Case Conference: Post-Mastectomy Radiotherapy
Outline

• Case
• Intro to PMRT
• Guidelines
• Studies
• Case conclusion
• Summary
Clinical Case

• 36F self-palpated a left breast mass 6/2011. Mammogram revealed suspicious mass at the 10:00 position. US-guided core biopsy showed IDC, grade 3, triple negative.

• MRI: 7.9cm area of non-masslike enhancement in the left breast and also several enlarged axillary LNs on the left level 1-2 up to 2.3cm in size.

• PET CT: Hypermetabolic left breast tumor, subpectoral LN and left axillary LNs:
  • Clinical stage: cT3N1M0 stg IIIA breast cancer.

• ISPY2 trial: randomized to standard therapy with AC+T.

• 1/3/12 – Bilateral mastectomies, left ALND and tissue expander placement. The right breast was benign. The left breast showed IDC, 8.2cm, grade 3. Her axillary dissection showed 6/6 LNs positive with large areas of extracapsular extension. LVI was widely present. Margins were clear >1cm.
  • Pathologic stage: ypT3N2a
Clinical Case

1. If you are Her2 positive you will also receive Trastuzumab.
2. An investigational drug may be used instead of Trastuzumab if you are Her2 positive.
Clinical Case

• PMH: Depression, Anxiety
• Meds: MVI
• ALL: NKDA
• SH: She does not use tobacco or alcohol
• FH: grandfather with colon CA, aunt with breast CA
• PE: BREAST: She is s/p bilateral mastectomy with tissue expanders in place. The skin is healing well. There are no palpable masses on the chest wall or axilla bilaterally.
T1 Sagittal oblique level 1 lymph node 2.3 x 1.7 cm, level 2 lymph node 2.0 x 1.7 cm

T2 Axial T2 non-masslike reticular enhancement involving the upper and lower inner quadrants
Intro to PMRT

- Breast Cancer Statistics 2015 ACS
  
  New Diagnoses: 234,190
  Deaths: 40,730

- Significant risk of loco-regional failure following mastectomy:
  - 15-35% for 4+ positive LN (pN2)
  - 20-30% for T3 tumor (>5cm)

- PMRT reduces LRF in these high risk groups by ~5-10%

Outline
- Case
  - Intro
  - Guidelines
  - Studies
  - Case Conclusion
- Summary
## Intro to PMRT

### Outline
- Case
- Intro
- Guidelines
- Studies
- Case Conclusion
- Summary

---

### Primary Tumor (T) staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Tis (DCIS)</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>Tis (LCIS)</td>
<td>Lobular carcinoma in situ</td>
</tr>
<tr>
<td>Tis (Paget’s)</td>
<td>Paget’s disease (Paget 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.</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤20 mm in greatest dimension</td>
</tr>
<tr>
<td>T1mi</td>
<td>Tumor ≤1 mm in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor &gt;1 mm but ≤5 mm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;5 mm but ≤10 mm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt;10 mm but ≤20 mm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;20 mm but ≤50 mm in greatest dimension</td>
</tr>
<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>
<tr>
<td>T4a</td>
<td>Extension to the chest wall, not including only pectoralis muscle adherence/invasion</td>
</tr>
<tr>
<td>T4b</td>
<td>Ulceration and/or (palpable) satellite nodules and/or edema (including peau d’orange) of the skin, which do not meet the criteria for inflammatory carcinoma</td>
</tr>
<tr>
<td>T4c</td>
<td>Both T4a and T4b</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory carcinoma</td>
</tr>
</tbody>
</table>

**Posttreatment ypT**: The use of neoadjuvant therapy does not change the clinical (pretreatment) stage. Clinical (pretreatment) T will be defined by clinical and radiographic findings, while pathologic (posttreatment) T will be determined by pathologic size and extension. The ypT will be measured as the largest single focus of invasive tumor, with the modifier “m” indicating multiple foci. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed.
Intro to PMRT

