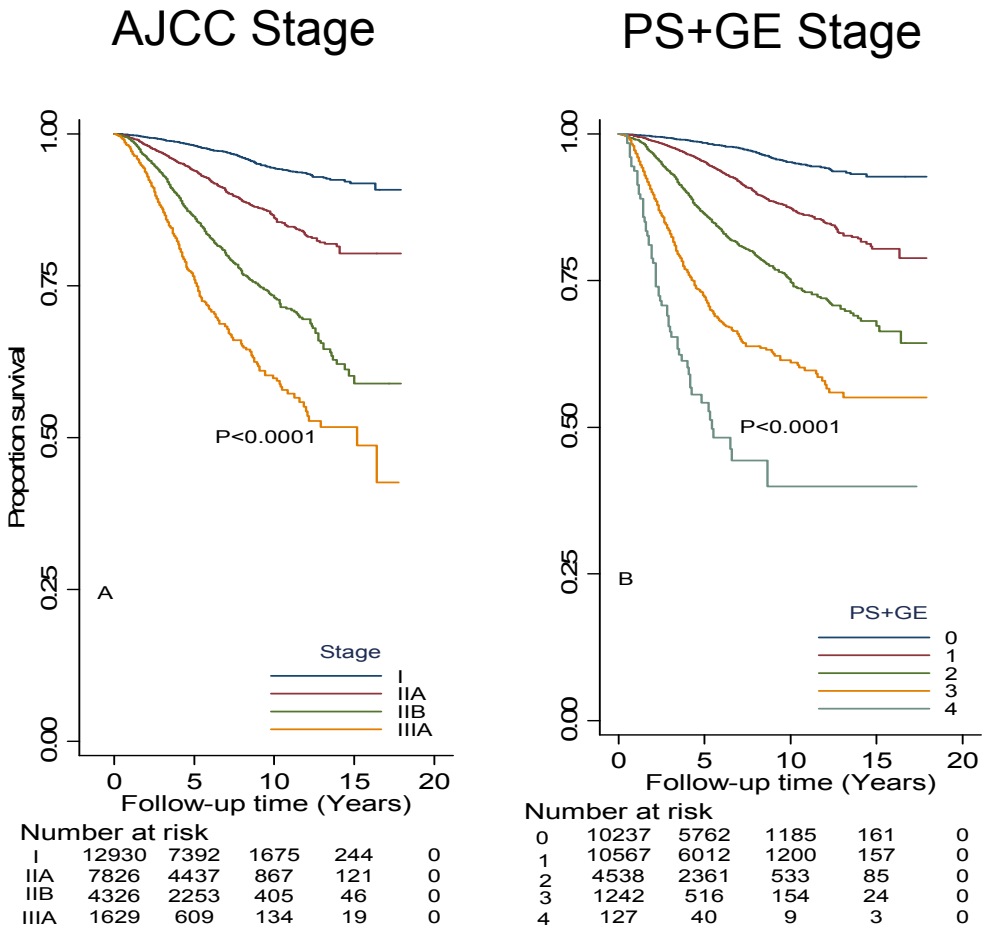
Yi M et al. *J Clin Oncol* 2011;29:4654-4661

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

Yi M et al. *J Clin Oncol* 2011;29:4654-4661

Novel Staging System Incorporating Tumor Biology



Yi M et al. *J Clin Oncol* 2011;29:4654-4661

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 erros
    - 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

Mittendorf EA et al. *Ann Surg Oncol* 2017 Jul 19 [Epub ahead of print]

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

Mittendorf EA et al. *Ann Surg Oncol* 2017 Jul 19 [Epub ahead of print]

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

Mittendorf EA et al. *Ann Surg Oncol* 2017 Jul 19 [Epub ahead of print]

