Radiation Therapy after Neoadjuvant Chemotherapy for Breast Cancer
Outline

- Case presentation
- Why neoadjuvant chemo in breast cancer?
- Diagnosis and work-up
- Surgical management of breast and axilla
- Impact of subtype (ER/PR/HER2)
- RT indications
- Case discussion
53 yo F presented in March 2013 when she palpated a “golfball-sized lump” in her right upper outer breast.

Diagnostic mammogram and US on 3/21/13 demonstrated a 3.8 cm oval lesion with a microlobulated margin at the 10:00 position in the R UOQ. US-guided core needle biopsy revealed infiltrating ductal carcinoma, grade 3, ER/PR/Her-2 negative with no LVI.

Patient was referred to surgeon Dr. Parsons on 4/3/13 for consultation.

Staging work-up with MRI brain (4/13/13) for visual changes, MRI cervical spine (4/13/13) for neck pain, and PET (4/15/2013) confirmed only a hypermetabolic 2.7 x 2.5 cm right breast mass without evidence of nodal or metastatic disease.

SLNB done on 4/17/2013, however, revealed 1/3 nodes positive for micrometastatic disease.

Patient referred to med onc and underwent neoadjuvant chemo with adriamycin/cytoxan (4 cycles) followed by taxotere (completed 10/3/13).

She is currently scheduled to undergo bilateral mastectomies with axillary lymph node dissection and tissue expander placement on 11/4/2013.

She is here for discussion of potential PMRT.
Rationale for Neoadjuvant Chemotherapy

- Reduces tumor volume \(\rightarrow\) facilitate BCS
- Early systemic therapy (avoid post-op delay)
- In vivo assessment of systemic therapy effectiveness
- Improved tumor vascularity before surgery may allow for improved bioavailability..?
Randomized Trials - NSABP

- B-18 = Does AC administered pre-op improve DFS or OS (vs. post-op AC)?

- B-27 = Does adding Taxol pre-op to AC improve DFS or OS (vs. pre-op AC alone)?
NSABP B-18

- 1988-1993
- 1523 patients with T1-3No-1 "operable, palpable, non-fixed"
- Surgery = lumpectomy + ALND or mastectomy
  - Had to disclose surgery choice before chemo
- AC = q 3wk
- All BCS got breast RT
- No PMRT allowed
- Tamoxifen for all ≥50yo, and none <50 (no ER status)

Fisher B, JCO 1997; Wolmark N JNCI 2001; Rastogi P, JCO 2008
NSABP B-18

- pCR rate 13%
- 16-yr DFS 42% vs. 39% (NS)
  - DFS “conditional on being event free for 5 yrs” trend favored NEO (p=0.053)
- 16-yr OS both 55%

Rastogi P JCO 2008
Breast Conservation in B-18

- NEO had a greater frequency of lumpectomy
  - 67% vs 60%
  - “12% improvement”

- Largest benefit seen for tumors >5 cm
  - 22% vs. 8%
  - “175% improvement”

Fisher B et al. JCO 1997
NSABP B-27

- 1995-2000
- 2353 women, only palpable disease allowed (breast or axilla); T1-3N0-1
  - Except <2cm with N0
- 3-arms →
- Surgery = lumpectomy + ALDN or mastectomy
  - ~50% underwent mastectomy
- PMRT again not permitted.
- All pts (regardless of age) received tamoxifen x 5 yrs regardless of ER/PR status.

NSABP B-27

- pCR rate AC* 13% vs. ACT 26% (SS)
  - *AC→S and AC→S→T
  - Having pCR significant predictor for DFS and OS

- DFS 5-year 68-71% (NS); 8-year 59-62% (NS)

- OS 5-year 82-83% (NS); 8-year 74-75% (NS)

Rastogi P, JCO 2008
**Women <50yo**

*Trends favored preop in women <50yo:*

**DFS:**
HR = 0.85, P = 0.09 →

**OS:**
HR = 0.81, P = 0.06 →

Rastogi P, JCO 2008
Work-up per NCCN (3.2015)

