Changes in the AJCC 8th Edition to Breast Cancer Staging

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American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

TNM System Origins

- Developed between 1943 and 1952 by French surgeon Pierre Denoix

Pierre Denoix, MD
L-Institut Gustave Roussy

The goal was a COMMON LANGUAGE

TNM System Origins

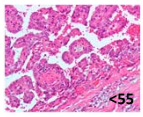
- Used in 1959 to reflect the risk of distant recurrence and death after surgery
- At the time, limited understanding of the biology of breast cancer and no effective systemic therapy
- Primary objective was to provide standard nomenclature for prognosis after surgery

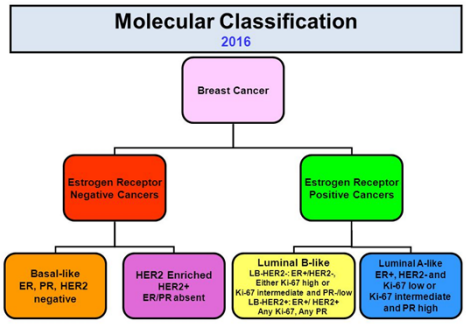
Since 1959

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

Other organ systems

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



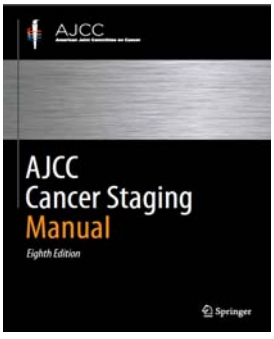


Fundamental Changes

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

AJCC Staging 8th Edition

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

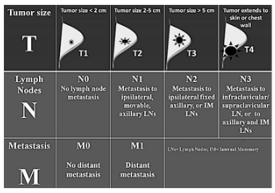


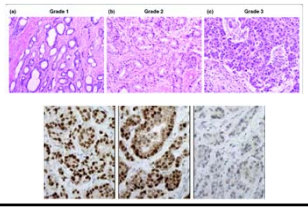
Adopted as of January 1, 2018

What are the changes?

Major Changes

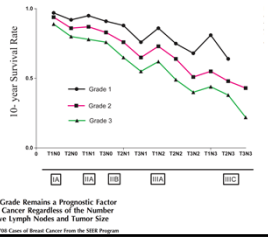
- Changes in the TNM aspect of staging
- Addition of Grade and Biomarkers into Stage determination





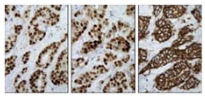
The clinical utility of biologic factors such as grade, hormone receptor expression, HER2 overexpression and/or amplification, and genomic panels has become at least as important as the anatomic extent of disease to predict survival.

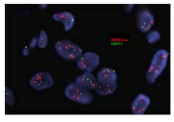
These factors enable accurate determination of prognosis and selection of systemic therapy and increasingly are affecting locoregional management.

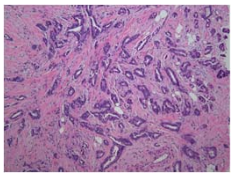


Histologic Grade Remains a Prognostic Factor for Breast Cancer Regardless of the Number of Positive Lymph Nodes and Tumor Size

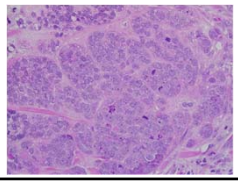
A Study of 163 706 Cases of Breast Cancer From the SEER Program







74 y/o
1 cm Mass
ER+
PR+
HER2-



44 y/o
1 cm Mass
ER-
PR-
HER2-

To address the importance of tumor biology, in addition to defining AJCC anatomic stage groups, the breast expert panel has defined biologic factor-based prognostic stage groups for the eighth edition that take into consideration tumor grade; HER2, ER, and PR status; and multigene panel (such as Oncotype DX) status

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

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

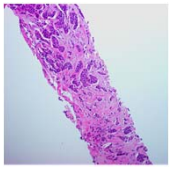
Now incorporated **into parallel prognostic stage groups that recognize intrinsic tumor biology.**