<table>
<thead>
<tr>
<th>Pathologic (pN)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNX</td>
</tr>
<tr>
<td>pNO</td>
</tr>
<tr>
<td>pNO(-)</td>
</tr>
<tr>
<td>pNO(+)</td>
</tr>
<tr>
<td>pNO(mo(-))</td>
</tr>
<tr>
<td>pNO(mo(+))</td>
</tr>
<tr>
<td>pT1</td>
</tr>
<tr>
<td>pT1mi</td>
</tr>
<tr>
<td>pT1a</td>
</tr>
<tr>
<td>pT1b</td>
</tr>
<tr>
<td>pT1c</td>
</tr>
<tr>
<td>pT2</td>
</tr>
<tr>
<td>pT2a</td>
</tr>
<tr>
<td>pT2b</td>
</tr>
<tr>
<td>pT3</td>
</tr>
<tr>
<td>pT3a</td>
</tr>
<tr>
<td>pT3b</td>
</tr>
<tr>
<td>pT3c</td>
</tr>
</tbody>
</table>
Guidelines: NCCN 2015 (paraphrased)

1. PMRT is RECOMMENDED when >3 positive nodes (to CW, SC, IC, STRONGLY CONSIDER IM)

2. PMRT should be STRONGLY CONSIDERED when 1-3 +N AND >5cm tumor or +margin (if given: CW, SC, IC, STRONGLY CONSIDER IM)

3. PMRT should be STRONGLY CONSIDERED* when 1-3 +N (if given: CW, SC, IC, STRONGLY CONSIDER IM)

4. PMRT should be CONSIDERED for node-negative patients with >5cm primary or +margin (if given: CW +/- SC and IC, STRONGLY CONSIDER IM)

5. PMRT usually not given for node-negative/clear margin/ <5cm, but CONSIDER (if given: CW only) if high risk of recurrence via:
   Close margins <1mm, >2cm tumor, premenopausal, LVI, triple negative

*Divided NCCN panel on this rec, some think PMRT should be mandatory, others think it should only be considered
Guidelines: NCCN 2015 (paraphrased)

- **≥4 positive axillary nodes**
  - Postchemotherapy radiation therapy to chest wall (category 1) + infraclavicular and supraclavicular areas. Strongly consider radiation therapy to internal mammary nodes (category 2B).

- **1–3 positive axillary nodes**
  - Strongly consider postchemotherapy radiation therapy to chest wall + infraclavicular and supraclavicular areas; if radiation therapy is given, strongly consider internal mammary node radiation therapy (category 2B).

- **Total mastectomy with surgical axillary staging (category 1)**
  - Negative axillary nodes and tumor ≥5 cm or margins positive
    - Consider postchemotherapy radiation therapy to chest wall ± infraclavicular and supraclavicular nodes. Strongly consider radiation therapy to internal mammary nodes (category 2B).
  - Negative axillary nodes and tumor ≤5 cm and negative margins but <1 mm
    - Consider postchemotherapy radiation therapy to chest wall.
  - Negative axillary nodes and tumor ≤5 cm and margins ≥1 mm
    - No radiation therapy.

Outline - Case – Intro – Guidelines – Studies - Case Conclusion – Summary
Notable Studies of PMRT

**Should we PMRT?**
- Danish 82b (CMF +/- PMRT to CW, SC, IM)
- Danish 82c (Tamoxifen x1y +/- PMRT to CW, SC, IM)
- British Columbia (CMF +/- PMRT-cobalt60 to CW, SC+PAB, IM)

**A closer look at N1 (1-3 +Nodes)**
- EBCTCG Meta-analysis (4 v 16% LRF)
- Harvard/MGH (10y DFS 75% vs 93%)

**A closer look at T3 (Tumor >5cm)**
- MGH/MDACC/Yale (PMRT warranted for T3 with LVI: 4 v 21% LRF)

**A closer look at T2 (Tumor <5cm) with adverse features**
- China (Triple negative T1/2N0/1 Chemo +/- PMRT 5y OS 90 v 80% favoring RT)

**A closer look at fields**
- Korean Supraclavicular (N1 without PMRT. Rate of isolated SC recurrence 2.7%)
- French Internal mammary (N1 or medial tumor, +/- IMN RT, No OS/DFS difference)
- EORTC (+/- Regional nodal irradiation, trend for OS, sig. benefit for DFS, CSS)
- MA20 (+/- Regional nodal irradiation, no OS benefit, sig. benefit for DFS)
Notable Studies of PMRT

**Should we PMRT?**
- Danish 82b (CMF +/- PMRT to CW, SC, IM)
- Danish 82c (Tamoxifen x1y +/- PMRT to CW, SC, IM)
- British Columbia (CMF +/- PMRT-cobalt60 to CW, SC+PAB, IM)