Preoperative Systemic Therapy Guideline

CLINICAL STAGE

WORKUP

Stage IIA
T2, N0, M0
- History and physical exam
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Diagnostic bilateral mammogram; ultrasound as necessary
- Pathology review
- Determination of tumor ER/PR status and HER2 status
- Genetic counseling if patient is high risk for hereditary breast cancer
- Breast MRI (optional), with special consideration for mammographically occult tumors
- Fertility counseling if premenopausal

Stage IIB
T2, N1, M0
T3, N0, M0

Stage IIIA
T3, N1, M0

and

Fulfills criteria for breast-conserving surgery except for tumor size

Consider systemic staging (particularly if signs and symptoms are present):
- Chest diagnostic CT
- Abdominal ± pelvic diagnostic CT or MRI
- Bone scan or sodium fluoride PET/CT (category 2B)
- FDG PET/CT (optional, category 2B)

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The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast.
[http://www.cap.org](http://www.cap.org)

See Principles of HER2 Testing (BINV-A).

See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

See Principles of Dedicated Breast MRI Testing (BINV-B).

See Fertility and Birth Control (BINV-C).

Routine systemic staging is not indicated for early breast cancer in the absence of symptoms.

If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.

FDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

In cases where breast-conserving surgery may not be possible but patient will need chemotherapy, neoadjuvant treatment remains an acceptable option.
For patients with clinically or radiographically positive lymph nodes, biopsy is indicated.

- If biopsy+, ALND is recommended
- If biopsy-, SLN is acceptable
Marking of sampled axillary nodes with a tattoo or clip should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery.

Among patients shown to be node-positive prior to neoadjuvant systemic therapy, SLNB has a >10% false-negative rate when performed after neoadjuvant systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.
Is ALND really needed for all cN+?

- **Rationale:**
  - >40% of cN1 become ypNo (properly selected by tumor subtype and era of targeted therapy)
  - ALND is morbid
  - B-27 retrospectively calculated FNR 10.7% in cNo-1 with SLNB

- **ACOSOG Z1070 enrolled...687 patients with cTo-4N1-M0 with biopsy-proven nodal disease**

- **Prospective observational** phase II to evaluate accuracy of SLNB (≥2 nodes) after NAC in patients with cN+

- pCR in NODES → 39%

- For cN1, false negative rate on SLNB was 12.6%

*Boughey et al JAMA 2013; Boughey et al JCO 2015*
Axillary ultrasound post-chemo

- Pre-specified **secondary endpoint** in ACOSOG Z1070
  - Images taken in all patients, archived, reviewed by central radiologist blinded to other imaging and final path
  - FNR for ultrasound alone was 15%

*Boughey et al JCO 2015*
Combining axillary US and SLNB post-chemo

Above the pre-set 10% threshold...

Fig 2. Comparison of false-negative rates (FNRs) when using (A) sentinel lymph node (SLN) surgery irrespective of axillary ultrasound (AUS) imaging findings or (B) using AUS imaging results for selective use of SLN surgery. The study participants from the American College of Surgeons Oncology Group Z1071 trial were used with the observed rates in our study. ALND, axillary lymph node dissection.

Boughey et al JCO 2015
Ongoing Alliance A11202 trial

Clinical T1–T3 N1 M0 breast cancer

NACT

Breast-conserving surgery or mastectomy and sentinel lymph-node surgery

SLN negative

Randomization

ALND plus breast/chest wall and nodal XRT (without XRT to dissected axilla)

SLN positive

No further axillary surgery, but breast/chest wall and nodal XRT
SENTINA Trial

- Repeat SLNB only 60% sensitive, so this is not recommended.

SENTINA Trial [9]. The SENTINA trial was designed to evaluate the relationship of sentinel lymph node dissection in patients who received neoadjuvant chemotherapy; the study arms are depicted below.
Biological heterogeneity!

