The New AJCC 8th Edition Breast Cancer Staging

Prognostic Stage Groups & What They Mean

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Disclosures –

My husband is head of translational medicine for the New Indication and Discovery Unit at Novartis.

I will not be talking about any Novartis products.
Why is Cancer Staging Important?

For individual patients:

Aids in estimating prognosis (survival) for individual patients

Breast cancer

Stage 0 (DCIS) >97% 20 year survival
Stage IV (metastatic) <10% 20 year survival

Guides choices for local and systemic treatment
Why is Cancer Staging Important?

For the health care system and research:

Organizes patients into similar groups

Essential for clinical studies, research studies, and epidemiologic studies

Important for comparisons by location (country, state, institution), patient groups, and over time

Therefore, it is essential to stage cancer consistently and accurately for optimal cancer care.
A historical interlude . . .

Pierre Denoix, MD (1912-1990)
L’Institut Gustave Roussy

He pioneered the Tumor Nodes Metastasis classification of cancers.

TNM was adopted by the Union for International Cancer Control (UICC) in the 1950’s.

TNM was adopted by the American Joint Committee on Cancer (AJCC) and issued their first edition in 1977.

Although there were refinements, breast cancer staging remained substantially the same over ~60 years.
Metastasis (distant)

~5% of women with breast cancer have distant metastases at the time of first diagnosis in the US.

Defines Stage IV.

Most important prognostic factor for these women.
N odes –

Second most important prognostic factor -

60% of women with palpable carcinomas have positive nodes.

15% of women with nonpalpable carcinomas have positive nodes.
**Tumor**

**Tis** Carcinoma in situ

**T1mic to T3** Size of invasive carcinoma

**T4** Skin and/or chest wall involvement or inflammatory carcinoma.

![Tumor Diagrams](image)
T, N, and M are combined to create 5 stages:

<table>
<thead>
<tr>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
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<tbody>
<tr>
<td>Stage 0</td>
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<td>Stage IA</td>
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<td>Stage IIIB</td>
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<td>Stage IIIIC</td>
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<td>Stage IV</td>
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</table>
Anatomic stage is highly predictive of survival.
Originally published in October 2016.

A revised version of the Breast Chapter was released on-line on November 10, 2017.

There are substantial changes compared to the original chapter.

Only use the updated chapter provided on the AJCC website:

https://cancerstaging.org/About/news/Pages/Updated-Breast-Chapter-for-8th-Edition.aspx
AJCC Breast Cancer Stage – 8th Edition

7th vs 8th edition clarifications and changes –

Clarifications:

“m” modifier

pMX

Changes:

LCIS no longer classified as Tis

Prognostic stage groups (UICC did not adopt this change and continues to use anatomic staging)

The “m” modifier is used to identify patients with multiple invasive cancers.

It has different uses depending on whether or not the patient has received neoadjuvant (pre-surgical) therapy.
In the absence of treatment, “m” is only used when multiple cancers are identified macroscopically (on gross examination) and confirmed microscopically.

The presence of multiple separate cancers is usually evident by breast imaging and/or gross examination.

Additional foci of invasive cancer only detected microscopically do not qualify for the “m” designation.

The size for T classification is the largest contiguous focus of carcinoma – the sizes of multiple cancers are not added.
Multiple Invasive Cancers – Types (no prior treatment)

Extensive DCIS with multiple foci of invasion – if grossly evident, use “m”.

Carcinoma with surrounding satellite foci – usually not grossly evident and are part of the main carcinoma.

Carcinoma with extensive lymphovascular invasion with small foci of invasion – usually not grossly evident.

Two biologically separate carcinomas – usually detected by imaging or palpation.

In this case, two close but clearly separate cancers are seen by imaging and were marked by two separate wires for the surgeon.

Grossly and microscopically, the cancers are separate and this would be indicated by the modifier “m”.

Smaller foci not evident by imaging or grossly (e.g. the focus marked by the arrow) would not qualify for the modifier “m” on their own.
After treatment, if there is an incomplete response, multiple foci of invasive carcinoma may be present within a tumor bed.

Minimal response - slightly smaller after treatment

Moderate/marked response – Multiple foci of invasive carcinoma in the tumor bed

Complete response - No residual invasive carcinoma
In this tumor bed (marked by black arrows), there are two residual foci of invasive carcinoma (marked by blue arrows).

