Eighth Edition AJCC TNM: A Breast Cancer Staging Update

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Disclosure

I do not have any relevant financial relationship(s) with any commercial interest that pertains to the content of my presentation.
The AJCC Cancer Staging Manual, Eighth Edition is dedicated to all **CANCER REGISTRARS** in recognition of their:

- education and unique commitment to the recording and maintenance of data that are so vital for the care of the cancer patient;

- professionalism in the collection of factors that are fundamental to sustaining local, state and national cancer registries;

- dedication to the cataloging of information crucial to cancer research;

- leadership, support and promulgation of the principles of cancer staging;

- AND THEIR POSITIVE IMPACT ON CANCER PATIENT OUTCOMES
AJCC Vision

The Transition from Population Based to a more “Personalized” Approach

AJCC/UICC TNM Stage (Basic Classification)

AJCC Stage (Advanced Clinical Relevance)

AJCC “Personalized” (Advanced Clinical + Personalized Relevance)

Population Survival Outcomes

Personalized Survival Outcomes
EXAMPLES OF PREDICTIVE TESTS

- HER2: Predict response to HER2 targeted therapy (breast cancer)
- Estrogen receptor: Predict response to endocrine therapy (breast cancer)
- EGFR mutation: Predict response or resistance to EGFR inhibitor TKI therapy (lung adenocarcinoma)
- ALK or ROS1 gene rearrangement: Predict response to treatment with Crizotinib (lung adenocarcinoma)
- PD-L1: Predict response to treatment with checkpoint inhibitors (multiple cancer types)
- BRAF V600E: Predict response to treatment with vemurafenib (melanoma)
- RAS mutation: Resistance to anti-EGFR treatment (colon cancer)
- KIT activating mutation: Predict response to imatinib/sunitinib (GIST, melanoma)
- Oncotype Dx: Predict response to chemotherapy (ER+ breast cancer), this test is both prognostic and predictive
Tumor Related Prognostic Factors

- Pathology
  - morphology, grade, growth pattern,
- Anatomic tumor extent
  - TNM, tumor bulk, number, tumor markers
- Tumor biology
  - proliferation indices, molecular markers, genetic markers
- Symptoms
- Performance status
## Traditional Prognostic Parameters for Human Mammary Carcinoma

<table>
<thead>
<tr>
<th>Tumor Factors</th>
<th>Host Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node status</td>
<td>Age</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Menopausal status</td>
</tr>
<tr>
<td>Histologic/nuclear grade</td>
<td>Familial history</td>
</tr>
<tr>
<td>Lymphatic/vascular invasion</td>
<td>Previous neoplastic disease</td>
</tr>
<tr>
<td>Pathologic stage (TNM)</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Steroid receptor status (ER/PR)</td>
<td>Host inflammatory response</td>
</tr>
<tr>
<td>DNA content (ploidy, S-phase)</td>
<td>Nutrition</td>
</tr>
<tr>
<td>EIC (<em>in situ</em>)</td>
<td>Prior chemotherapy</td>
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<td></td>
<td>Prior radiation</td>
</tr>
</tbody>
</table>
**Summary: Breast**

- **Axillary nodes (routine H&E or IHC)**
  - **N1** 1 to 3
  - **N2** 4 to 9
  - **N3** 10+
- **Intraclavicular nodes are N3**
- **Supraclavicular nodes reclassified as N3**
Breast - Additional Descriptors

“sn” suffix: Based only on sentinel lymph node dissection without an axillary node dissection
eg. pN0(sn) or pN1(sn)

“f” suffix: FNA or core biopsy of node
Challenges for Breast Cancer Staging for the 8th Edition

- Lymph node ratio
- Effect of multifocality and multicentricity on staging and survival
- Review of sub-classification of T4
- Addition of prognostic factors - ER, PR, HER/2 and grade
- What about LCIS?
Isolated Tumor Cells (ITC) (single tumor cells or small clusters) (≤ 0.2 mm) VS Micrometastases (≤ 0.2 cm in greatest dimension)
**Isolated Tumor Cells and Micrometastasis**