Tumor Subtypes

- Luminal A: ER+ and/or PR+, HER2-, grade 1-2
- Luminal B/HER2-: ER+ and/or PR+, HER2-, grade 3
- Luminal B/HER2+: ER+ and/or PR+, HER2+, all grades
- HER2+ (non-luminal): ER-/PR-/HER2+, all grades
- **Triple negative** (TNBC) = ER-/PR-/HER2-, all grades

Von Minckwitz et al. JCO 2012.
Impact of subtype on pCR rate

- Meta-analysis of 30 studies including 11,695
  - IQR 2001-2005
- pCR correlated with tumor subtype:
  - 8.3% ER+/HER2-
  - 18.7% ER+/HER2+
  - 38.9% ER-/HER2+ ➔ significantly greater than TNBC, though very similar when HER2 directed therapy excluded
  - 31.1% TNBC
- Conclusion:
  - independent association between subtype and pCR
  - TNBC and HER2+/ER- highest pCR rates

Impact of pCR on DFS by subtype

- Pooled analysis of 7 German RCTs that treated 6,377 patients with neoadj chemo* 1998-2006
- RT given to all patients after BCS and for mastectomy patients with stage ≥ cT3 or cN2**
- Median age 50 yrs
- Median f/u 4 yrs
- pCR was associated with improved DFS in:
  - luminal B/HER2-
  - HER2+/non-luminal***
  - Triple negative (TNBC)***
  - but not luminal A or luminal B/HER2+
- Patients with ypN+ had the worst DFS and OS

Von Minckwitz et al. JCO 2012.
How define pCR?

Von Minckwitz et al. JCO 2012
pCR improves DFS in select subtypes

Von Minckwitz et al. JCO 2012

Fig 2. Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype. (A) Patients with luminal A-like tumors, (B) luminal B/human epidermal growth factor receptor 2 (HER2) negative-like tumors, (C) luminal B/HER2-positive-like tumors, (D) HER2-positive (nonluminal) -like tumors, and (E) triple-negative tumors; (F) comparison of DFS in 717 patients achieving pCR according to breast cancer intrinsic subtype.
Evidence for PMRT in the Neoadjuvant Setting

**NO RCTS!**

In fact, NSABP B-18 and B-27 prohibited PMRT

But MDACC has a long history of using neoadjuvant chemo
NSABP B-18 and B-27

• What we CAN learn from these trials is ...

PATTERNS OF FAILURE!

• Caveats...
  ○ no ER/PR/HER2 status
  ○ no N2

Mamounas et al. JCO 2012
Tamoxifen x 5 yrs for all patients in B-27 and pts over 50 yr in B-18

Mamounas et al. JCO 2012
LRR incidence on NSABP

- 12.6% among 1,947 patients treated with mastectomy
  - 9.0% local
  - 3.6% regional

- 10.3% among 1,100 patients treated with lumpectomy plus breast XRT
  - 8.1% local
  - 2.2% regional

Mamounas et al. JCO 2012
MVA for LRR in NSABP

- **Mastectomy:** cT3+, cN+, ypT+, **ypN+**
- **BCS:** same...also AGE <50

Mamounas et al. JCO 2012
LRR after Lumpectomy in NSABP

≥50 yo vs <50 yo

Mamounas et al. JCO 2012
LRR after **Mastectomy** in NSABP

<table>
<thead>
<tr>
<th>Clinically node negative</th>
<th>Clinically node positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy ≤ 5 cm</td>
<td>Mastectomy &gt; 5 cm</td>
</tr>
</tbody>
</table>

**A**

- Clinically node negative:
  - Mastectomy ≤ 5 cm:
    - ypN(-)/Breast pCR: (n = 46) 4.3%
    - ypN(-)/No breast pCR: (n = 178) 2.3%
    - ypN(-)/Breast pCR 3.4%
    - ypN(-)/No breast pCR: (n = 21) 0%
    - ypN(+): (n = 37) 6.4%

- Mastectomy > 5 cm:
  - ypN(-)/Breast pCR: (n = 16) 6.2%
  - ypN(-)/No breast pCR: (n = 95) 0%
  - ypN(-)/Breast pCR: (n = 95) 0%
  - ypN(-)/No breast pCR: (n = 11) 9.2%
  - ypN(+): (n = 84) 4.8%