**A closer look at N1 (1-3 +Nodes)**
- EBCTCG Meta-analysis (4 v 16% LRF)
- Harvard/MGH (10y DFS 75% vs 93%)

**A closer look at T3 (Tumor >5cm)**
- MGH/MDACC/Yale (PMRT warranted for T3 with LVI: 4 v 21% LRF)

**A closer look at T2 (Tumor <5cm) with adverse features**
- China (Triple negative T1/2N0/1 Chemo +/- PMRT 5y OS 90 v 80% favoring RT)

**A closer look at fields**
- Korean Supraclavicular (N1 without PMRT. Rate of isolated SC recurrence 2.7%)
- French Internal mammary (N1 or medial tumor, +/- IMN RT, No OS/DFS difference)
- EORTC (+/- Regional nodal irradiation, trend for OS, sig. benefit for DFS, CSS)
- MA20 (+/- Regional nodal irradiation, no OS benefit, sig. benefit for DFS)
Notable Studies of PMRT: Should we PMRT?

• Prospective RCT (1982-1989)

• 1708 premenopausal women s/p mastectomy & ALND (median of 7 LNs removed)

• With one or more risk factors including positive axillary LN, tumor > 5 cm, invasion of skin or pectoral fascia.

• Randomized to CMF +/- PMRT (CW, SCV, IMNs)

• 50Gy/25fx or 48Gy/22fx

• 10-yr LRR 9% vs 32% in favor of PMRT

• 10-yr OS 54% vs 45% in favor of PMRT

Notable Studies of PMRT: Should we PMRT?

Danish 82c

- Prospective RCT (1982-1990)
- 1375 postmenopausal women s/p mastectomy & ALND
- With one or more risk factors including positive axillary LN, tumor > 5 cm, invasion of skin or pectoral fascia.
- Randomized to Tamoxifen (1 yr) +/- PMRT (CW, SCV, IMNs)
- 50Gy/25fx or 48Gy/22fx
- 10-yr LRR 8% vs 35% in favor of PMRT
- 10-yr OS 45% vs 36% in favor of PMRT

Notable Studies of PMRT: Should we PMRT?

British Columbia

- Prospective RCT (1979-1986)

- 318 premenopausal women s/p mastectomy & ALND with positive axillary LN

- Randomized to CMF +/- PMRT (cobalt-60)
  - CW = 37.5Gy/16 fx w/ tangents
  - SCV (w/ PAB), 35 Gy/16 fx
  - Bilat. IM, 37.5 Gy/16fx

- 20yr LRR 10% vs 28% in favor of PMRT

- 20yr OS 37% vs 47% in favor of PMRT

Notable Studies of PMRT

Should we PMRT?
- Danish 82b (CMF +/- PMRT to CW, SC, IM)
- Danish 82c (Tamoxifen x1y +/- PMRT to CW, SC, IM)
- British Columbia (CMF +/- PMRT-cobalt60 to CW, SC+PAB, IM)

A closer look at N1 (1-3 +Nodes)
- EBCTCG Meta-analysis (Better LRC, CSS)
- Harvard/MGH (10y DFS 75% vs 93%)

A closer look at T3 (Tumor >5cm)
- MGH/MDACC/Yale (PMRT warranted for T3 with LVI: 4 v 21% LRF)

A closer look at T2 (Tumor <5cm) with adverse features
- China (Triple negative T1/2N0/1 Chemo +/- PMRT 5y OS 90 v 80% favoring RT)

A closer look at fields
- Korean Supraclavicular (N1 without PMRT. Rate of isolated SC recurrence 2.7%)
- French Internal mammary (N1 or medial tumor, +/- IMN RT, No OS/DFS difference)
- EORTC (+/- Regional nodal irradiation, trend for OS, sig. benefit for DFS, CSS)
- MA20 (+/- Regional nodal irradiation, no OS benefit, sig. benefit for DFS)
Notable Studies of PMRT: A closer look at N1 (1-3 +Nodes)

EBCTCG Meta-analysis 2014

- Meta-analysis of 22 randomized trials
- N= 8100 randomized +/- PMRT
- Median follow-up 9.4 years per woman ~1300 had 1-3 positive nodes
- PMRT reduced locoregional recurrence (2p<0.00001), overall recurrence (RR 0.68, 95% CI 0.57–0.82, 2p=0.00006), and breast cancer mortality (RR 0.80, 95% CI 0.67–0.95, 2p=0.01).
- pN1–3=one to three pathologically positive nodes

