Advanced Breast Cancer and Special Problems

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Advanced Breast Cancer and Special Problems

- Large tumors (T3-4), +/- LN (N0-3)
- Stage IIIA, IIIB
- Locally advanced inoperable breast cancer (often neglected)
- Inflammatory breast cancer
- Local-regional recurrence
  - Post-lumpectomy breast recurrence
  - Post-mastectomy chest wall recurrence
  - Nodal recurrence
- Cardiac risks
- Implants and Reconstruction
- Re-irradiation
- Other relative contraindications to RT
- Phyllodes
Locally advanced breast cancer

68 year old writer
- MVA, taken to ER
- Fixed Lt breast mass
- Biopsy IDC, ER+
- “Disappeared” to finish book for 18 mo
- Ulcerating breast mass, bulky ax LN
- Hormonal therapy
- Local RT

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Invasive Breast Cancer

**Preoperative Chemotherapy for Locally Advanced Invasive Breast Cancer**
- Doxorubicin- or epirubicin-based or paclitaxel- or docetaxel-based preoperative chemotherapy preferred.

**Locoregional Treatment**
- Total mastectomy + surgical axillary staging + RT to chest wall and supraclavicular nodes (plus internal mammary nodes if involved) ± delayed breast reconstruction
- Consider lumpectomy + surgical axillary staging + RT to breast and supraclavicular nodes (plus internal mammary nodes if involved)
- High dose RT alone (category 3)
- Additional chemotherapy + hormonal therapy if estrogen receptor positive or unknown

**Adjuvant Treatment**
- Consider additional systemic chemotherapy and/or preoperative radiation
- Response - See above pathway
- No response → Individualized treatment

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Follow-up/Surveillance (BINV-15)
Management of Locally Advanced Disease

- Pre-operative anthracycline and taxane chemotherapy
- If response – lumpectomy (T2/3) or mastectomy and axillary dissection (sentinel nodes)
- Post-operative RT if lumpectomy/positive nodes or Stage 3 at presentation
- ? nodal RT if nodes negative post-chemo
- ? IM nodal RT
- ? Nodal staging prior to RT vs following chemo

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Local control in LABC

• Aggressive local therapy in high risk breast cancer improves survival

• Local control of paramount importance
  – QOL
  – Morbidity

• “Aggressive palliation”
Chemo + RT

- Induction chemo
  - High response rates 90%
  - >50% achieve CR
  - Biopsy, mammogram, MR or pathologic
  - CR associated with better outcome

- Radical RT
  - NCI
    - path neg, EBRT 60 Gy
    - LRR: IIIA 0%, IIB 20%, Inflammatory IIIB 40%

Danforth. Ann Surg Oncol 98. 5:150
Chemo + Mastectomy or Chemo + RT?

- 2 trials
  - Equivalent results
  - High LRR 20-30% both arms

- Retrospective studies
  - Addition of RT after mastectomy
    - Reduces LRR from 20-30% to 5-15%
  - When chemo achieves path CR, lowest LRR
    - Treat aggressively with loco-regional RT

RT Doses

- Post op, no residual disease
  - 45-50 Gy in 25# over 5 weeks

- Higher risk, +ve margins etc
  - Boost 10-20 Gy

- Gross disease
  - 60-70 Gy
Locally Advanced Breast Cancer – IM Nodes

- 46 year old woman breast lump
- Mastectomy & dissection of matted LN in axilla
- 4.4 cm Grade III/III invasive ductal ca, multifocal, ER/PR -ve, 6/8 LN +ve
- Pre-op CT shows small internal mammary node
- T2 N2 M0 = stage IIIa
- Med. Oncologist: CEF chemo, internal mammary node responds
- Rad. Oncologist: XRT recommended
Locally Advanced with Nodal Disease

Wide Tangents to IM Nodes with Heart Block
Inflammatory breast cancer

- 53 year old woman
- “Mastitis” x 2 mo
- Localized, then diffuse erythema
- Induction CEF, taxol, then Mastectomy
- RT
- Well x 2 yr
- Rt IBC, Lt C/W +, liver mets

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Cardiac Toxicity

- **Excess cardiac deaths**
  - concurrent anthracyclines, nodal RT (IMN), large volume
    