**B**

- Clinically node positive:
  - Mastectomy ≤ 5 cm:
    - ypN(-)/Breast pCR: (n = 143) 10.6%
    - ypN(-)/No breast pCR: (n = 143) 2.7%
    - ypN(-)/Breast pCR: (n = 143) 8.1%
    - ypN(-)/No breast pCR: (n = 143) 2.7%
    - ypN(+): (n = 143) 6.4%

- Mastectomy > 5 cm:
  - ypN(-)/Breast pCR: (n = 179) 12.3%
  - ypN(-)/No breast pCR: (n = 179) 12.3%
  - ypN(-)/Breast pCR: (n = 179) 2.3%
  - ypN(-)/No breast pCR: (n = 179) 2.3%
  - ypN(+): (n = 128) 17.6%

Mamounas et al. JCO 2012
LRR in ypN+ in NSABP

- LRR >10% for 1-3 positive nodes
  - (except for cN0 patients ≥50yo with BCS)

Mamounas et al. JCO 2012 (appendix)
MDACC retrospective

  - Doxorubicin-based NAC $\rightarrow$ +/- PMRT
  - 542 patients with PMRT vs. 132 patients no PMRT (non-randomized)

- PMRT associated with improved 10 yr LRR in patients with:
  - cT3 (24% without vs 8% with, p=0.002)
  - cT4 (46% vs 15%, p<0.0001)
  - cN2/3 (40% vs 12%, p<0.0001)
  - pT3 (31% vs 14%, p=0.002)
  - pT4 (52% vs 13%, p=0.001)
  - 4 or more +nodes on final path (59% vs 16%, p<0.0001)

- PMRT improved 10-year CSS for patients with:
  - Clinical stage $\geq$ IIIB (22% without vs 44% with, p=0.002)
  - cT4 (24% vs 45%, p=0.007)
  - cN2/3 (27% vs 49%, p=0.024)
  - 4 or more pN+(18% vs 44%, p=0.005).

Huang et al JCO 2004
Table 4. Multivariate Analysis of LRR

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No radiation</td>
<td>4.68</td>
<td>2.70 to 8.13</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>≥ 20% sampled nodes positive</td>
<td>3.58</td>
<td>2.11 to 6.08</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Stage ≥ IIIB</td>
<td>2.38</td>
<td>1.42 to 4.02</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No tamoxifen</td>
<td>2.19</td>
<td>1.19 to 4.06</td>
<td>0.012</td>
</tr>
<tr>
<td>Minimal or worse clinical response to neoadjuvant chemotherapy</td>
<td>1.88</td>
<td>1.10 to 3.23</td>
<td>0.021</td>
</tr>
<tr>
<td>Estrogen receptor-negative</td>
<td>1.69</td>
<td>1.04 to 2.76</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Abbreviation: LRR, local-regional recurrence.

Huang et al JCO 2004
MDACC Recommendations

- **Recommend:**
  - clinical T3–T4
  - clinical N2–N3
  - *most* with node-positive disease at resection

- **Consider:**
  - clinical stage II disease with pN+ or other high risk features including young age (<35), ER-, poor response to chemo

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Hoffman et al, Lancet 2012
UC Athena Network Recommendations

- Based on a literature review, and 7 UC expert consensus

- “Little or no benefit” from PMRT:
  - clinical stage II (T1N0-1, T2N0), >40 yo, with ER+ disease who have a pCR or 0-3 positive axillary nodes without LVI or ECE

- high-risk features warranting consideration of PMRT:
  - <40yo
  - advanced clinical or pathologic stage and TNBC
  - presence of LVI
  - presence of ECE

Fowble et al, IJROBP 2012
Case

- 53yo post-menopausal F with triple-negative cT2N1M0 invasive ductal carcinoma of R breast now s/p bilateral mastectomies and R ALND with pCR.

- PMRT was not recommended.