**pNO:** No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITC)

**pNO(i-):** No regional lymph node metastasis histologically, negative morphologic findings for ITC

**pNO(i+):** No regional lymph node metastasis histologically, positive morphologic findings for ITC

Armando E. Giuliano, MD; James L. Connolly, MD; Stephen B. Edge, MD; Elizabeth A. Mittendorf, MD, PhD; Hope S. Rugo, MD; Lawrence J. Slinkin, MD; Donald L. Weaver, MD; David J. Winchester, MD; Gabriel N. Hortobagyi, MD

ABSTRACT: The revision of the eighth edition of the primary tumor, lymph node, and metastasis (TNM) classification of the American Joint Commission of Cancer (AJCC) for breast cancer was determined by a multidisciplinary team of breast cancer experts. The panel recognized the 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. AJCC levels of evidence and guidelines for all tumor types were followed as much as possible. The panel felt that, to maintain worldwide value, the tumor staging system should remain based on TNM anatomic factors. However, the recognition of the prognostic influence of grade, hormone receptor expression, and HER2 amplification mandated their inclusion into the staging system. The value of commercially available gene-based assays was acknowledged and prognostic input added. Tumor biomarkers and low-OncoType DX recurrence scores can alter prognosis and stage these updates are expected to provide additional precision and flexibility to the staging system and were based on the extent of published information and analysis of large, as yet unpublished databases. The eighth edition of the AJCC TNM staging system, thus, provides a flexible platform for prognostic classification based on traditional anatomic factors, which can be modified and enhanced using patient biomarkers and multifactorial prognostic panel data. The eighth edition remains the worldwide basis for breast cancer staging and will incorporate future online updates to remain timely and relevant. CA Cancer J Clin 2017;67:290-303. © 2017 American Cancer Society.

Keywords: biomarkers, distant metastases, ductal carcinoma in situ, estrogen receptor, human epidermal growth factor 1 (HER1), infiltrating ductal carcinoma, infiltrating lobular carcinoma, lobular carcinoma in situ, lymph node metastases, neoadjuvant chemotherapy

Practical Implications for Continuing Education

> Immunohistochemically detected tumor markers that are known to have great practical treatment importance are now incorporated into the staging system to refine prognosis.

> The eighth edition of the staging system also uses gene expression assays when available to downstage some estrogen receptor-positive, lymph node-negative tumors.

> Lobular carcinoma in situ is removed from the staging system because it is not a malignancy but a risk factor. It is no longer considered Tis.
Summary

- Most significant change is the addition of Prognostic Stage Groups
  - Addition of grade, ER, PR and HER2
  - Use of multigene panels in specific situations

- Chapter text provides important information
  - Clinical, pathological, and post neoadjuvant therapy staging
  - Determining tumor size and nodal involvement size
  - General information and guidance for staging
  - Additional factors recommended for clinical care
Summary of Changes – Breast Cancer

- Three stage group options:

- Anatomic Stage – Use T, N, M only and for use where biomarkers (grade, ER, PR, HER2) not available

- Clinical Prognostic Stage – History, PE, imaging (not required), relevant biopsies along with T, N, M, tumor grade, HER2, ER, and PR

- Pathological Prognostic Stage--- Surgical resection as initial treatment before systemic or radiation treatment and based on all clinical information, biomarker data and resected tissue. Results of multigene panels (Oncotype Dx, Breast Cancer Index, EndoPredict, Mammaprint, PAM50) testing may be included, but are not required for staging
Selecting Appropriate Stage Group Table

- Anatomic Stage Groups
  - Based solely on anatomic extent of cancer
  - Defined only by T, N, and M categories