    *EBCTG. Lancet 2000;355:1757-1770*

- **Population studies of excess fatal MI’s**
  - Rt vs Lt breast RT, few had nodal RT
  - Ontario study: risk increased from 1% to 2%
  - PMH study: no excess in cardiac deaths at 10 yr

### Cardiac Mortality Following RT

**Darby et al, Lancet Oncol. 2005 Aug;6(8):557-65**

<table>
<thead>
<tr>
<th>Years from breast cancer diagnosis to cardiac death</th>
<th>No radiotherapy</th>
<th>Radiotherapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac deaths left/right</td>
<td>Cardiac mortality ratio, left-sided vs right-sided (95% CI)</td>
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<tr>
<td>Diagnosed 1973–82</td>
<td></td>
<td></td>
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<tr>
<td>&lt;5 years</td>
<td>717/679</td>
<td>0.98 (0.89–1.09)</td>
</tr>
<tr>
<td>5–9</td>
<td>673/614</td>
<td>1.04 (0.93–1.15)</td>
</tr>
<tr>
<td>10–14</td>
<td>469/441</td>
<td>1.00 (0.87–1.13)</td>
</tr>
<tr>
<td>≥15</td>
<td>515/480</td>
<td>1.01 (0.89–1.15)</td>
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<tr>
<td>Diagnosed 1983–92</td>
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<tr>
<td>&lt;5 years</td>
<td>880/785</td>
<td>1.06 (0.96–1.16)</td>
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<tr>
<td>5–9</td>
<td>815/729</td>
<td>1.07 (0.97–1.18)</td>
</tr>
<tr>
<td>≥10</td>
<td>390/361</td>
<td>1.04 (0.90–1.20)</td>
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<tr>
<td>Diagnosed 1993–2001</td>
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<tr>
<td>&lt;5 years</td>
<td>567/508</td>
<td>1.05 (0.93–1.18)</td>
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<tr>
<td>5–9</td>
<td>144/136</td>
<td>1.02 (0.81–1.29)</td>
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</table>
Cardiac Morbidity Following Breast RT
SEER 1986-93 Giordano et al, JCO 2005

Time-to-event curves for patients with left- versus right-sided breast cancer for hospitalization for ischemic heart disease (A), valvular heart disease (B), conduction abnormalities (C), and heart failure (D)
Bilateral Breast Cancer

Issues
- Overlap
- Lung and heart doses
- Risk of interaction with chemo
**Indications for Mastectomy**

**Absolute**
- Pregnancy (delayed RT)
- Diffuse malignant calcifications
- Positive pathologic margin despite attempts at re-excision
- Multicentric disease involving multiple quadrants

**Relative**
- Active connective tissue disease/vasculitis involving skin
- Positive pathologic margin (if focal)
- Prior breast radiation
- Occult Primary
- Young women with BRCA 1/2 mutation
<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>N</th>
<th>F-up</th>
<th>CVD (%)</th>
<th>Control (%)</th>
<th>p</th>
<th>CVD (%)</th>
<th>Ctrl (%)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Ross</td>
<td>1:1 matched controlled trial</td>
<td>61</td>
<td>16 mos</td>
<td>11%</td>
<td>7%</td>
<td>0.4</td>
<td>10%</td>
<td>7%</td>
<td>0.7</td>
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<tr>
<td>Phan</td>
<td>1:1 matched controlled trial</td>
<td>38</td>
<td>35 mos</td>
<td>7%</td>
<td>7%</td>
<td></td>
<td>7%</td>
<td>7%</td>
<td></td>
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<tr>
<td>Morris</td>
<td>Large retrospective trial</td>
<td>209</td>
<td>6 yrs</td>
<td>10%</td>
<td>na</td>
<td></td>
<td>23%</td>
<td>na</td>
<td></td>
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<tr>
<td>Chen</td>
<td>2:1 matched controlled trial</td>
<td>26</td>
<td>12.5 yrs</td>
<td>14%</td>
<td>8%</td>
<td>0.4</td>
<td>17%</td>
<td>3%</td>
<td>0.01</td>
</tr>
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</table>

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Toxicity Depends on Type of CTD and Organs at Risk