- Patient proceeded with reconstruction and surveillance.
Case discussion

- What were her risk factors?
  - What if she were ER+?
- PET indicated?
- SLNB before chemo?
- Mastectomy for T2 → pCR?
  - If planned upfront, why NAC at all?
- ALND if post-NAC SLNB neg?
- (prophy bilateral mastectomies??)
- Adjuvant chemo for TNBC?
- Ongoing trials??
# Consensus to omit PMRT after NAC

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (y)</th>
<th>Clinical stage</th>
<th>Location primary</th>
<th>Size primary (cm)</th>
<th>Evaluation axilla</th>
<th>Histology primary</th>
<th>Receptor</th>
<th>Genetic testing</th>
<th>Neoadjuvant chemotherapy</th>
<th>Mastectomy pathology</th>
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<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>T2N0M0 IIA</td>
<td>Left UOQ</td>
<td>2.5</td>
<td>Clinical N0</td>
<td>IDC Gr 3</td>
<td>ER+ PR+ HER2-</td>
<td>Negative</td>
<td>AC × 4</td>
<td>pCR</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>T2N0M0 IIA</td>
<td>Right UOQ</td>
<td>3</td>
<td>SNB 0/4 +</td>
<td>IDC Gr 3 LVI-</td>
<td>ER- PR- HER2-</td>
<td>Negative</td>
<td>TH × 1 y</td>
<td>2.8 cm DCIS 0/1 SN+</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>T3N0M0 IIB</td>
<td>Right LOQ</td>
<td>5.2</td>
<td>Clinical N0</td>
<td>IDC Gr 3</td>
<td>ER+ PR+ HER2-</td>
<td>BRCA2+</td>
<td>AC × 4</td>
<td>ypT1N0 60%-90%</td>
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<tr>
<td>4</td>
<td>42</td>
<td>T2N1M0 IIB</td>
<td>Left subareolar</td>
<td>3.5</td>
<td>US FNA+</td>
<td>IDC Gr 3</td>
<td>ER- PR- HER2-</td>
<td>BRCA1+</td>
<td>AC × 4</td>
<td>pCR 0/10 nodes +</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>T2N1M0 IIB</td>
<td>Left subareolar</td>
<td>3</td>
<td>US FNA+</td>
<td>IDC Gr 2</td>
<td>ER- PR- HER2+</td>
<td>NI</td>
<td>AC × 4</td>
<td>ypT1N0 0/1 SN+ 0/8 NSN+</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>T2N1M0 IIB multifocal</td>
<td>Left UIQ</td>
<td>2.5</td>
<td>US FNA+</td>
<td>IDC Gr 2</td>
<td>ER- PR- HER2-</td>
<td>Negative</td>
<td>AC × 4</td>
<td>TH × 12</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>T2N1M0 IIB</td>
<td>Right UIQ</td>
<td>3.5</td>
<td>US FNA+</td>
<td>ILC Gr 1</td>
<td>ER+ PR+ HER2-</td>
<td>NI</td>
<td>AC × 4</td>
<td>ypT2N1 3 cm ILC classic, Gr 1, LVI-, 1/1 SN+ (4 mm), ECE+, 0/8 NSN+</td>
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<tr>
<td>8</td>
<td>35</td>
<td>T2N1M0 IIB</td>
<td>Left LOQ</td>
<td>4.5</td>
<td>US FNA+</td>
<td>IDC Gr 2</td>
<td>ER+ PR+ HER2-</td>
<td>Negative</td>
<td>AC × 4</td>
<td>ypT2N1 2.5 cm IDC, Gr 2, LVI- 2/2 SN+ (3 mm, 4 mm) ECE-, 0/10 NSN+</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>T2N1M0 IIB</td>
<td>Left UOQ</td>
<td>4</td>
<td>US FNA+</td>
<td>IDC Gr 3</td>
<td>ER+ PR+ HER2-</td>
<td>NI</td>
<td>AC × 4</td>
<td>ypT2N1 3 cm Gr 3 IDC, LVI-, 1/1 SN+ (1.5 mm), ECE-, 0/8 NSN+</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>T2N1M0 IIB</td>
<td>Right UIQ</td>
<td>5</td>
<td>US FNA+</td>
<td>IDC Gr 2</td>
<td>ER+ PR+ HER2-</td>
<td>NI</td>
<td>AC × 4</td>
<td>ypT2N1 4.5 cm IDC, Gr 2</td>
</tr>
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</table>
Ongoing NSABP B-51/RTOG 1304 (NRG 9353) Trial