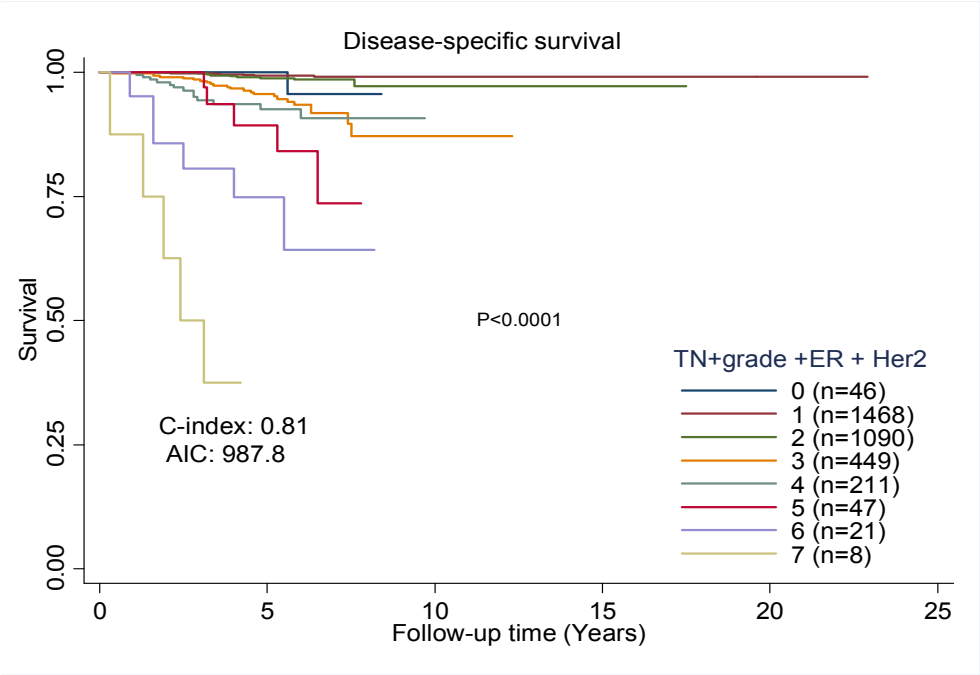
Bioscore – Model Building

- 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

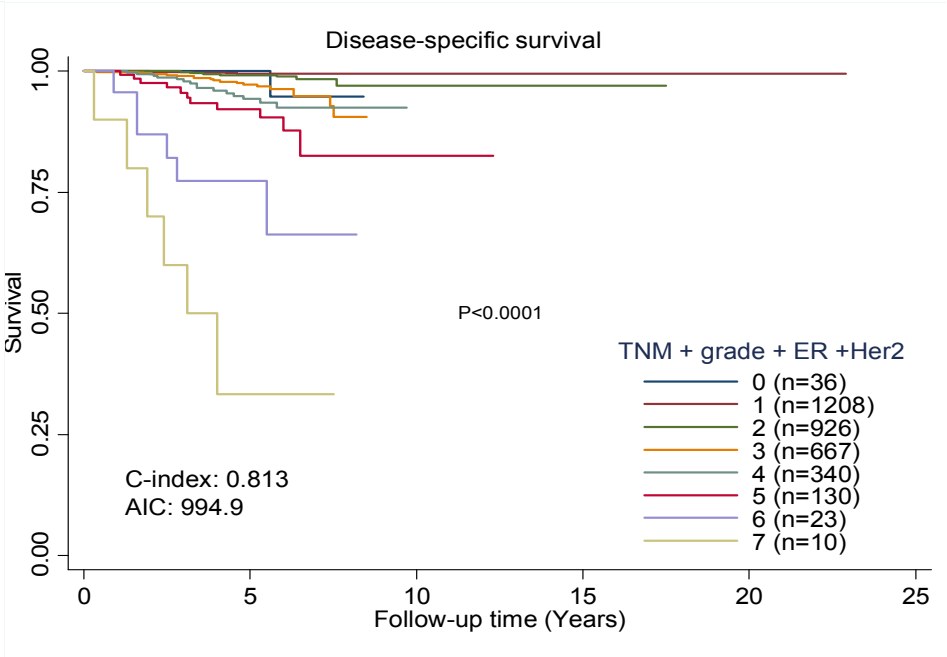
Mittendorf EA et al. *Ann Surg Oncol* 2017 Jul 19 [Epub ahead of print]

The Winners…….

AJCC stage + grade + ER + HER2



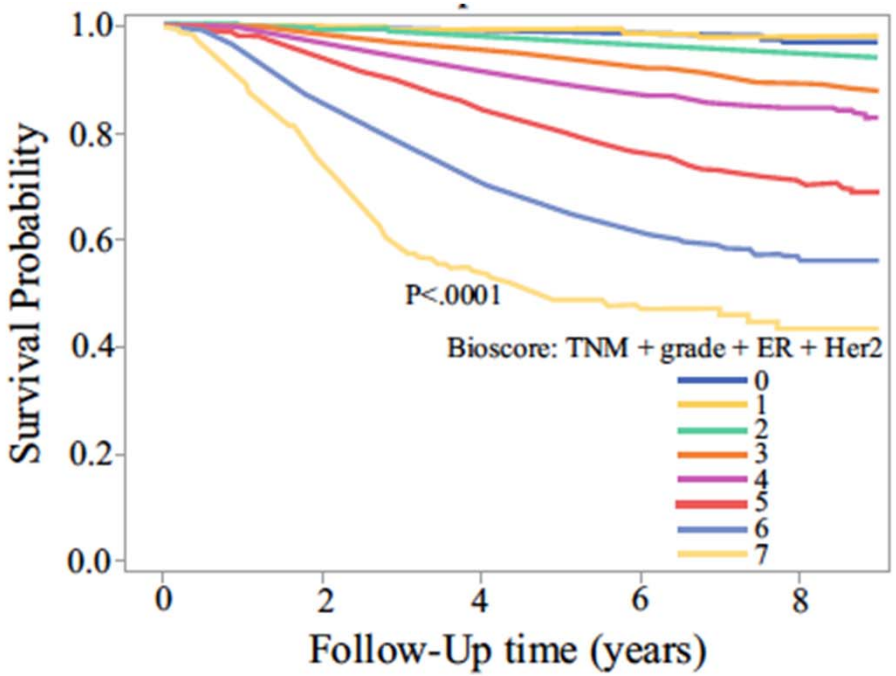
T + N + grade + ER + HER2

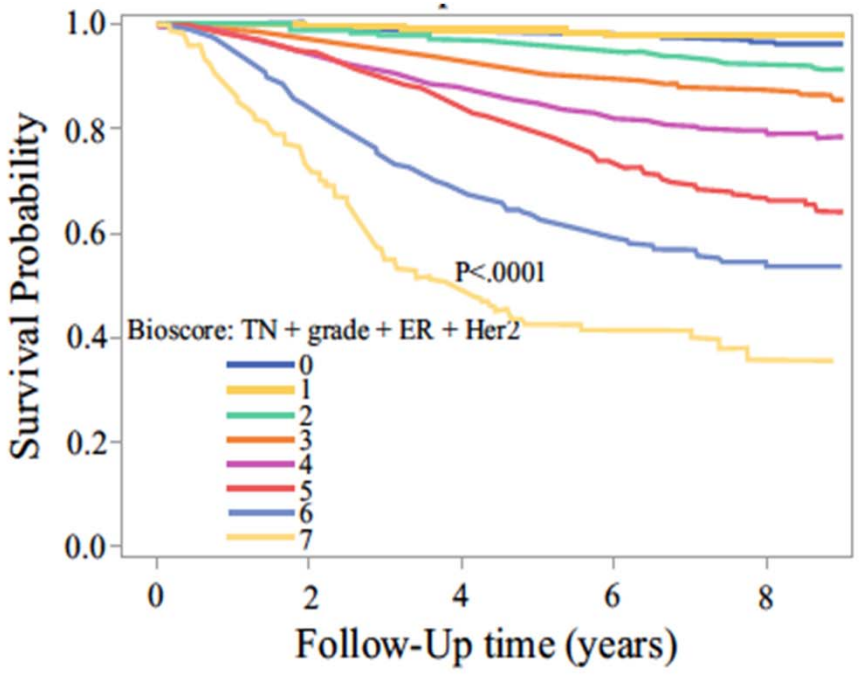


Mittendorf EA et al. *Ann Surg Oncol* 2017 Jul 19 [Epub ahead of print]

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





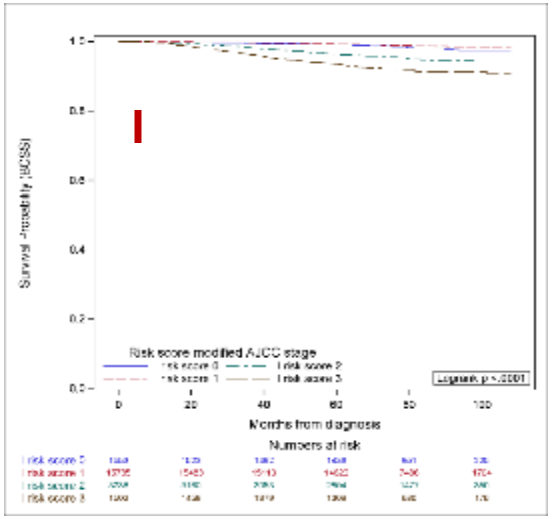
Mittendorf EA et al. *Ann Surg Oncol* 2017 Jul 19 [Epub ahead of print]