- Adult rheumatoid arthritis not associated with increased risk
- Abdomen and pelvis associated with greatest risk
- Scleroderma, SLE, dermatomyositis associated with greater risk than Sjogren’s, MCTD etc.
- Severity and degree of CTD control, skin involvement may be risk factors
Incidence of Grade 3+ Late Effects in Non-RA CTD Patients According to Treated Site
Incidence of Grade 3+ Late Effects in Non-RA CTD Patients According to Type of CTD
Treatment-Related CTD

- January 2008
  - 56F: Left UOQ T2 (4.5cm) N2 (5/11) M0 IDC (G3 ER/PR- Her2+).
  - Closest margin 3mm posteriorly, LVSI neg
    - Mastectomy and axillary clearance
    - FEC-D + Herceptin (completed 30 Dec 2008)
    - 50Gy in 25 fractions to chest wall and SCF (completed 13 Aug 2008)
  - Otherwise healthy
Treatment-Related CTD

V20 < 30%

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Treatment-Related CTD

- January 2009
  - Admission to ICU for respiratory support: bilateral persistent pleural effusion (non malignant, non infectious, Gr 1 LV function)
  - L lung collapse + chest wall fibrosis & L arm “cellulitis”
  - acute renal failure needing dialysis
  - SCLERODERMA (markers negative)
  - Since then, sister also diagnosed with CREST
Postulated mechanisms

- Taxanes enhance cytokine production
- Paclitaxel disrupts microtubular network
- Centromere, involved in the genesis of autoantibodies in SCLERODERMA
Focally Positive Pathologic Margin

Consider RT in following circumstances

• Older women with lower risk features e.g. no extensive DCIS, low grade, no lymph-vascular invasion
• After chemotherapy
• With adjuvant hormones

If RT used, add boost to tumour bed
The Number of Positive Margins Influences the Outcome of Women Treated With Breast Preservation for Early Stage Breast Carcinoma

DiBiase, SJ; Komarnicky, LT; Schwartz, GF; et al.   Cancer 82(11), 1998
Benefits of Boost RT Significant For All Age Groups

A <= 40

B 40 - 50

C 50 - 60

D > 60

Previous Breast Radiation to Moderate Dose

e.g. Hodgkin’s, lymphoma, ovarian cancer

- Typically not to full dose or to entire breast (e.g. 2500 to 3500 cGy)
- Long interval from previous breast RT
- Avoid if significant prior radiation toxicity
- Careful treatment planning to avoid heart and lung
- Well-informed patient who wishes to avoid mastectomy and recognizes increased risk of radiation fibrosis and poor cosmetic result

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Breast Ca with Previous HD

- 40 year old, T2 N0 triple negative ca left breast with previous history of mantle and upper abdo RT for Hodgkin's 1986
- Refused mastectomy, completed chemo and repeat resection lumpectomy cavity with no residual tumour
Re-irradiation

• A choice between
  – Certainty of disease progression
  – Risk of RT toxicity
    • Previous RT side effects
    • Previous dose and # size
    • Interval & repair
    • Type of organ

• Cautiously aggressive
  – Conformal planning
  – Small # sizes to a decent dose (e.g. 36-45 Gy in 1.8 –2 Gy fractions)
  – Careful selection
Axillary Nodes with Occult Breast Primary

- Axilla treated with dissection and RT
- Imaging will detect occult primary in most cases
  - (MR)
- Aggressive systemic therapy
- Consider RT vs. mastectomy if imaging negative
### Outcome in Patients With Breast Preservation Compared With Patients Who Underwent Mastectomy for Occult Breast Primary

<table>
<thead>
<tr>
<th>Median 6 - 7.5 yrs follow-up</th>
<th>Breast conservation (N = 32)</th>
<th>Mastectomy (N = 13)</th>
<th>P</th>
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<tbody>
<tr>
<td>LR Recurrence</td>
<td>13%</td>
<td>15%</td>
<td>NS</td>
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<tr>
<td>DFS at 10 yrs</td>
<td>63%</td>
<td>56%</td>
<td>NS</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>64%</td>
<td>66%</td>
<td>NS</td>
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</table>