But first some definitions

- Anatomic Stage
  - Based solely on TNM
  - Intended for use worldwide where biomarkers are NOT available
- Clinical Prognostic Stage
  - Used for ALL patients based on history, exam, imaging, biopsies.
  - Incorporates TNM, Grade, Biomarker Data
- Pathologic Prognostic Stage
  - Used to assign stage in patients with surgery as initial treatment before systemic or radiation therapy
  - Incorporates all clinical, biomarker, and anatomic markers

Clinical vs Pathologic Prognostic Staging

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



CHANGE	DETAILS OF CHANGE	LEVEL OF EVIDENCE
AJCC anatomic and prognostic stage groups	There are 2 stage group tables presented in this chapter:	II
	1. The anatomic stage group table is based solely on anatomic extent of cancer as defined by the T, N, and M categories.	
	2. The prognostic stage group table is based on populations of persons with breast cancer that have been offered—and most treated with—appropriate endocrine and/or systemic chemotherapy, which includes anatomic T, N, and M plus tumor grade and the status of the biomarkers human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR).	
Selecting the appropriate stage group table	The prognostic stage group table is preferred for patient care and is to be used for reporting of all cancer patients in the United States.	
	The anatomic stage group table is provided so that stage can be assigned in regions of the world where the biomarkers cannot be routinely obtained.	N/A

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

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

Lack of level I evidence available to support the impact of biologic factors on prognosis.

No prospective trials, no "no-treatment" arm.

Large data sets with complete data and adequate follow-up not available

Recent analyses of large retrospective studies

VOLUME 29 · NUMBER 35 · DECEMBER 10 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

MD Anderson Group

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 patients who were treated between 1997 and 2006
-Developed a staging system that incorporated grade, ER and PR status with pathologic stage
-Validated with 26,711 patients from the SEER

Ann Surg Oncol (2017) 24:3502–3509
DOI 10.1245/s10434-017-6009-x
Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY
CrossMark
ORIGINAL ARTICLE – BREAST ONCOLOGY

Bioscore: A Staging System for Breast Cancer Patients that Reflects the Prognostic Significance of Underlying Tumor Biology

Elizabeth A. Mittendorf, MD, PhD[1], Mariana Chavez-MacGregor, MD, MSC[2,3], Jose Vila, MD[1], Min Yi, MD, PhD[1], Daphne Y. Lichtensztajn, MD[4], Christina A. Clarke, PhD, MPH[4,5], Sharon H. Giordano, MD, MPH[2,3], and Kelly K. Hunt, MD[1]

3327 patients with invasive breast cancer treated with surgery as a first intervention at MD Anderson between 2007 and 2013

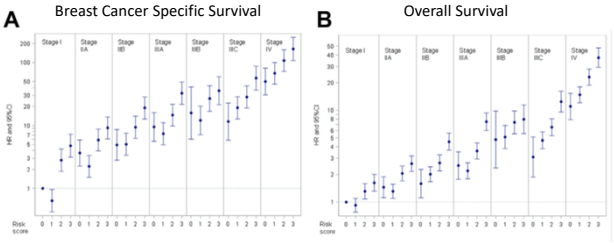
306 patients with HER2-positive breast cancer that were treated with trastuzumab.

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

Table 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

MD Anderson Cohort 3327 patients and validated with 43,938 patients in the California Cancer Registry



Risk score :
1 point if estrogen receptor negative
1 point if HER2 negative
1 point for grade 3 disease
Reference group was stage 1 risk 0.

Additional Study- National Cancer Database

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

Hortobagyi GN, Connolly JL, Edge SB, et al. Breast. AJCC cancer staging manual. 8th edition. New York: Springer International Publishing; 2016.

NCDB Findings

NATIONAL CANCER DATABASE

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

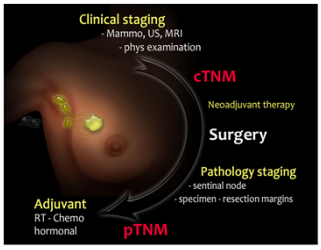
Two Analyses Performed

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

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

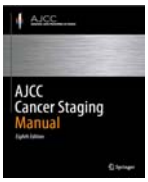
Neoadjuvant?