Lancet 2014;383:2127-2135
Notable Studies of PMRT: **A closer look at N1 (1-3 +Nodes)**

Harvard (MGH)

- Retrospective data from Harvard (1990-2004)
- 230 pts pT1/2 N1 treated with mastectomy
- Compared outcomes for those who did/didn’t receive PMRT
- 10-yr DFS was 75% without PMRT vs. 93% with PMRT

Notable Studies of PMRT

**Should we PMRT?**
- Danish 82b (CMF +/- PMRT to CW, SC, IM)
- Danish 82c (Tamoxifen x1y +/- PMRT to CW, SC, IM)
- British Columbia (CMF +/- PMRT-cobalt60 to CW, SC+PAB, IM)

**A closer look at N1 (1-3 +Nodes)**
- EBCTCG Meta-analysis (Better LRC, CSS)
- Harvard/MGH (10y DFS 75% vs 93%)

**A closer look at T3 (Tumor >5cm)**
- MGH/MDACC/Yale (PMRT warranted for T3 with LVI: 4 v 21% LRF)

**A closer look at T2 (Tumor <5cm) with adverse features**
- China (Triple negative T1/2N0/1 Chemo +/- PMRT 5y OS 90 v 80% favoring RT)

**A closer look at fields**
- Korean Supraclavicular (N1 without PMRT. Rate of isolated SC recurrence 2.7%)
- French Internal mammary (N1 or medial tumor, +/- IMN RT, No OS/DFS difference)
- EORTC (+/- Regional nodal irradiation, trend for OS, sig. benefit for DFS, CSS)
- MA20 (+/- Regional nodal irradiation, no OS benefit, sig. benefit for DFS)
**Notable Studies of PMRT: T3 (Tumor >5cm)**

**MGH/MDACC/Yale (1981-2002)**

- Retrospective: 70 pts T3N0 treated with mastectomy + chemo, but no RT
- Median f/u of 7yrs
- 5-yr LRF was 7.6% overall (with 4/5 occurring at chest wall)
- LVI was a/w worse LRF (21% vs. 4%), DFS and OS
- Conclusion: T3 N0 alone may not need RT, but if LVI+ then it is warranted.

Notable Studies of PMRT

**Should we PMRT?**
- Danish 82b (CMF +/- PMRT to CW, SC, IM)
- Danish 82c (Tamoxifen x1y +/- PMRT to CW, SC, IM)
- British Columbia (CMF +/- PMRT-cobalt60 to CW, SC+PAB, IM)

**A closer look at N1 (1-3 + Nodes)**
- EBCTCG Meta-analysis (Better LRC, CSS)
- Harvard/MGH (10y DFS 75% vs 93%)

**A closer look at T3 (Tumor >5cm)**
- MGH/MDACC/Yale (PMRT warranted for T3 with LVI: 4 v 21% LRF)

**A closer look at T2 (Tumor <5cm) with adverse features**
- China (Triple negative T1/2N0/1 Chemo +/- PMRT 5y OS 90 v 80% favoring RT)

**A closer look at fields**
- Korean Supraclavicular (N1 without PMRT. Rate of isolated SC recurrence 2.7%)
- French Internal mammary (N1 or medial tumor, +/- IMN RT, No OS/DFS difference)
- EORTC (+/- Regional nodal irradiation, trend for OS, sig. benefit for DFS, CSS)
- MA20 (+/- Regional nodal irradiation, no OS benefit, sig. benefit for DFS)
Notable Studies of PMRT: T2 (Tumor <5cm) with adverse features

CHINA

- Conversely there are studies suggesting that T2 N0 tumors with risk factors (Grade 3, LVI, close margin) can have recurrence rates as high as 20-40%.

- A phase III RCT from China of stage II triple negative pts (T1/2 N0/1) s/p mastectomy showed a RFS and OS benefit to PMRT & chemo vs. chemo alone.

- Therefore T/N stage should not be used alone when making treatment decisions about PMRT.