- Appropriate for regions of world where biomarkers cannot be routinely obtained

- Not appropriate where biomarkers are used for patient care
## Anatomical TNM-8th Edition

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<th>IB</th>
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BREAST CANCER
SURVIVAL ACCORDING TO AJCC STAGE

SURVIVAL RATE

YEARS AFTER DIAGNOSIS

STAGE 0
STAGE 1
STAGE IIA
STAGE IIB
STAGE IIIA
STAGE IIIB
STAGE IV
Selecting Appropriate Stage Group Table

- Prognostic Stage Groups
  - Based on populations of breast cancer patients offered and mostly treated with endocrine and/or chemotherapy and/or anti-HER2 therapy
  - Includes T, N, M, tumor grade, ER, PR, and HER2
  - Includes multi-gene panels

- Preferred for patient care

- Must be used for reporting of all cancer patients in the United States
Assessment of T Category

- **Lobular carcinoma in situ removed from Tis category**
  - Removed because benign entity with an associated risk for developing cancer
  - Pleomorphic LCIS – also not included in pTis category due to insufficient evidence for definitive treatment recommendations

- **Rounding tumor size to the nearest mm**
  - Exception: Tumors >1.0 – 1.5 mm are rounded up to 2 mm (pT1a)
  - Tumors ≤ 1.0 mm are microinvasive (pT1mi)

- **T4b satellite tumor nodules**
  - Must be separate from primary tumor
  - Must be macroscopically identified
  - Those identified on microscopic exam only do not qualify for T4b
T4 Category-Breast
Assessment of T Category

- Staging multiple tumors in the same breast
  - T category is based on the single largest tumor focus
  - Do not include satellite foci when measuring tumor size
  - Size of the largest tumor focus is used for T classification; tumor sizes are not added

- Staging multiple tumors if bilateral
  - Stage each side separately
Assessment of N Category

- cN0 assigned when
  - Evaluation of nodes is possible
  - Physical exam or imaging is negative for nodal involvement

- cNX only valid if nodal basin removed
  - Cannot be examined by imaging or physical exam

- Criteria for microscopic measurement of node metastases
  - Largest contiguous tumor deposit used for pN
  - Do not use dimension of area containing several or multiple tumor deposits
Assessment of N Category

- Metastases to lymph nodes from the following sites are regional nodes and categorized as pN: Axillary, intramammary, interpectoral, internal mammary and supraclavicular

- Metastases to any other lymph nodes including cervical or contralateral internal mammary or contralateral axillary lymph nodes are categorized as pM1

- Nodes with isolated tumor cells (ITCs) only are not included in the overall count of positive nodes

  Example: 10 nodes: 2 with macrometastases and 2 with ITCs

  Number of positive nodes is 2/10 = pN1a (not 4/10)
Assessment of M Category

- pM0 and MX are not valid categories

- Valid M categories for clinical and pathological staging
  - cM0 – no signs or symptoms of distant metastases
  - cM1 – signs, symptoms, or imaging evidence of distant metastases
  - pM1 – microscopic confirmation of distant metastases
Post Neoadjuvant Therapy Staging

- Assigned after neoadjuvant therapy and surgical resection

- ypT category
  - Largest focus of residual tumor
  - Treatment-related fibrosis near invasive tumor NOT used
  - Multiple foci of residual tumor, use (m) modifier

- ypN category
  - Largest focus of residual tumor in nodes
  - Treatment-related fibrosis near nodal tumor deposits NOT used

- M category
  - If M1 prior to therapy, remains M1 following neoadjuvant therapy
  - Regardless of observed response to therapy

- Pathological complete response (pCR), no residual invasive cancer
  - ypT0ypN0cM0 or ypTisN0 no stage group assigned
Biomarkers improved stratification of DSS by stage

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

- All invasive carcinomas should have the following determined by appropriate assays whenever possible:
  - Estrogen receptor (ER) status
  - Progesterone receptor (PR) status
  - Human epidermal growth factor receptor 2 (HER2) status – best scored by 2013 ASCO/CAP standards