Young Women with BRCA 1/2 Mutation

Issues

• DNA repair defect, increased toxicity
• Risk of ipsilateral breast tumour recurrence – mastectomy vs BCT
• Contralateral breast cancer risk/Prophylactic mastectomy
• Hormonal prophylaxis (Oophorectomy/Tamoxifen)
No Difference in Overall In-breast Tumor Recurrence Between BRCA1/2 Mutation Carriers and Sporadic Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>No. of Events</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>455</td>
<td>35</td>
<td>1.37</td>
<td>.19</td>
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<tr>
<td>Genetic</td>
<td>160</td>
<td>19</td>
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Ipsilateral Breast Tumor Recurrence Among BRCA1/2 Mutation Carriers and Sporadic Controls

Prophylactic Oophorectomy (or tamoxifen)

No Oophorectomy

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### Graph A

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>No. of Events</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Non-BO sporadic</td>
<td>435</td>
<td>34</td>
<td>0.39</td>
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<tr>
<td>BO genetic</td>
<td>160</td>
<td>19</td>
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### Graph B

<table>
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<th>Group</th>
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<th>No. of Events</th>
<th>HR</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>435</td>
<td>34</td>
<td>1.94</td>
<td>0.03</td>
</tr>
<tr>
<td>Genetic</td>
<td>104</td>
<td>17</td>
<td></td>
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</tr>
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</table>
Multifocal/Multicentric Disease

- Multifocal disease in same quadrant can be treated with BCT if margins clear
- Very little data on BCT for multicentric disease
- Mastectomy is preferred for multicentric tumours in different quadrants

No patients with multicentric disease were treated with BCT!
Conclusions

• Some previously absolute contra-indications to RT may now be considered relative (CTD, previous breast RT)
• New technology can contribute to reduced radiation toxicity (e.g. partial breast RT, Intensity-modulated RT to reduce dose to surrounding normal structures, Intra-operative RT)
Breast Expanders/Implants/Reconstruction
XRT & Breast Reconstruction

• Augmented breast
  – breast conservation
    • partial mastectomy + XRT

• Chest Wall Reconstruction
  – post-mastectomy
  – autogenous tissue transfer (flaps) - preferred
  – tissue expanders & implants
  – immediate or delayed
Issues

Multiple small series reported

– Tumour control
  • No adverse effect
– Complications
  • 30–60%
– Patient satisfaction
  • High
– Cosmesis
  • Fair
Saline Augmentation

- Most series show very good results
- The prosthesis **does not** affect the radiation
  - phantom dosimetric studies
  - minor differences in physical density and Z
- Radiation **does** affect the prosthesis
  - but only above 6000 cGy
    - colour change
    - hardening/capsular contracture

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Post-Mastectomy Tissue Transfer Flaps (TRAM, DIEP)

• Immediate reconstruction (or following chemo)
  – no dosimetric issues
  – doses of <6000 cGy well tolerated

• Delayed reconstruction
  – post chest wall XRT
  – fibrosis makes surgery more challenging
  – wound healing issues
  – complication rates ~ 30%

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Post-Mastectomy
Tissue Expander + Implant

• **Immediate reconstruction**
  – no dosimetric issues
  – higher complication rate, esp Si implant
    • Boost dose may be too high

• **Delayed reconstruction**
  – after chest wall XRT
  – loss of elasticity
  – expansion painful, high complication rate
Best Outcomes

- Immediate reconstruction, before XRT
  - Flap
  - Expander
    - logistic issues: coordination of Chemo, RT
- Delayed reconstruction, after XRT
  - Expander
  - Flap

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Borderline and Malignant Phyllodes Tumors Have Significant Risk of Relapse After Conservative Surgery with Clear Margins