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

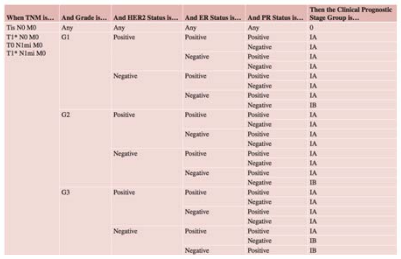


NCDB data lead to formation of Clinical and Anatomic *Prognostic* Stages

NATIONAL CANCER DATABASE



Clinical Prognostic Stage

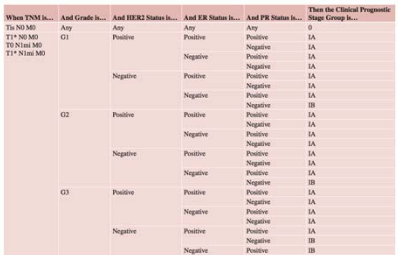


When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0	G1	Positive	Positive	Positive	IA
T0 N1mi M0				Negative	IA
T1* N1mi M0			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB

T1N0M0 G2, 3x- Stage IB

Used for ALL patients with available markers

Pathologic Prognostic Stage



When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0	G1	Positive	Positive	Positive	IA
T0 N1mi M0				Negative	IA
T1* N1mi M0			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB

T1N0M0 G3, Her2-, ER+, PR- Stage IB

If PR+, then stage IA

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

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

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

NCDB Analyses

NATIONAL CANCER DATABASE

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

Excellent correlation with the MD Anderson analyses*

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

Addition of Multigene Assays

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

oncotype DX® Breast Recurrence Score

EndoPredict®

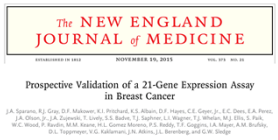
Breast Cancer INDEX

mammaprint decoding breast cancer.

prosigna™ Breast cancer gene signature assay PAM50

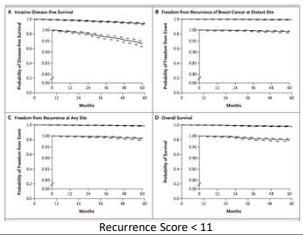
Oncotype Dx incorporated into staging

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


The NEW ENGLAND JOURNAL of MEDICINE

NOVEMBER 19, 2015

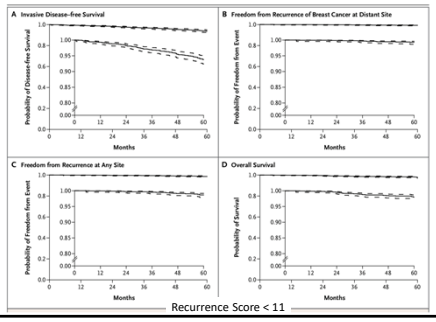
Prospective Validation of a 21-Gene Expression Assay in Breast Cancer



Recurrence Score < 11

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

Oncotype Dx incorporated into staging



Recurrence Score < 11

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

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

No upstaging based on a high recurrence score at this time

Genomic Profile for Pathologic Prognostic Staging

When Oncotype Dx Score is Less than 11…

And TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Notes:

1. Obtaining genomic profiles is NOT required for assigning Pathological Prognostic Stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx® test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned Pathological Prognostic Stage Group IA.
2. If OncotypeDx® is not performed, or if it is performed and the OncotypeDx® score is not available, or is 11 or greater for patients with T1–2 N0 M0 HER2–negative, ER-positive cancer, then the Prognostic Stage Group is assigned based on the anatomic and biomarker categories shown above.
3. OncotypeDx® is the only multigene panel included to classify Pathologic Prognostic Stage because prospective Level I data supports this use for patients with a score less than 11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to Prognostic Stage Groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

ONLY for T1/T2 ER+, HER2-, Node Negative disease

What about the other multigene assays?

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

Expect Updates

Validation of the new Staging

JAMA Oncology | Original Investigation

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

Anna Weiss, MD; Mariana Chavez-MacGregor, MD, MSc; Daphne Y. Lichtenzutajn, MS; Min Yi, MD, PhD; Audree Tadros, MD; Gabriel N. Hortobagyi, MD; Sharon H. Giordano, MD, MPH; Kelly K. Hunt, MD; Elizabeth A. Mittendorf, MD, PhD JAMA Oncol. 2018;4(2):203-209.

The University of Texas MD Anderson Cancer Center (n = 3327, years of treatment 2007-2013, median follow-up of 5 years)

California Cancer Registry (n = 54,727, years of treatment 2005-2009, median follow-up of 7 years).