The presence of multiple foci of invasive carcinoma in a tumor bed is indicated by the use of the “m” modifier.

These foci are typically seen microscopically and are not evident on gross examination.
AJCC Breast Cancer Stage – 8th Edition

7th vs 8th edition clarifications and changes –

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In the 7th edition, the designation MX was eliminated for the following reasons:

A “p” designation for T or N supersedes a “c” designation (pathologic classification is more important than clinical classification).

However, a cM1 or cM0 designation supersedes pMX.

The different rules for T and N compared to M has been confusing to tumor registrars.

Therefore, because pMX does not add information and can be confusing, it should not be used.
AJCC Breast Cancer Stage – 8th Edition

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LCIS (including both “classical” and “non-classical”/pleomorphic) types is no longer classified as Tis.

The explanation provided is:

“LCIS is a benign condition and is not treated as a carcinoma. It is properly considered a proliferative disease with associated risk for developing breast cancer in the future and, therefore, is no longer included in this cancer staging system.”
It is important to understand that this change is not based on any new understanding of the biology of LCIS.

LCIS is a clonal population of cells.

LCIS increases the risk of developing invasive cancer.

In some cases, LCIS is a true precursor of invasive cancer and shares common mutations.

However, because the location of LCIS is not a good predictor of the site of a subsequent invasive carcinoma, treatment is generally increased surveillance, chemoprevention with endocrine treatment, and only rarely surgery (bilateral prophylactic mastectomy).
The current recommendations for the treatment of LCIS are based on studies of the “classical” type of LCIS:

Nuclei are not high grade.

There is no necrosis.

~100% are estrogen receptor positive.

~100% are HER2 negative.

Almost all are detected as incidental findings in biopsies for other lesions.
Less is known about rare “non-classical” types of LCIS:

Nuclei can be high grade ("pleomorphic").

Some are estrogen receptor negative.

Some are HER2 positive.

There can be extensive central necrosis.

Some are detected as mammographic calcifications or small masses.

In the past, these cases were likely classified and treated as DCIS.
The optimal treatment for non-classical forms of LCIS is currently unknown and will be difficult to study due to the rarity of this lesion.

Unfortunately, excluding all forms of LCIS from databases may be premature, as continued documentation of these lesions could provide data on outcomes that would help guide management in the future.
For example -

In the National Cancer Database (NCDB) (2005-2015) there were 4,674 cases of LCIS for which nuclear grade was provided.

If the nuclear grade was low, <5% of patients received radiation.

If the nuclear grade was high, >18% of patients received radiation.

If data on LCIS continued to be collected, more information on treatment and outcomes would be available (issue for 9th edition?).
AJCC Breast Cancer Stage – 8th Edition

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Prognostic stage groups

In addition to stage, prognosis also depends on the biologic type of breast cancer as determined by grade, hormone receptor expression, and HER2 expression.

**Anatomic Stage**
- **Tumor**
- **Node**
- **Metastasis**

**Biologic Type**
- **Grade**
- **ER & PR**
- **HER2**
Breast Cancer – Classification into Biologic Types

All breast cancers can be divided into 3 major biologic (also called “molecular” or “intrinsic”) types based on expression of estrogen receptor (ER) and HER2:

“Luminal Cancer”* - ER positive/HER2 negative

“Triple Negative Breast Cancer” (TNBC)* - ER negative/HER2 negative

“HER2 Cancer”* - ER positive or negative/HER2 positive

The expression (or non-expression) of ER and HER2 is highly correlated with the additional expression of dozens to hundreds of other genes as well as specific types of DNA alterations.