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of local recurrences/total patients</th>
<th>Median follow-up (y)</th>
<th>Median time to recurrence (mo)</th>
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<tr>
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<td>Borderline Malignant Total</td>
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<tr>
<td>Reinfuss et al.</td>
<td>1996</td>
<td>3/15 0/4 3/19</td>
<td>8</td>
<td>&lt;20</td>
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<tr>
<td>de Roos et al.</td>
<td>1998</td>
<td>0/1 0/1 0/2</td>
<td>ND</td>
<td>–</td>
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<td>Zissis et al.</td>
<td>1998</td>
<td>– 0/3 0/3</td>
<td>6.6</td>
<td>–</td>
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<td>Holthouse et al.</td>
<td>1999</td>
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<td>10</td>
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<td>Chaney et al.</td>
<td>2000</td>
<td>– 0/6 0/6</td>
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<td>–</td>
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<td>Kapiris et al.</td>
<td>2001</td>
<td>– 4/14 4/14</td>
<td>9</td>
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<td>Kok et al.</td>
<td>2001</td>
<td>1/3 1/1 2/4</td>
<td>3.1</td>
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<td>Asoglu et al.</td>
<td>2004</td>
<td>2/3 6/19 8/22</td>
<td>7.5</td>
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<td>Fou et al.</td>
<td>2006</td>
<td>– 4/17 4/17</td>
<td>4.3</td>
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<td>Abdalla et al.</td>
<td>2006</td>
<td>4/11 2/5 6/16</td>
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<td>Taira et al.</td>
<td>2007</td>
<td>0/5 1/6 1/11</td>
<td>8.2</td>
<td>18</td>
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<td>Barrio et al.</td>
<td>2007</td>
<td>– 5/40 5/40</td>
<td>8.3</td>
<td>24</td>
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<td>Lenhard et al.</td>
<td>2007</td>
<td>2/10 2/6 4/16</td>
<td>7.1</td>
<td>72</td>
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<tr>
<td>Total</td>
<td></td>
<td>12/50 (24%) 25/124 (20%) 37/174 (21%)</td>
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</table>

*ND not described*

*a No distinction was made between borderline and malignant tumors in this study*
A Prospective, Multi-Institutional Study of Adjuvant Radiotherapy After Resection of Malignant Phyllodes Tumors

Forty-six women treated at 30 different institutions

- Thirty patients (65%) had malignant tumors; rest were borderline
- Eighteen patients had a negative margin on the first excision
  - Median size of the negative margin was 3.5 mm
- Twenty-eight patients had re-excision because of positive margins
- None of the 46 patients developed a local recurrence (95% confidence interval, 0–8%)
  - Median follow-up of 56 months (range, 12–129 months)

Margin-negative resection combined with adjuvant radiotherapy is very effective therapy for local control of borderline and malignant phyllodes tumors, with significantly less recurrence than that observed in patients treated with margin-negative resection alone.
Local Recurrence

- 40 yr woman
- T2 N2 treated with Sx, adj chemo, RT
- 6/12 later had c/w rec
- Chemo & hormones for 2.5 yrs
- Rpt RT to right c/wall
- Pall RT to left breast

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Case Study

1988 Rt Mastectomy
• no details as TGH chart destroyed!!

1989 Lt mastectomy
No adjuvant therapy (we think)

Jan 2002 Rt chest wall mass
• wide excision 2 cm
• Adenocarcinoma with positive margins, dermal involvement, ER positive
• further excision-residual in deep skeletal muscle with 1.5 mm margin
Case Study

Just before second excision noted second nodule inferior to scar, FNA positive, started letrozole

Staging negative

Further wide local excision recommended with myocutaneous flap

Referred for RT opinion
- long tight chest wall scar
- 5 subcutaneous mm nodule

Discussion ensued
- further excision with rotation flap
- RT to chest wall tangents 50 Gy with alternate day bolus
Local Control of Recurrence

- 10% of all breast cancers
  - Depends on stage, treatment etc
- After breast conservation
  - Surgery, lumpectomy if no prior RT, vs. mastectomy
- After mastectomy
  - More likely to be associated with distant mets
  - 5 yr OS 35%
  - RT if not previously treated

Prognostic factors
- Disease free interval >2 yr
- Site of recurrence
- # of sites/nodules
- Type of primary
- ER status
- Dose of radiation used
Regional Recurrence

- Generally managed as advanced breast ca
- Isolated SC recurrence may be salvageable with chemotherapy and RT
- Axillary recurrence – surgery if operable
  - Systemic therapy followed by RT
  - Include axillary node boost if residual
Significant toxicities

- Lymphedema
- Brachial plexopathy
- Radiation pneumonitis ?taxanes
- Malignancy
  - contralateral breast cancer
  - sarcoma (1/1000 pts per decade of f/up)
- Cardiac disease – anthracyclines/herceptin
Late effects of XRT

- Determined by
  - total dose and dose/fraction
  - volume
  - RT energy/modality
  - concurrent drugs or morbidities
  - individual sensitivity
Questions?