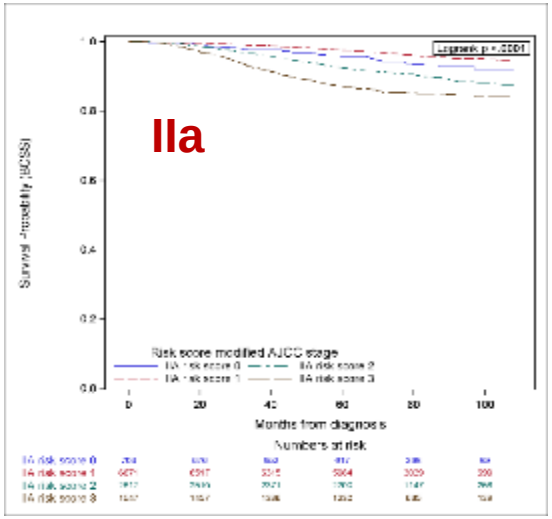
More Models: Risk Score

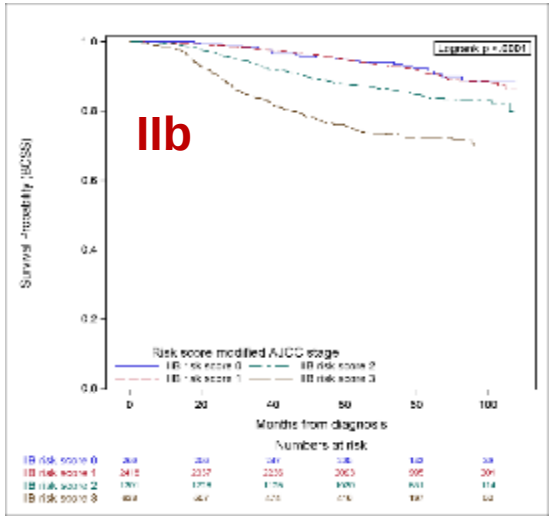
- 43,938 patients with primary BC stage I-IV diagnosed 2005-2008 in the CCR
- Cox model identified grade, ER and HER2 as the most important prognostic factors in addition to stage
- Risk score point based system
  - One point for:
    - Grade 3
    - ER-negative
    - Her2-negative to complement the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

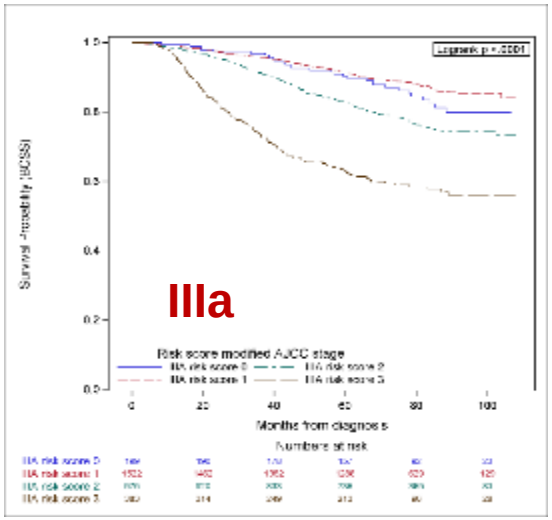
Chavez-MacGregor, et al. *The Oncologist* 2017 Jun 7 [Epub ahead of print]

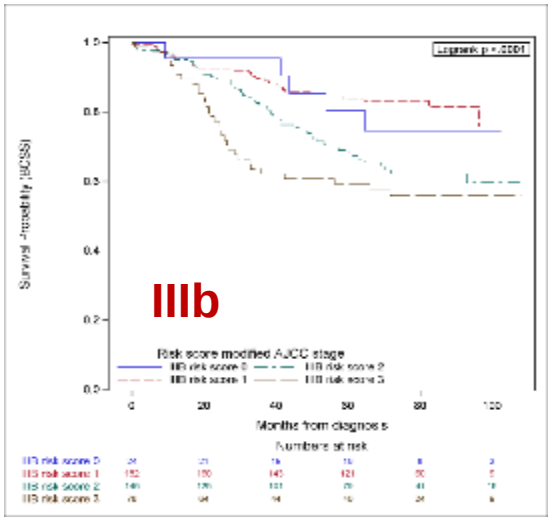
Risk Score – BCSS Stage I-III

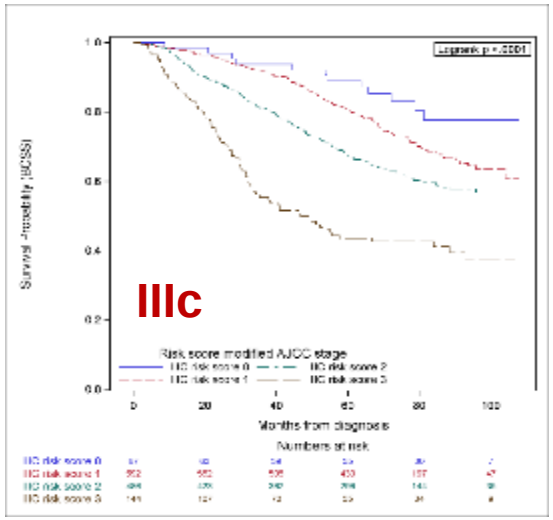












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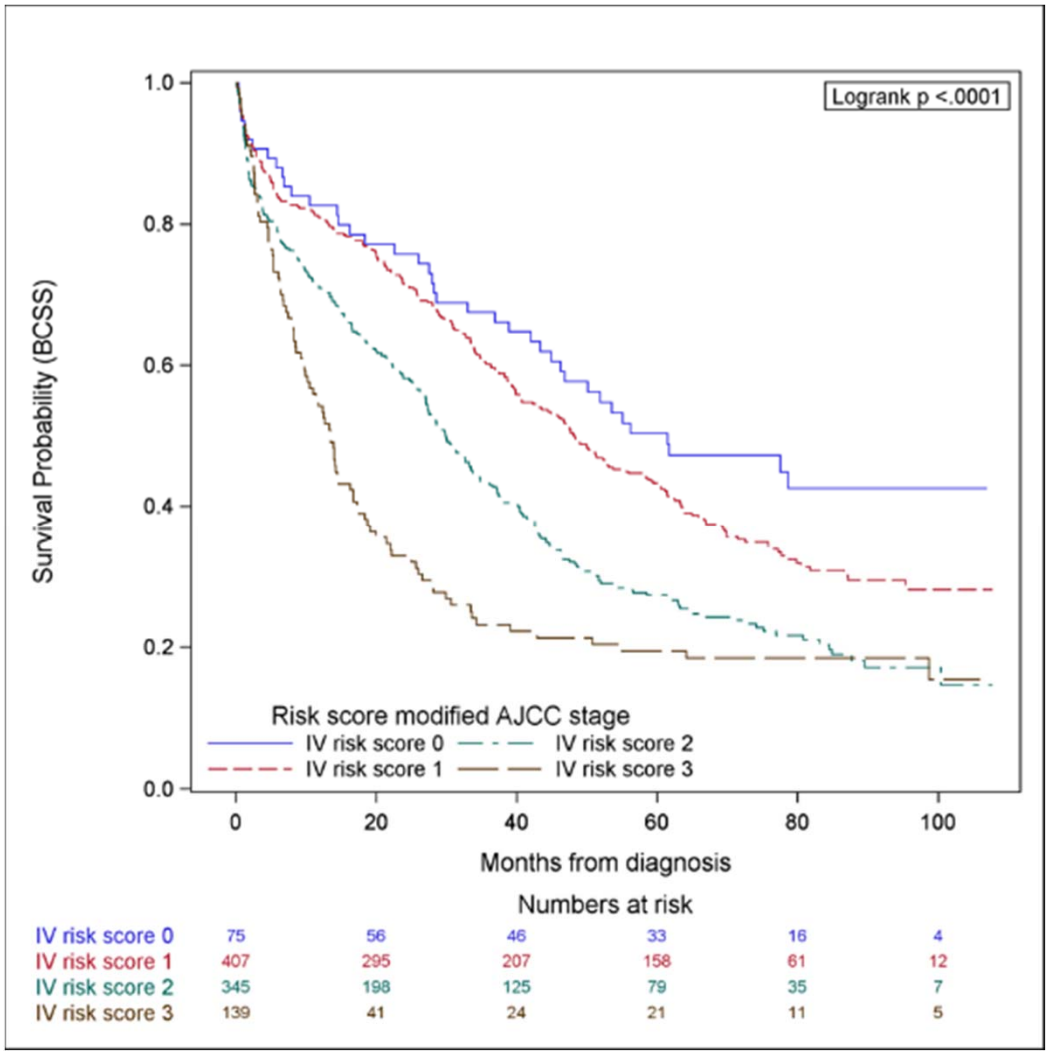
Risk Score – BCSS Stage IV