* These are useful terms to refer to these 3 groups of cancers, although they are not used as diagnostic terminology.
# Biologic Types of Cancer

<table>
<thead>
<tr>
<th>Features</th>
<th>Luminal ER positive/HER2 negative</th>
<th>HER2* HER2 positive</th>
<th>TNBC ER/HER2 negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of cancers</td>
<td>Grade 1 &amp; 2: 40-55% (“luminal A”)</td>
<td>Grade 3: 10% (“luminal B”)</td>
<td>~20%</td>
</tr>
<tr>
<td>Common mutations</td>
<td>$PIK3CA$ (~45%) $TP53$ (~10%)</td>
<td>$PIK3CA$ (~30%) $TP53$ (~30%)</td>
<td>$PIK3CA$ (~40%) $TP53$ (~75%)</td>
</tr>
<tr>
<td>Special histologic types</td>
<td>Tubular, lobular, mucinous, papillary</td>
<td>Lobular</td>
<td>Some apocrine, some micropapillary</td>
</tr>
<tr>
<td>Patients likely to have these cancers</td>
<td>Older women, men $BRCA2$ mutation carriers</td>
<td>$TP53$ mutation carriers</td>
<td>$BRCA1$ mutation carriers</td>
</tr>
<tr>
<td>Complete response to chemotherapy</td>
<td>&lt;10%</td>
<td>10%</td>
<td>ER positive (~30%) ER negative (~60%)</td>
</tr>
<tr>
<td>Usual treatment</td>
<td>Endocrine therapy</td>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Endocrine therapy</td>
<td>HER2 targeted therapy</td>
<td>HER2 targeted therapy</td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>Low rate over many years</td>
<td>Early peak, late recurrence possible</td>
<td>Early and late peaks</td>
</tr>
<tr>
<td>Metastatic pattern</td>
<td>Bone (~50%) more common than viscera or brain</td>
<td>Viscera and brain &gt; bone</td>
<td>Viscera and brain &gt; bone</td>
</tr>
</tbody>
</table>

* In some classification systems, ER positive/HER2 positive cancers are called “luminal B” cancers.

** Some rare types of TNBC have a favorable prognosis – adenoid cystic carcinoma, secretory carcinoma, low grade adenosquamous carcinoma.
Luminal (black) – low rate, but over decades. Grade 3 (blue) show an early peak.

TNBC (red) – majority recur in first 5 years. Recurrences after ~8 years are very rare.

HER2 – has early and late peaks of recurrence:

ER positive (purple) – small early peak and larger late peak.

ER negative (green) – large early peak and smaller late peak.

Luminal: ~50% to bone – long term survival with distant metastasis is possible.

HER2 and TNBC: Only ~25% to bone. Majority are to visceral sites and brain. Long term survival with distant metastasis is unusual.
The likelihood, timing, and location of metastatic disease results in different patterns of survival.

- **Luminal – grade 1 and 2**
- **HER2 – ER positive**
- **Luminal – grade 3**
- **HER2 – ER negative**
- **Triple negative**

*Parise, CA, Caggiano, V. Breast cancer survival defined by the ER/PR/HER2 subtypes and a surrogate classification according to tumor grade and immunohistochemical biomarkers. J Cancer Epidem 2014.*
Conundrum – How to Combine Biologic Type and Anatomic Stage?

**Prognosis – Biologic Type**

- Luminal A
- Luminal B/HER2-
- HER2 overexpressing
- Luminal B/HER2+

**Prognosis – Anatomic Stage**
Within each anatomic stage, the actual survival varies with the biologic type of breast cancer.
The new Prognostic Stage Groups were determined using National Cancer Database information.

Groups of patients were organized according to anatomic stage (T, N, M) and biologic type of cancer (grade, ER, PR, and HER2 expression). For example, all patients with stage III TNBC would form a group.

The survival of each group was compared to the survival of all patients having the same anatomic stage at 3 years.
In general, some cancers with favorable biology were moved to a prognostic stage group lower than the anatomic stage.

If the survival of a group was above the 95% confidence interval of the assigned anatomic stage at 3 years, this group was moved to a lower prognostic stage group.

In general, some cancers with favorable biology were moved to a prognostic stage group lower than the anatomic stage.
In general, some cancers with less favorable biology are moved to a prognostic stage group higher than the anatomic stage.

If the survival of a group was below the 95% confidence interval of the assigned anatomic stage at 3 years, this group was moved to a higher prognostic stage group.
~1/3 of patients are assigned a different prognostic stage group compared to anatomic stage.

Prognostic stage groups are a mixture of multiple biologic types of cancer and multiple anatomic stages.