- Modified Nottingham (Bloom Scarf Richardson) tumor grade should be documented

- Marker of proliferation is also recommended
  - Ki-67
  - Mitotic count
Grade

- All invasive breast cancer should be assigned histologic grade
  - Nottingham modification of SBR grading system recommended

- Nottingham grade determined by totaling scores for
  - Tubule formation
  - Nuclear pleomorphism
  - Mitotic count

- Grade table to equate SBR score of points to G1-G3

<table>
<thead>
<tr>
<th>G</th>
<th>G Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Low combined histologic grade (favorable); SBR score of 3–5 points</td>
</tr>
<tr>
<td>G2</td>
<td>Intermediate combined histologic grade (moderately favorable); SBR score of 6–7 points</td>
</tr>
<tr>
<td>G3</td>
<td>High combined histologic grade (unfavorable); BSR score of 8–9 points</td>
</tr>
</tbody>
</table>
ER and PR

- ER and PR expression measured primarily by IHC
- >1% of cells stained considered positive for ER-positive and PR-positive
- Multiple results always use positive results
  - If biopsy and resection specimens are tested, and one is positive, while the other is negative, then use the positive results to assign the stage group
HER2 Equivocal

- HER2 determined to be “equivocal”
  - By ISH (FISH or CISH) testing
  - Under the 2013 ASCO/CAP HER2 testing guidelines

- Categorize HER2 “equivocal” by ISH as HER2 “negative”
  - For assigning stage in Prognostic Stage Group Table
RECURRENCE SCORE-21 GENE PANEL

Proliferation
- Ki67
- STK15
- Survivin
- CCNB1 (cyclin B1)
- MYBL2

HER2
- GRB7
- HER2

Estrogen
- ER
- PGR
- BCL2
- SCUBE2

GSTM1

Invasion
- MMP11 (stromolysin 3)
- CTSL2 (cathepsin L2)

CD68

BAG1

Reference
- ACTB (β-actin)
- GAPDH
- RPLPO
- GUS
- TFRC
OUTCOMES of RECURRENCE SCORE
Multigene Panels

- Patients with
  - ER/PR-positive, HER2-negative, node-negative tumors
  - Size less than or equal to 5 cm (T1-2)
  - Combined with any of the following multigene panels
    - Oncotype Dx® recurrence score <11
    - Mammaprint® low-risk score
    - EndoPredict® low-risk score
    - PAM50® risk of recurrence score in low range
    - Breast Cancer Index in low-risk range
  - Stage IA: Are in same prognostic category as T1a-T1b N0 M0 with ER Positive, HER2 negative
Multigene Panels

- Although AJCC does not endorse any particular assay, at the time the manuscript was printed, there was Level 1 evidence available with 21-gene Oncotype Dx Recurrence score and none with any other assay.

- Results of MINDACT were published in NEJM August 2016
  - Offers Level 1 evidence

- Recommendations from ASCO
  - MammaPrint for clinical high-risk, hormone receptor-positive, HER2-negative, node-negative breast cancer to inform decisions on withholding chemotherapy
  - MammaPrint to help inform treatment decisions in clinical high-risk, early-stage breast cancer patients with 1 to 3 positive lymph nodes
### 3. AJCC 8th Edition (American Joint Committee on Cancer) Updates

The AJCC has included the use of molecular biomarkers or "Multigene Panels" as "Stage Modifiers". This marks the first time that genomic testing has been formally incorporated by the AJCC to help inform more accurate disease classification.