Wang J, Radiother Oncol. 2011 Aug;100(2):200-4
Notable Studies of PMRT

**Should we PMRT?**
- Danish 82b (CMF +/- PMRT to CW, SC, IM)
- Danish 82c (Tamoxifen x1y +/- PMRT to CW, SC, IM)
- British Columbia (CMF +/- PMRT-cobalt60 to CW, SC+PAB, IM)

**A closer look at N1 (1-3 +Nodes)**
- EBCTCG Meta-analysis (Better LRC, CSS)
- Harvard/MGH (10y DFS 75% vs 93%)

**A closer look to T3 (Tumor >5cm)**
- MGH/MDACC/Yale (PMRT warranted for T3 with LVI: 4 v 21% LRF)

**A closer look at T2 (Tumor <5cm) with adverse features**
- China (Triple negative T1/2N0/1 Chemo +/- PMRT 5y OS 90 v 80% favoring RT)

**A closer look at fields**
- Korean Supraclavicular (N1 without PMRT. Rate of isolated SC recurrence 2.7%)
- French Internal mammary (N1 or medial tumor, +/- IMN RT, No OS/DFS difference)
- EORTC (+/- Regional nodal irradiation, trend for OS, sig. benefit for DFS, CSS)
- MA20 (+/- Regional nodal irradiation, no OS benefit, sig. benefit for DFS)
Notable Studies of PMRT: A Closer Look at Fields

Korean Supraclavicular

- Retrospective study from Korea (1994-2003)

- 302 patients with pN1 breast cancer s/p mastectomy without chest wall or supraclavicular RT

- Median 17 axillary LNs removed

- Rate of SCV recurrence was 8.9%, but rate of SCV recurrence without distant recurrence was 2.7%

- Predictors for SCV recurrence were:
  - LVI, ECE, 2-3 + LNs (vs 1), involved level II/III axilla, >20% + LNs

- If >2 risk factors then SCV RFS was 73% vs. 97%

Notable Studies of PMRT: A Closer Look at Fields

French Internal Mammary

- Prospective RCT from France (1991-1997)
- 1334 patients with pN1 breast cancer or medial tumors s/p mastectomy treated with RT to chest wall and SCV
- Randomized to +/- IMN RT (50Gy)
- Median follow-up of 8.6 years
- No difference in DFS or OS

Notable Studies of PMRT: A Closer Look at Fields

EORTC Regional Nodes

Phase III RCT, 1996-2004
N=4004 with early stage BC (76% BCT)
All had central/medial tumor or externally located tumor with axillary involvement.
All with whole breast/chestwall XRT but randomized to +/- IM and SCV node irradiation (50/25)

Primary Endpoint: OS
Secondary Endpoints: DFS, SFDD, CSM

Median F/U 10.9 years

OS 82.3 vs 80.7% (p=0.06)
DFS 72.1 vs 69.1 (p= 0.04)
SFDD 78 vs 75% (p=0.02)
CSM 12.5 v 14.4% (P=0.02)

Notable Studies of (PMRT): A Closer Look at Fields

MA20 Regional Nodes

Not PMRT (all had breast conserving surgery)
N= 1832, whole breast +/- regional nodal
Regional nodal XRT: IM, SCV, Axillary (50/25)
Median f/u 9.5y
All had node+ or high risk node- (>5cm primary, <10 nodes with at least 1 grade 3 histology ER-, LVI)

Primary outcome: OS
Secondary outcomes: DFS, LRDFS, DDFS

OS: 82.8 v. 81.8% P=0.38
DFS: 82 v 77 % P=0.01
LRDFS: 95.2 v 92.2% P=0.009
DDFS: 86.3 v 82.4% P=0.03

Lymphedema 8.4 v 4.5% P= 0.001
36 y/o woman with cT3N1M0 stg IIIa left breast IDC s/p neoadjuvant AC+T f/b bilateral mastectomies and left ALND (pT3N2aM0 stg IIIA)

She was treated with tangent photon fields (w/ bolus), a medial electron field, a supraclavicular field, and a posterior axillary boost.

Prescribed dose was 50.4Gy in 28fx
Case Conclusion: Fields and Borders
Case: PMRT was clearly indicated

 Intro to PMRT: Can reduce LRF in high risk groups by ~5-10%

 Guidelines: Treat >3 +N, most +M, >5cm

 Studies: Danish/Canadian (+/- PMRT), EORTC/MA20* (+/- regional nodes)

 Case conclusion: Pt unfortunately had distant failure, passed as inpatient in 2013