Clinically T1-3, N1 Breast Cancer Documented Positive Axillary Nodes by FNA or by Core Needle Biopsy

Minimum of 12 Weeks of Standard Neoadjuvant Chemotherapy Plus Anti-HER2 Therapy for Patients with HER2-Positive Tumors

Definitive Surgery with Histologic Documentation of Negative Axillary Nodes (Either by Axillary Dissection or by Sentinel Node Biopsy = Axillary Dissection)

STRATIFICATION
- Type of surgery (mastectomy, lumpectomy)
- Hormone receptor status (ER-positive and/or PgR-positive; ER- and PgR-negative)
- HER2 status (negative, positive)
- Adjuvant chemotherapy (yes, no)
- pCR in breast (yes, no)

RANDOMIZATION

Arm 1
(Groups 1A and 1B)*, **
No Regional Nodal XRT
- Group 1A Lumpectomy: No regional nodal XRT with WBI
- Group 1B Mastectomy: No regional nodal XRT and no chestwall XRT

Arm 2
(Groups 2A and 2B)*, **
Regional Nodal XRT
- Group 2A Lumpectomy: Regional nodal XRT with WBI
- Group 2B Mastectomy: Regional nodal XRT and chestwall XRT
Ongoing Alliance A11202 trial

Clinical T1–T3 N1 M0 breast cancer → NACT → Breast-conserving surgery or mastectomy and sentinel lymph-node surgery

SLN negative

ALND plus breast/chest wall and nodal XRT (without XRT to dissected axilla)

SLN positive

Randomization

No further axillary surgery, but breast/chest wall and nodal XRT
THANK YOU

QUESTIONS?
UCSD Neoadjuvant chemo algorithm

- **General paradigm for post-op chemo:**
  - T1b+ for TNBC or HER+
  - Oncotyope to decide, even in N+
    - N0 → TCx4 (12 weeks)
    - N+ → AC*4 → T**
      - AC prefer dose-dense AC which is q2wk + GCSF
      - T can be dose-dense (q2wk for 4 doses) or weekly x12

- **Neoadjuvant**
  - TNBC: AC → T → surgery → +/- carbo
    - At UCSD we do carbo concurrently with RT for ypN+
  - HER2+: PTCHx6 (q3wk)
    - Pertuzumab, taxotere, carboplatin, Herceptin (continues for 1 yr)
  - ER+/HER2-: ACx4 → T OR TC
    - AC preferred dose-dense (q2wk + GCSF) → paclitaxel (weekly or q2wk)
    - TC = docetaxel and cyclophosphamide x4 (12 weeks)
What is a pCR and when does it matter?

Definitions of path CR across studies:

\[
y_pT0 \ y_pN0. \ No \ invasive \ or \ noninvasive \ residual \ in \ breast \ or \ nodes. \ Used \ by \ the \ German \ study \ groups \ (German \ Breast \ Group \ [GBG] \ and \ Arbeitsgemeinschaft \ Gynäkologische \ Onkologie—Breast \ Group \ [AGO-B]) \ as \ part \ of \ the \ Sinn \ score.^{10}
\]

\[
y_pT0/is \ y_pN0. \ No \ invasive \ residual \ in \ breast \ or \ nodes; \ noninvasive \ breast \ residuals \ allowed. \ Used \ by \ MD \ Anderson \ Cancer \ Center, \ Austrian \ Breast \ and \ Colorectal \ Cancer \ Study \ Group, \ and \ Neo-Breast \ International \ Group.^{6,11,12}
\]

\[
y_pT0/is \ y_pN0/+ . \ No \ invasive \ residual \ in \ the \ breast; \ noninvasive \ breast \ residuals \ and \ infiltrated \ lymph \ nodes \ allowed. \ Used \ by \ National \ Surgical \ Adjuvant \ Breast \ and \ Bowel \ Project.^{5,13}
\]

\[
y_pT\leq1mic \ y_pN0/+ . \ No \ gross \ invasive \ residuals \ in \ the \ breast; \ focal \ invasive \ and \ noninvasive \ residuals \ in \ breast \ and \ infiltrated \ lymph \ nodes \ allowed. \ Used \ by \ French \ groups \ using \ the \ Sataloff \ index.^7
\]