<table>
<thead>
<tr>
<th>Change</th>
<th>Details of Change</th>
<th>Proportion Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion of Multigene Panels (when available) as Stage Modifiers - MammaPrint</td>
<td>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 in the same prognostic category as T1a-T1b N0 M0 (Level II)</td>
<td>75% Low Risk³</td>
</tr>
<tr>
<td>Inclusion of Multigene Panels (when available) as Stage Modifiers - 21-Gene Recurrence Score</td>
<td>For patients with hormone receptor-positive, HER2-negative and lymph node-negative tumors, a <strong>21-gene recurrence score less than 11</strong>, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0 M0 and staged using the AJCC Prognostic Stage table as Stage I (Level I)</td>
<td>16% Low risk (RS&lt;11)⁶</td>
</tr>
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</table>
When Genomic Profiling Score (Oncotype Dx Score) is less than 11...

<table>
<thead>
<tr>
<th>And TNM is...</th>
<th>And Grade is...</th>
<th>And HER2 Status is...</th>
<th>And ER Status is...</th>
<th>And PR Status is...</th>
<th>Then the Pathological Prognostic Stage Group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 N0 M0</td>
<td>Any</td>
<td>Negative</td>
<td>Positive</td>
<td>Any</td>
<td>IA</td>
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<tr>
<td>T2 N0 M0</td>
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</table>

Obtaining genomic profiles is **NOT** required for assigning Pathological Prognostic Stage. However genomic profiles may be performed for use in determining appropriate treatment.

The AJCC Breast Expert Panel included one multigene panel in Pathological Prognostic Staging, but others may be equally useful for clinical decision making.

Inclusion in the staging system **does not imply AJCC recommendation** or endorsement of one multigene panel over any other for use in clinical care.
**Prognostic Group Staging**


<table>
<thead>
<tr>
<th>Traditional TNM Factors</th>
<th>Expanded Non-Anatomic Factors</th>
<th>The Prognostic Stage Group is…</th>
</tr>
</thead>
<tbody>
<tr>
<td>When T is…</td>
<td>When N is…</td>
<td>When M is…</td>
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<td>T3</td>
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Impact of New 8\textsuperscript{th} Edition Staging Manual in Early Stage Breast Cancer

“Compared to the [7\textsuperscript{th} 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 8\textsuperscript{th} Edition Cancer Staging Manual, page 616
Clinical Implications of the New Staging System

<table>
<thead>
<tr>
<th>TNM Groups</th>
<th>Anatomic Staging Groups</th>
<th>Pathologic Prognostic Staging Groups</th>
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</thead>
<tbody>
<tr>
<td>T1 N0 M0</td>
<td>IA</td>
<td>IA, IB</td>
</tr>
<tr>
<td>T1 N1 M0</td>
<td>IIA</td>
<td>IA, IB, 2A</td>
</tr>
<tr>
<td>T3 N0 M0</td>
<td>IIB</td>
<td>IA, IB, IIA, IIB, IIIA</td>
</tr>
<tr>
<td>T3 N2 M0</td>
<td>IIIA</td>
<td>IA, IB, IIA, IIB, IIIA</td>
</tr>
</tbody>
</table>
### 8th Edition: Patients Now Considered Stage IIIA

Some T1N1 and Node-negative Patients Are Now Included

<table>
<thead>
<tr>
<th>What the T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>And G is...</th>
<th>And HER2 status is...</th>
<th>And ER status is...</th>
<th>And PR status is...</th>
<th>The Prognostic Stage Group Is...</th>
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AJCC Vision

...and Where It Fits in the 8th Edition:

- Cancer Stage
- Definitions of TNM
- Prognostic Factors
- Clinical Trial Stratification
- Prognostic and Risk Assessment Models

Comprehensive Cancer Profile

Population

Personalized
Adjuvant! for Breast Cancer (Version 7.0)

**Patient Information**
- **Age:** 60
- **Comorbidity:** Minor Problems
- **ER Status:** Positive
- **Tumor Grade:** Grade 3
- **Tumor Size:** 2.1 - 3.0 cm
- **Positive Nodes:** 1 - 3
- **Calculate For:** Mortality
- **10 Year Risk:** 45 Prognostic