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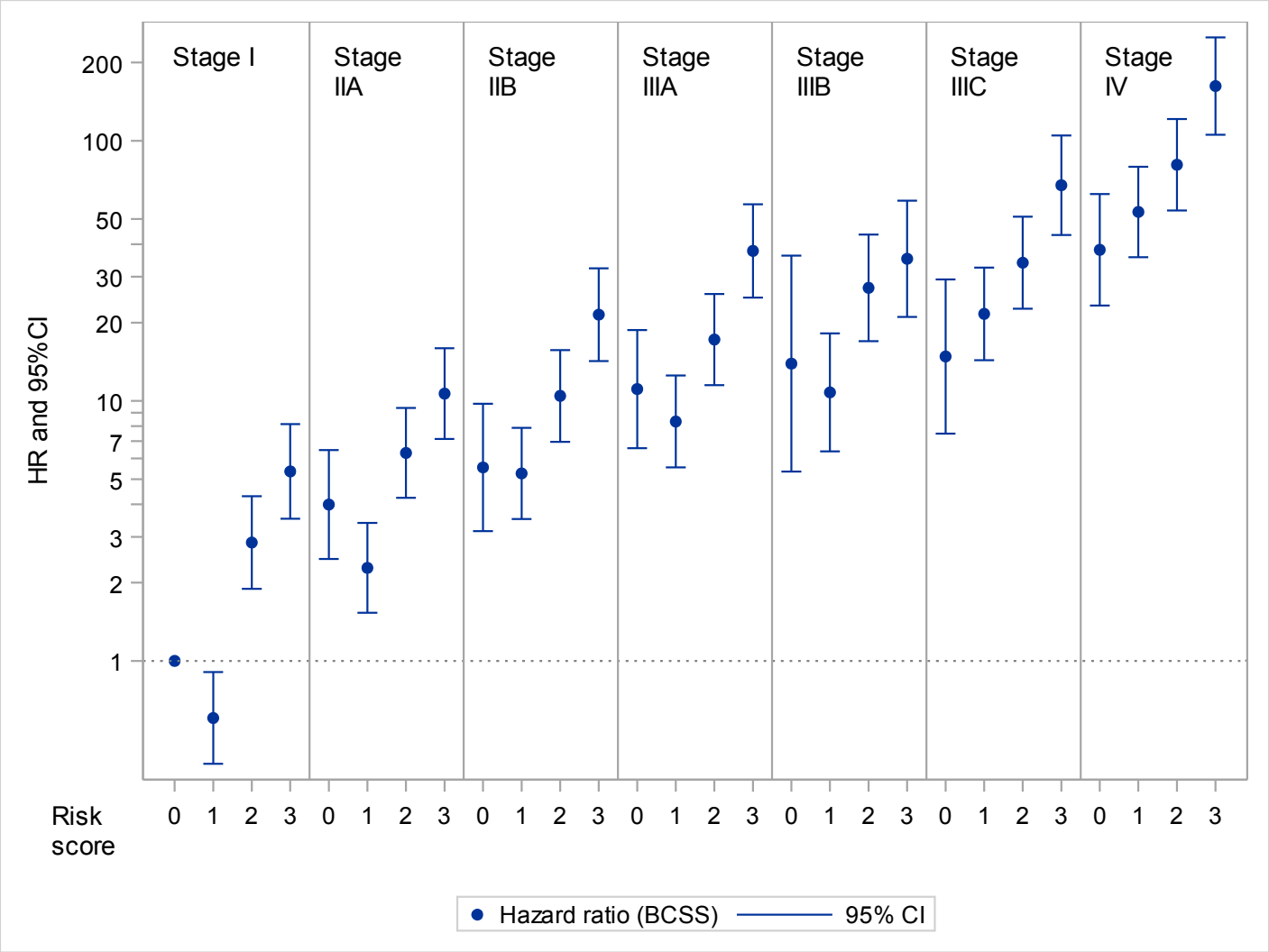
Risk Score Hazard Ratios



Chavez-MacGregor, et al. *The Oncologist* 2017 Jun 7 [Epub ahead of print]

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]

AJCC 8th Edition

- 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

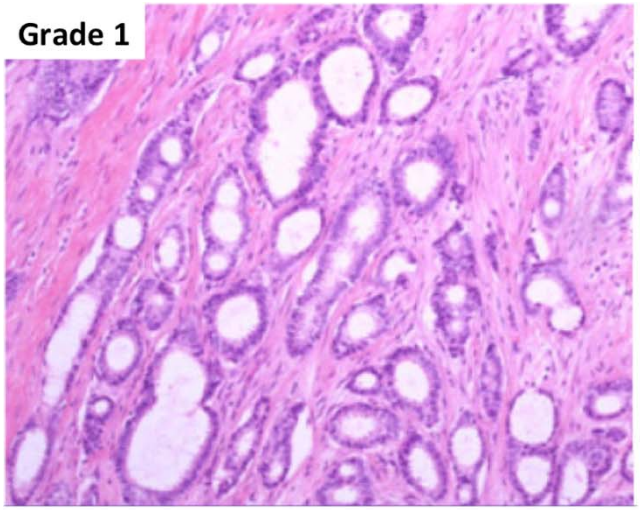
Hortoabgyi G, et al. AJCC Manual 8th ed.