Von Minckwitz et al. JCO 2012
**American Joint Committee on Cancer (AJCC)**

**TNM Staging System For Breast Cancer**

**Primary Tumor (T)** The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript “c” or “p” modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

<table>
<thead>
<tr>
<th>T2</th>
<th>Tumor &gt;20 mm but ≤50 mm in greatest dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>Tumor &gt;50 mm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).</td>
</tr>
</tbody>
</table>

**Note:** Invasion of the dermis alone does not qualify as T4

- **T4a** Extension to the chest wall, not including only pectoralis muscle adherence/invasion
- **T4b** Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d’orange) of the skin, which do not meet the criteria for inflammatory carcinoma
- **T4c** Both T4a and T4b
- **T4d** Inflammatory carcinoma

**TX** Primary tumor cannot be assessed

**T0** No evidence of primary tumor

**Tis** Carcinoma in situ

**Tis (DCIS)** Ductal carcinoma in situ

**Tis (LCIS)** Lobular carcinoma in situ

**Tis (Paget’s)** Paget’s disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget’s disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget’s disease should still be noted

**T1** Tumor ≤20 mm or less in greatest dimension

- **T1mi** Tumor ≤1 mm in greatest dimension
- **T1a** Tumor >1 mm but ≤5 mm in greatest dimension
- **T1b** Tumor >5 mm but ≤10 mm in greatest dimension
- **T1c** Tumor >10 mm but ≤20 mm in greatest dimension
### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Pathologic (pN*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NX</strong></td>
<td>Regional lymph nodes cannot be assessed (e.g., previously removed)</td>
</tr>
<tr>
<td><strong>N0</strong></td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>Metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td><strong>N2</strong></td>
<td>Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases</td>
</tr>
<tr>
<td><strong>N2a</strong></td>
<td>Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures</td>
</tr>
<tr>
<td><strong>N2b</strong></td>
<td>Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases</td>
</tr>
<tr>
<td><strong>N3</strong></td>
<td>Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement</td>
</tr>
<tr>
<td><strong>N3a</strong></td>
<td>Metastasis in ipsilateral infraclavicular lymph node(s)</td>
</tr>
<tr>
<td><strong>N3b</strong></td>
<td>Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)</td>
</tr>
<tr>
<td><strong>N3c</strong></td>
<td>Metastasis in ipsilateral supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

*Note: Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration.*

**Pathologic (pN)* |
| pNX | Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study) |
| pN0 | No regional lymph node metastasis histologically |

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Pathologic (pN*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pN0(i-)</strong></td>
<td>No regional lymph node metastasis histologically, negative IHC</td>
</tr>
<tr>
<td><strong>pN0(i+)</strong></td>
<td>Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&amp;E or IHC including ITC)</td>
</tr>
<tr>
<td><strong>pN0(mol-)</strong></td>
<td>No regional lymph node metastases histologically, negative molecular findings (RT-PCR)</td>
</tr>
<tr>
<td><strong>pN0(mol+)</strong></td>
<td>Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC</td>
</tr>
</tbody>
</table>

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for “sentinel node,” for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.
Table 1 (continued)

Pathologic (pN) (continued)

<table>
<thead>
<tr>
<th>pN3b</th>
<th>Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN3c</td>
<td>Metastasis in ipsilateral supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

*** “Not clinically detected” is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** “Clinically detected” is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Distant Metastasis (M)

<table>
<thead>
<tr>
<th>M0</th>
<th>No clinical or radiographic evidence of distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>cM0(I+)</td>
<td>No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm</td>
</tr>
</tbody>
</table>