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

Revisions…already

Mittendorf E.A., Ballman K.V., McCall L.M., et al: Evaluation of the stage IB designation of the American Joint Committee on Cancer staging system in breast cancer. J Clin Oncol 2015; 33: pp. 1119-1127

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

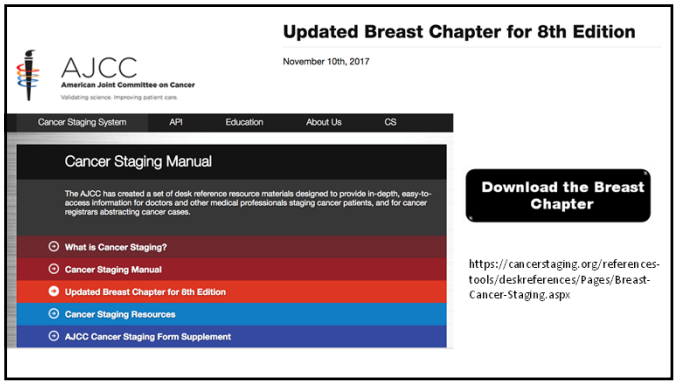
Revisions…already

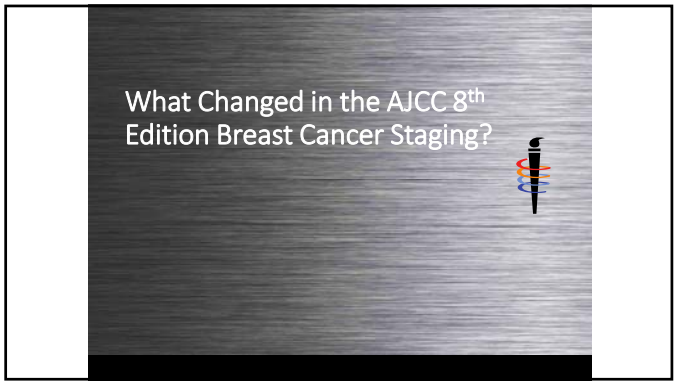
Cardoso F., Bogaerts J., et al: 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016; 375: pp. 717-729

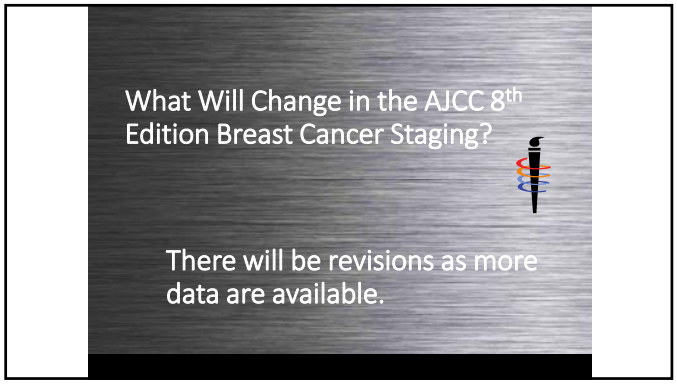
- Additional data available regarding the use of multigene molecular profiling.
  - MINDACT trial was published to provide Level I evidence for MammaPrint
  - 8th edition has still not adopted MammaPrint in the staging.
  - Could not calculate clinical risk of recurrence similar to MINDACT trial as they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

The Bottom Line

The application of the prognostic stages is more complicated but it more accurately predicts outcome


Updated Breast Chapter for 8th Edition
November 10th, 2017
AJCC
American Joint Committee on Cancer
Validating science. Improving patient care.
Cancer Staging System
API
Education
About Us
CS
Cancer Staging Manual
The AJCC has created a set of desk reference resource materials designed to provide in-depth, easy-to-access information for doctors and other medical professionals staging cancer patients, and for cancer registrars abstracting cancer cases.
What is Cancer Staging?
Cancer Staging Manual
Updated Breast Chapter for 8th Edition
Cancer Staging Resources
AJCC Cancer Staging Form Supplement
Download the Breast Chapter
https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx


What Changed in the AJCC 8th Edition Breast Cancer Staging?


What Will Change in the AJCC 8th Edition Breast Cancer Staging?
There will be revisions as more data are available.