**Adjuvant Therapy Effectiveness**
- **Horm:** Aromatase Inhibitor for 5 yrs
- **Chemo:** 3rd Generation Regimens

**No additional therapy:**
- Green: 50.0 alive in 10 years.
- Red: 43.3 die of cancer.
- Blue: 6.7 die of other causes.

**With hormonal therapy:** Benefit = 10.8 alive.

**With chemotherapy:** Benefit = 13.8 alive.

**With combined therapy:** Benefit = 21.6 alive.

Print PDF
Online Help
Circulating Tumor DNA


Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

Sarah-Jane Dawson, F.R.A.C.P., Ph.D., Dana W.Y. Tsui, Ph.D.,
Muhammed Murtaza, M.B., B.S., Heather Biggs, M.A.,
Oscar M. Rueda, Ph.D., Suet-Feung Chin, Ph.D., Mark J. Dunning, Ph.D.,
Davina Gale, B.Sc., Tim Forshaw, Ph.D., Betania Mahler-Araujo, M.D.,
Sabrina Rajan, M.D., Sean Humphray, B.Sc., Jennifer Becq, Ph.D.,
David Halsall, M.R.C.Path., Ph.D., Matthew Wallis, M.B., Ch.B.,
David Bentley, D.Phil., Carlos Caldas, M.D., F.Med.Sci.,
and Nitzan Rosenfeld, Ph.D.

ABSTRACT

The management of metastatic breast cancer requires monitoring of the tumor burden to determine the response to treatment, and improved biomarkers are needed. Biomarkers such as cancer antigen 15-3 (CA 15-3) and circulating tumor cells have been widely studied. However, circulating cell-free DNA carrying tumor-specific alterations (circulating tumor DNA) has not been extensively investigated or compared with other circulating biomarkers in breast cancer.
The presence of CTCs in the blood or DTC clusters (≤ 0.2 mm) in the bone marrow or other nonregional nodal tissues does not constitute M1 in the absence of other apparent clinical and/or radiographic findings of metastases that correspond to pathological findings. Designate cM0(i+).
Eighth Edition TNM Staging Forms

48. Breast

4 Definitions of AJCC TNM

Always refer to the specific chapter for explicit instructions on clinical and pathological classification for this disease.

4.1 Definition of Primary Tumor (T)

<table>
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<tr>
<th>T Category</th>
<th>T Criteria</th>
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<tbody>
<tr>
<td>T0</td>
<td>Primary tumor cannot be assessed</td>
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<tr>
<td>T1</td>
<td>Tumor ≤ 2.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤ 1.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 1.0 cm but ≤ 2.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt; 2.0 cm but ≤ 5.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 5.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor of any size with direct extension to the chest wall and/or to the skin (extension or microscopic nodules)</td>
</tr>
<tr>
<td>T4</td>
<td>Extension to the chest wall or to the skin or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4</td>
</tr>
<tr>
<td>T4a</td>
<td>Ultrasonation and/or spiculated macroscopic satellite nodules and/or edema (including peau d’orange) of the skin that does not meet the criteria for inflammatory carcinoma</td>
</tr>
<tr>
<td>T4b</td>
<td>Both T4a and T4b are present</td>
</tr>
<tr>
<td>T4c</td>
<td>Inflammatory carcinoma (see &quot;Rules for Classification&quot;)</td>
</tr>
</tbody>
</table>

* Notes: Lobular carcinoma in situ (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

AJCC Cancer Staging Form Supplement

AJCC Cancer Staging Manual, Eighth Edition

Last updated 15 December 2017

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AJCC American Joint Committee on Cancer

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All organizations need to know that virtually no program or activity will perform effectively for a long time without modification and redesign. Eventually every activity becomes obsolete....

—Peter Drucker
American Joint Committee on Cancer

Virginia Cancer Registrars Association