Staging continued on next page (ST-4)
**Table 1 (continued)**

<table>
<thead>
<tr>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
<th>Stage 0</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
<th>Stage IIC</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis N0 M0</td>
<td>Stage IIIA</td>
<td>T0 N2 M0</td>
<td>T1* N0 M0</td>
<td>T2 N0 M0</td>
<td>T2 N1 M0</td>
<td>T3 N1 M0</td>
<td>T4 N0 M0</td>
</tr>
<tr>
<td>T1* N1mi M0</td>
<td></td>
<td>T1 N2 M0</td>
<td>T2 N0 M0</td>
<td>T3 N2 M0</td>
<td>T4 N1 M0</td>
<td>T4 N2 M0</td>
<td>T4 N2 M0</td>
</tr>
<tr>
<td>T1* N1** M0</td>
<td></td>
<td>T3 N2 M0</td>
<td>T4 N0 M0</td>
<td>T4 N1 M0</td>
<td>T4 N2 M0</td>
<td>T4 N2 M0</td>
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</tr>
<tr>
<td>T2 N0 M0</td>
<td></td>
<td>T2 N0 M0</td>
<td>T3 N2 M0</td>
<td>T4 N1 M0</td>
<td>T4 N2 M0</td>
<td>T4 N2 M0</td>
<td>T4 N2 M0</td>
</tr>
<tr>
<td>T3 N0 M0</td>
<td></td>
<td>T3 N2 M0</td>
<td>T4 N1 M0</td>
<td>T4 N2 M0</td>
<td>T4 N2 M0</td>
<td>T4 N2 M0</td>
<td>T4 N2 M0</td>
</tr>
</tbody>
</table>

* T1 includes T1mi
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.
Predictors for LRR in ALL PATIENTS on NSABP

On MVA:
- Age < 50
- cT3+
- cN+
- Breast pCR
- ypN+

Table 2. Multivariate Analysis of Independent Predictors of 10-Year LRR in the Combined Data Set

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 50 v &lt; 50 years†</td>
<td>0.78</td>
<td>0.63 to 0.98</td>
<td>.03</td>
</tr>
<tr>
<td>Clinical tumor size &gt; 5 v ≤ 5 cm†</td>
<td>1.51</td>
<td>1.19 to 1.91</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Clinical nodal status cN(+) v cN(-)†</td>
<td>1.61</td>
<td>1.28 to 2.02</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Nodal/breast pathologic status</td>
<td>&lt; .001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypN(-)/no breast pCR v ypN(-)/breast pCR†</td>
<td>1.55</td>
<td>1.01 to 2.39</td>
<td></td>
</tr>
<tr>
<td>ypN(+) v ypN(-)/breast pCR†</td>
<td>2.71</td>
<td>1.79 to 4.09</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. The total No. of patients was 2,961, with 320 locoregional recurrence (LRR) events.

Abbreviations: HR, hazard ratio; pCR, pathologic complete response.
*Includes only patients for whom surgery type and all covariates are known.
†Category used as baseline for comparison of risk.

Mamounas et al. JCO 2012
cT3No

- A retrospective analysis of 162 patients with cT3No disease treated at MDACC showed a benefit for PMRT for 5-yr LRR (24% to 4%; p<0.001)

- For patients with cT3No but pN+ disease, PMRT improved 5-yr LRR (53% vs 5%, p<0.001)

- There was a trend towards improved 5-yr LRR with PMRT cT3No and pNo (14% vs 2%, p=0.06)
  - These LRR rates are higher than reported in the NSABP studies (6.2-11.8%) depending on breast pCR

Nagar IJROBP 2011
Young Age

- 107 women < 35 yrs with clinical stage IIA–IIIC treated at MDACC with NACT and mastectomy with or without PMRT

- PMRT improved 5-year recurrence 37% without vs 12% with, p=0·001

- PMRT improved 5 yr-OS (67% vs. 48%, p = 0.03)

- No OS or LRR benefit for clinical stage IIA

Garg et al IJROBP 2007
The Radiotherapy After Primary CHEMotherapy for breast cancer (RAPCHEM) trial (NCT01279304) at the Netherlands Cancer Institute (Amsterdam, Netherlands) is a non-randomised prospective trial, enrolling patients with \textbf{clinical T1–T2} invasive breast cancer with \textbf{one or more pathologically proven axillary lymph nodes} who \textbf{convert to node-negative} disease after neoadjuvant chemotherapy (ypTo–2 ypNo disease).

Patients undergoing mastectomy do \textbf{not} receive postmastectomy radiation and are followed to determine 5-year locoregional recurrence.