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

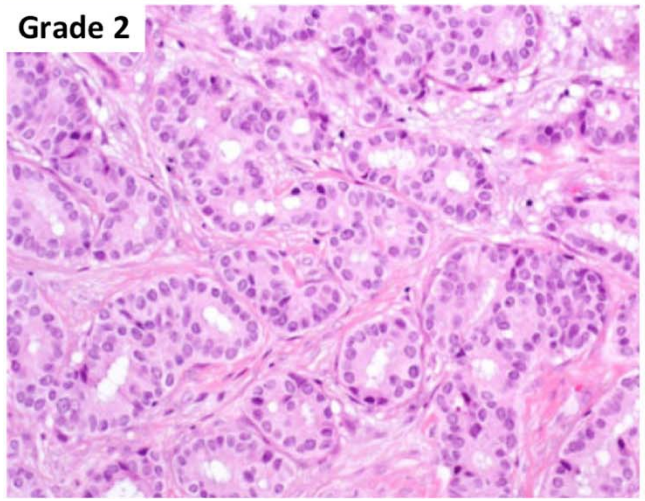
CAP Protocol; last modified 6/28/2017

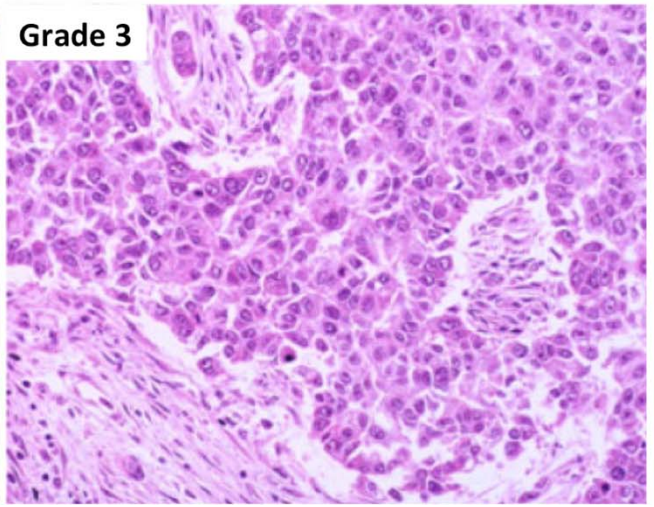
Grade



Nottingham Breast Cancer Grade

Total Feature Score	Tumor Grade	Appearance of Cells
3-5	Grade 1 Tumor	Well-differentiated (appear normal, growing slowly, not aggressive)
6-7	Grade 2 Tumor	Moderately-differentiated (semi-normal, growing moderately fast)
8-9	Grade 3 Tumor	Poorly-differentiated (abnormal, growing quickly, aggressive)





Estrogen receptor

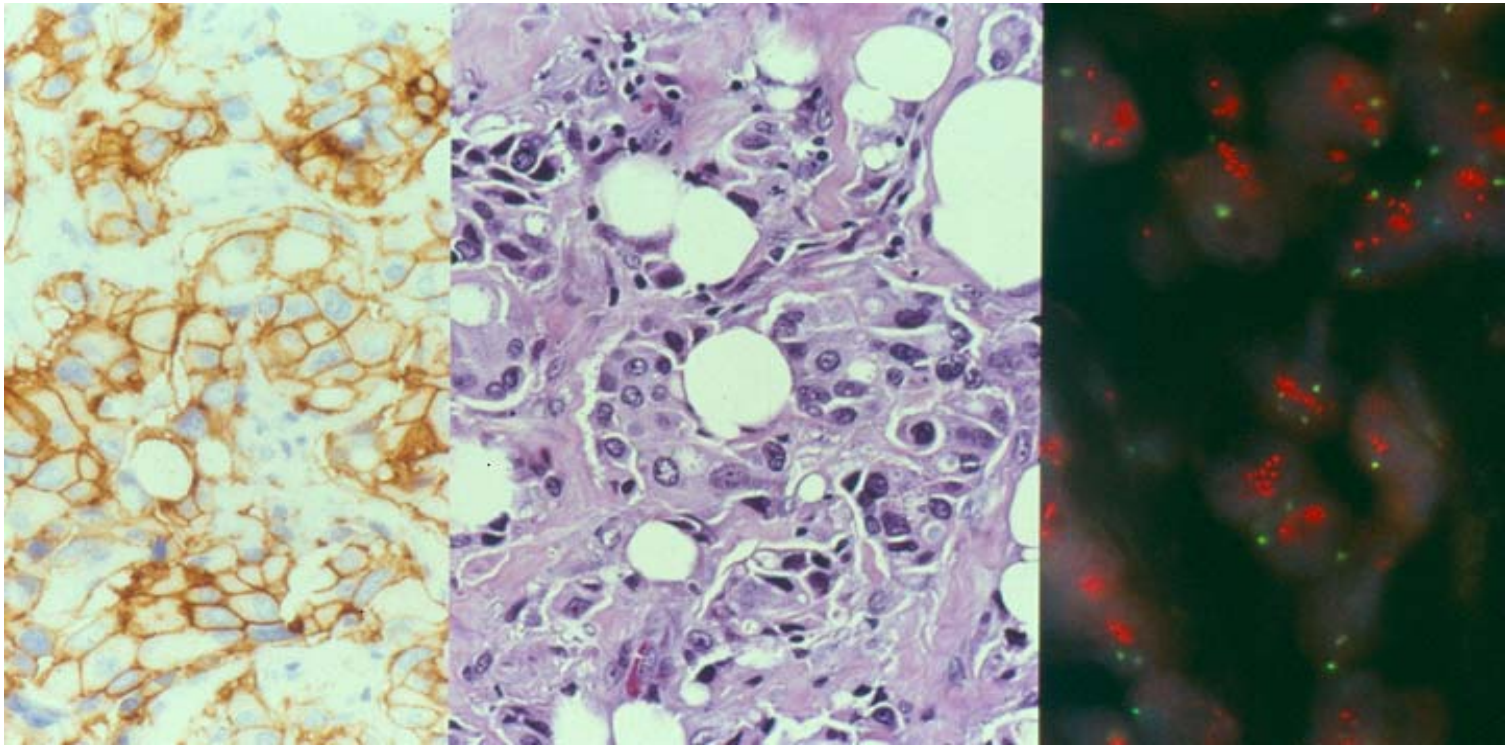
- Determined in FFPE sections by IHC
- Evaluating for nuclear staining
- Quantification may use the proportion of positive cells ± the intensity of immunoreactivity
- Reporting results:
  - Positive if immunoreactive tumor cells present (≥ 1%)*
  - Negative if <1% immunorecative tumor cells present

* 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

Hammond MEH et al. *J Clin Oncol* 2010;16:2784-2795

HER2

- Can test for HER2 protein expression (IHC assay) or *HER2* gene expression (ISH assay)