Of note, biologic type (grade, ER, PR, and HER2) is not included for stage 0 (DCIS) or stage IV (distant metastases).
The AJCC committee created two types of Prognostic Stage Groups that are used for different groups of patients:

**Pathological Prognostic Stage Group**

**Clinical Prognostic Stage Group**
Pathological Prognostic Stage Group:

Survival information was based on the subset of patients who underwent definitive surgery first prior to receiving other types of treatment. Pathological Prognostic Stage Group is only used for these patients. Does not include patients undergoing neoadjuvant treatment, patients who have not yet undergone surgery, and patients who are not surgical candidates.

T and N are determined by pathologic evaluation.

The GenomicHealth Recurrence score can be included if known and <11. If the patient has a T1 or T2 cancer and is N0, stage IA is assigned.

A recurrence score is not necessary in order to stage a cancer. Other multigene assays have not yet been approved for use in staging, although the implication is that some may be approved in the future.
Clinical Prognostic Stage Group:

Survival information was based on all patients. This classification is used for patients who cannot be assigned a Pathological Prognostic Stage Group:

- Patients who have not undergone surgery yet
- Patients who received neoadjuvant treatment
- Patients who are not surgical candidates

T and N can be determined clinically or pathologically.

The GenomicHealth Recurrence score is not included because pathologic T and N are not known with certainty.
Clinical Prognostic Stage Group:

Compared to Pathological Prognostic Stage Groups, 66% of patients have the same stage, 30% have a higher stage, and 4% have a lower stage.

The higher-stage assignments are due to the patient population used to calculate survival including patients with less favorable survival –

Patients who receive neoadjuvant therapy tend to have larger and more advanced cancers of unfavorable biologic types.

Patients who do not undergo surgery due to locally advanced disease or co-morbid factors are at greater risk for death.
It is important to note that the new Clinical Prognostic Stage Group is different than 7th edition clinical staging.

In the 1st though 7th editions, a clinical stage was the best approximation of the anatomic stage based on available information when pT and/or pN were not available.

The survival of patients with the same clinical and anatomic stage was expected to be the same if the clinical classification was accurate.

In contrast, the Clinical Prognostic Stage Group includes information about the biologic type of cancer and will be different than the corresponding anatomic stage in about 1/3 of cases.

It is also different from the Pathological Prognostic Stage Group as it includes patients of poorer prognosis.
31% of patients were upstaged and 21% were downstaged.

The prognostic stage provided a better separation of patient groups.

Recognizes importance of biologic type in determining prognosis.

Recognizes the importance of grade, ER, PR, and HER2 in determining biologic type.

Should provide better estimates of survival for patients at 3-5 years.
More complicated than anatomic stage . . .
It will likely be challenging for medical oncologists and tumor registrars to assign stage. Phone apps are available to help assign stage.

**Anatomic Stage Groups**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>T1*</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T0</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1*</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0</td>
<td>N1**</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1*</td>
<td>N1**</td>
<td>M0</td>
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<td>Stage IIIA</td>
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<td>N0</td>
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<tr>
<td>Stage IIIC</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IIIIB</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIIC</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
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**Prognostic Stage Groups**

<table>
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<tr>
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A “prognostic stage group” is a combination of cancers of various biologic types and various anatomic stages that have the same survival at 3-5 years.

However, because biologic types of cancer have different patterns of recurrence, metastatic pattern, and survival after metastasis, it is likely that these groups will not have similar survival over longer follow-up.

For example, HER2/ER positive cancers have a peak in recurrence at 6-8 years and thus survival may diverge for these patients with longer follow-up.
Stage IV is not included in Prognostic Stage Groups.

There are marked differences in survival for biologic types of cancer.

ER positive – often to bone, slow growing, growth inhibited by endocrine therapy.

ER negative – often to viscera, rapidly growing, currently therapeutic options are limited.

Bioscore system: Assigns points for anatomic stage, ER, HER2 and nuclear grade for a possible range from 0 to 7. This system shares the disadvantage of mixing biologic types of cancer and anatomic stage.

Survival according to biologic type: Separate survival curves for anatomic stage could be generated for each biologic type.

Anatomic Stage According to 3 Biologic Types

This data is prior to HER2 targeted therapy.

The AJCC 8th edition affirms that both biologic type of cancer and anatomic stage are important determinants of survival.

Pathologists play a key role in determining both biologic type and stage.

Continue to report T and N.

Only report M in the rare case for which pM1 can be assigned.
Thank you for your attention!