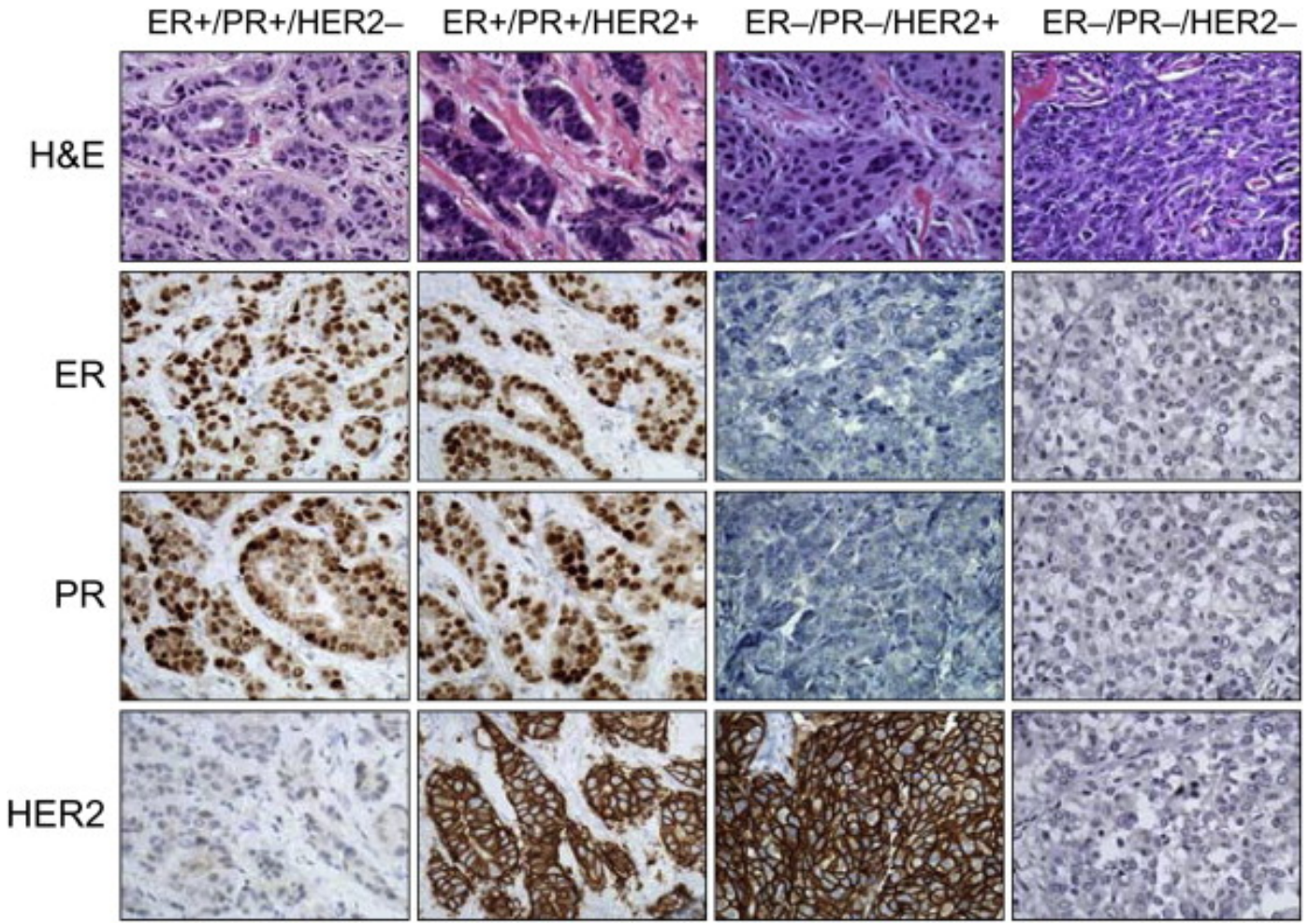


HER2

HER2 positive	• IHC 3+ based on circumferential membrane staining that is complete, intense • ISH positive based on: single-probe average *HER2* copy number ≥6.0 signals/cell dual-probe *HER2*/CEP17 ratio ≥2.0 with an ave *HER2* copy number ≥4.0 signals/cell dual-probe *HER2*/CEP17 ratio <2.0 with an ave *HER2* copy number <6.0 signals/cell
HER2 equivocal	• IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of invasive tumor cells; or complete and circumferential membrane staining that is intense and within ≤10% of invasive tumors cells • ISH equivocal based on: single-probe average *HER2* copy number ≥4.0 and <6.0 signals/cell dual-probe *HER2*/CEP17 ratio <2.0 with an ave *HER2* copy number ≥4.0 and <6.0 signals/cell
HER2 negative	• IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumors cells • 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 • ISH negative based on: single-probe average *HER2* copy number <4.0 signals/cell dual-probe *HER2*/CEP17 ratio <2.0 with an ave *HER2* copy number <4.0 signals/cell
HER2 indeterminate	Report as indeterminate if technical issues prevent tests from being reported as positive, negative or equivocal • Inadequate specimen handling • Artifacts that interfere with interpretation • Analysis testing failure

Wolf AC et al. *J Clin Oncol* 2013;31:3997-4014

ER/PR/HER2



Rivenbark AG, et al. *Am J Pathol* 2013;183:1113-1124

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

Hortoabgyi G, et al. AJCC Manual 8th ed.
Giuliano AE, et al. CA Cancer J Clin 2017;67:290-303

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

Hortoabgyi G, et al. AJCC Manual 8th ed.
Giuliano AE, et al. CA Cancer J Clin 2017;67:290-303

AJCC 8th Edition

Traditional TNM Factors + **Expanded Non-Anatomic Factors** Tumor Grade, HER2, ER, PR status = **8th Edition** Prognostic Stage Group

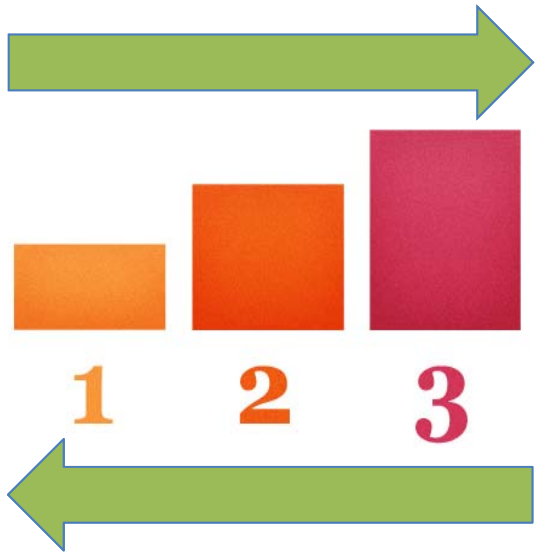
When T is…	When N is…	When M is…	And G is…	And HER2 Status is…	And ER Status is…	And PR Status is…	The Prognostic Stage Group is…
T1	N0	M0	1	Positive	Any	Any	IA
T1	N0	M0	1	Negative	Positive	Negative	IB
T2	N0	M0	1,2	Negative	Positive	Positive	IB
T1	N0	M0	1-3	Negative	Negative	Negative	IIA
T2	N0	M0	3	Negative	Positive	Positive	IIA
T3	N0	M0	1	Negative	Positive	Negative	IIIA

Hortoabgyi G, et al. AJCC Manual 8th ed.

AJCC 8th Edition

"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

Hortoabgyi G, et al. AJCC Manual 8th ed.

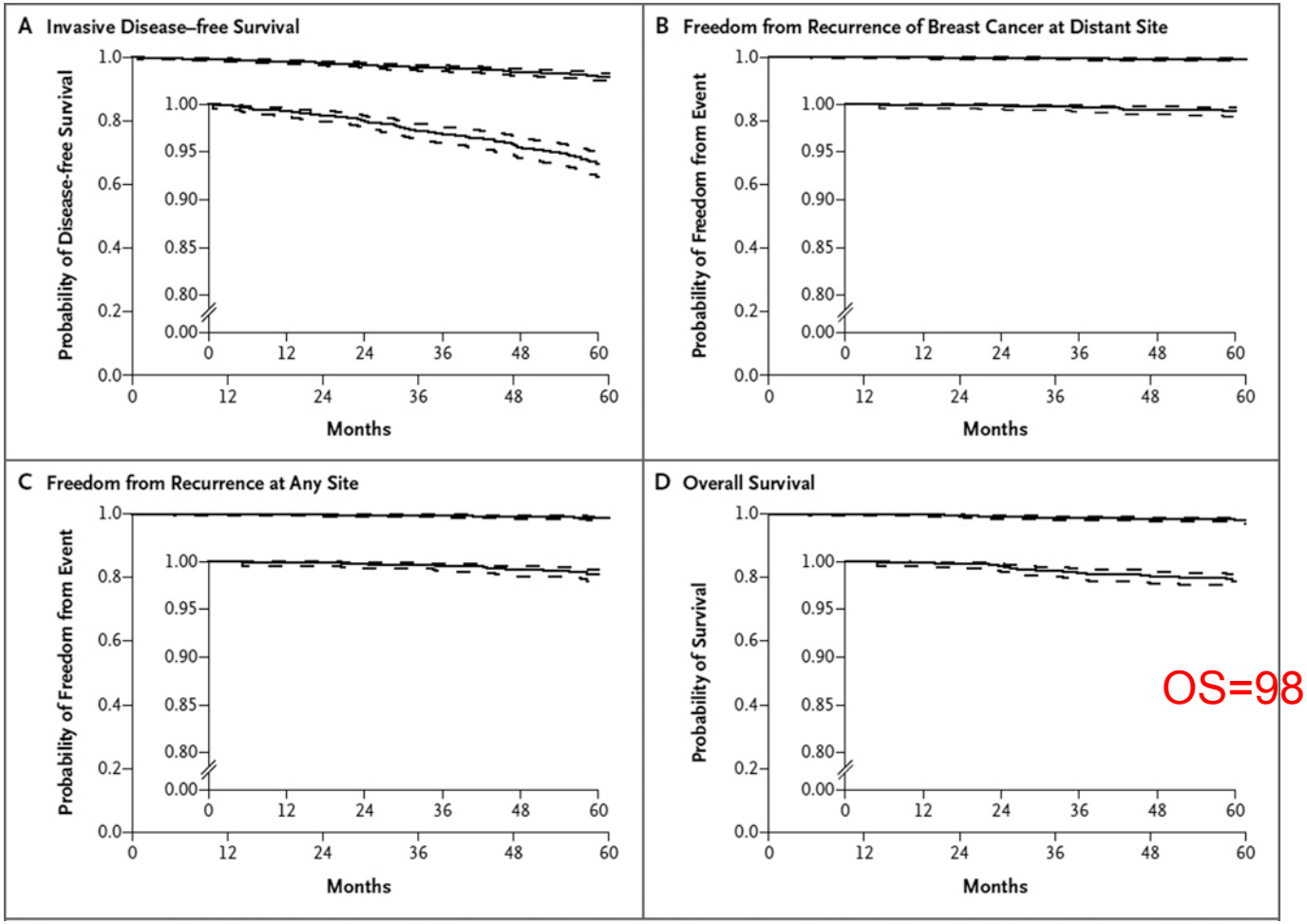
AJCC 8th Edition – Incorporation of Genomic Assays

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

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

Hortoabgyi G, et al. AJCC Manual 8th ed.
Sparano JA, et al. N Engl J Med 2015;365:1273-1283

TAILORx



OS=98% if RS<11

Sparano JA, et al. N Engl J Med 2015;365:1273-1283

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

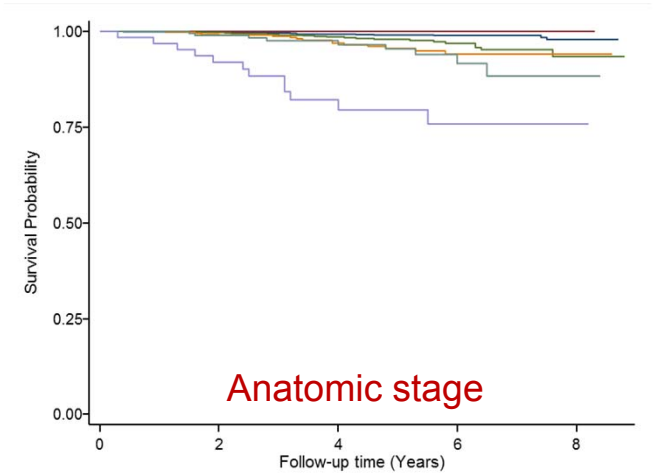
Validation of the AJCC 8th Edition

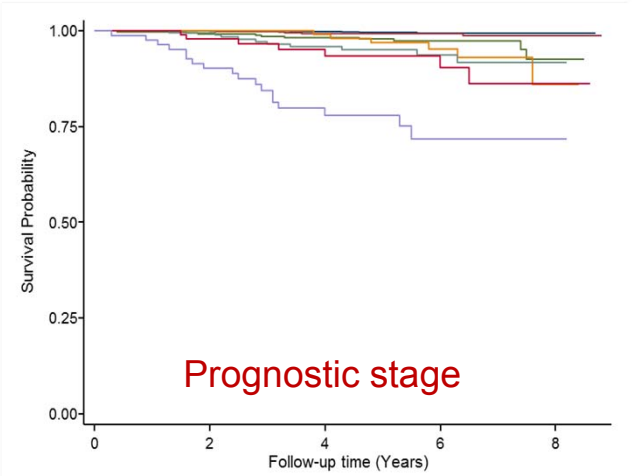
- CA Cancer Registry: 54,724 stage I-IV BC patients diagnosed 2005-2009
  - Compared to AJCC anatomic stage, the prognostic stage **upstaged 31.0%** of patients and **downstaged 20.6%**
  - The prognostic staging system provided more accurate stratification with respect to DSS than the anatomic stage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

Weiss A, Chavez-MacGregor M……Mittendorf EA. Manuscript under review

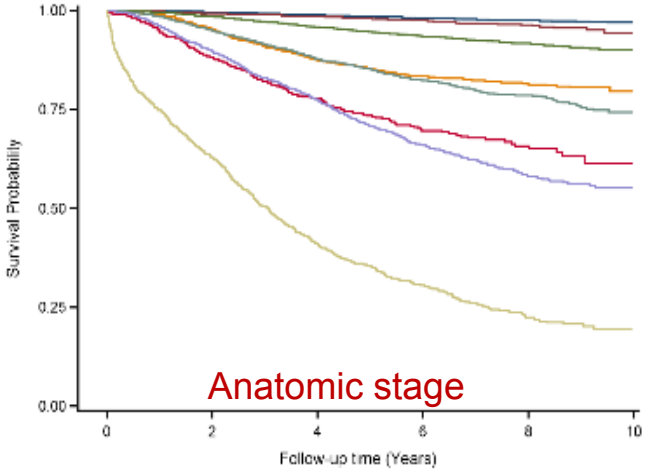
Validation of the AJCC 8th Edition

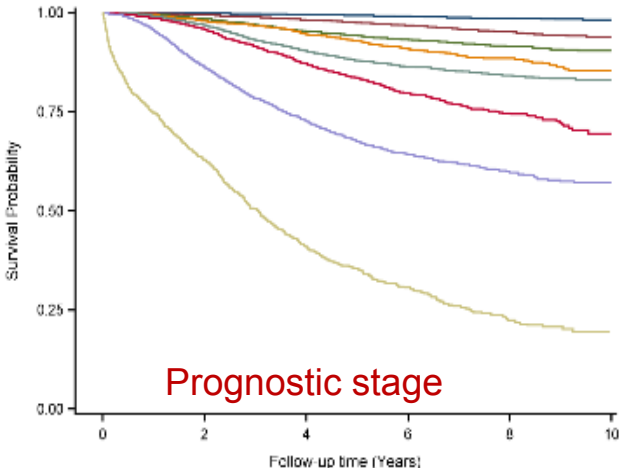
MD Anderson





CA Cancer Registry





AJCC 8th Edition – Summary of Significant Changes

- 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

Hortoabgyi G, et al. AJCC Manual 8th ed.

AJCC 8th 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?

AJCC 8th Edition - Opportunities

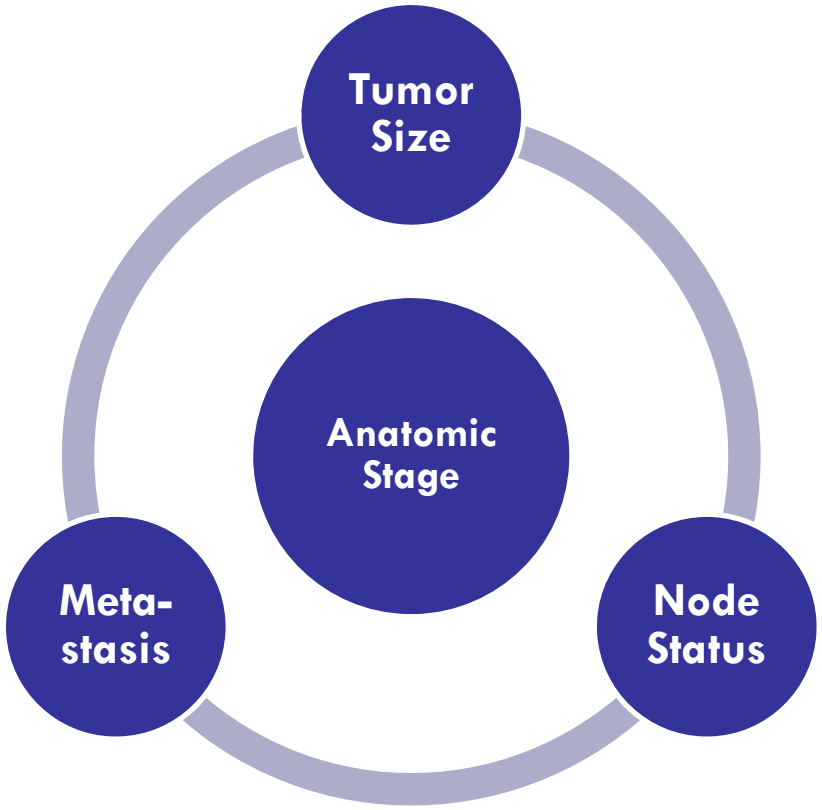
- Expert panel has repeated analyses of NCDB database
  - Accounts for all combinations of T,N,grade,ER,PR and HER2
  - Further refines prognostic stage → clinical prognostic stage and pathologic prognostic stage
  - Further discusses multiple genomic assays (i.e. MINDACT data discussed)
  - Pending approval, will be available online

AJCC 8th Edition - Opportunities

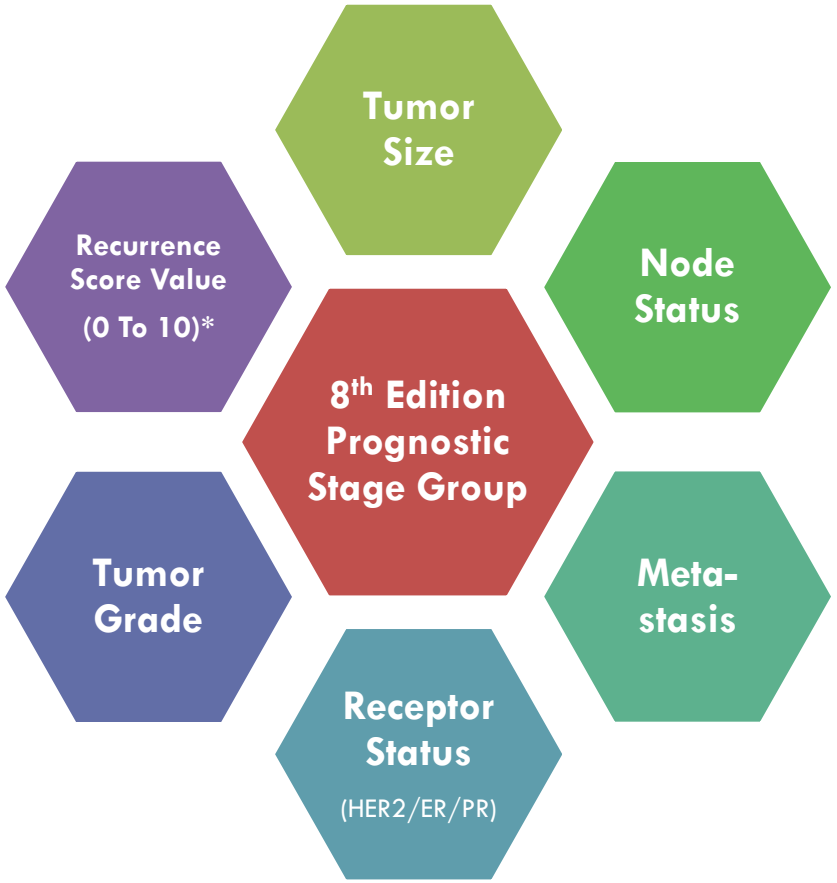
- Education
- Dissemination
- IT platforms to facilitate use
- May refine clinical trial eligibility criteria

AJCC 8th Edition

1977 - 2017



2018+



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