ASTRO Spring Refresher Course 2013:
Early Breast Cancer

Eleanor Harris, MD
Professor and Chair
Department of Radiation Oncology
Brody School of Medicine
East Carolina University
Objectives: Early Breast Cancer

1. Selection of patients with DCIS for post-lumpectomy radiation
2. Adjuvant post-lumpectomy radiation for early stage invasive breast cancer:
   - 1. Patient selection for breast-conserving surgery and radiation
   - 2. Patient selection for a tumor bed boost after whole breast irradiation
   - 3. Whole breast hypofractionation with or without concurrent boost
   - 4. Patient selection and techniques for accelerated partial breast irradiation
   - 5. Contouring of the breast and lumpectomy targets for radiation treatment planning
   - 6. Omission of radiation in certain patients with early stage invasive breast cancer
TAKE SURVEY NOW!
1. A 60 year old woman is treated with breast-conserving surgery for ER+, <5cm, invasive breast cancer. In which of the following situations is it acceptable to proceed with adjuvant radiation therapy WITHOUT axillary lymph node dissection (ALND)?

- **a)** Sentinel lymph node biopsy (SLNB) reveals 1 lymph node with micrometastasis and the patient had clinically suspicious axillary nodes on preoperative ultrasound.
- **b)** SLNB shows isolated tumor cells in 1 SLN and axilla were clinically negative.
- **c)** The patient has 1 positive SLN, clinically negative axilla and will receive partial breast irradiation.
- **d)** The patient has 2 positive SLNs, clinically negative axilla and declines chemotherapy.
- **e)** It is never acceptable to omit ALND.
I. SELECTION OF PATIENTS WITH DUCTAL CARCINOMA IN SITU (DCIS) FOR POST-LUMPECTOMY RADIATION
Effect of radiotherapy (RT) after breast-conserving surgery (BCS) (four trials, start dates 1985–1990, 3729 women): 10-year cumulative risks of any ipsilateral breast event (ie recurrent DCIS or invasive cancer). Vertical lines indicate 1 SE above or below the 5 and 10 year percentages.

EBCTCG
DCIS Meta-analysis

5-yr gain 10.5 % (SE 1.2)
10-yr gain 15.2 % (SE 1.6)
logrank 2P < 0.00001

J Natl Cancer Inst Monogr;2010:162-177
Effect of radiotherapy (RT) after breast-conserving surgery (BCS): ratio of annual event rates of any ipsilateral breast event by trial. SE = standard error; CI = confidence interval.

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/women allocated BCS + RT</th>
<th>Events/women allocated BCS</th>
<th>BCS + RT events Logrank Variance of O-E</th>
<th>Ratio of annual event rates BCS + RT : BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17</td>
<td>78/400 (19.5%)</td>
<td>139/398 (34.9%)</td>
<td>-36.8 52.3</td>
<td>0.49 (SE 0.10)</td>
</tr>
<tr>
<td>EORTC 10853</td>
<td>64/462 (13.9%)</td>
<td>118/456 (25.9%)</td>
<td>-28.8 43.9</td>
<td>0.52 (SE 0.11)</td>
</tr>
<tr>
<td>SweDCIS</td>
<td>59/511 (11.5%)</td>
<td>131/500 (26.2%)</td>
<td>-41.3 45.9</td>
<td>0.41 (SE 0.10)</td>
</tr>
<tr>
<td>UK/ANZ DCIS</td>
<td>28/505 (5.5%)</td>
<td>67/497 (13.5%)</td>
<td>-20.5 22.8</td>
<td>0.41 (SE 0.14)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>229/1878 (12.2%)</strong></td>
<td><strong>455/1851 (24.6%)</strong></td>
<td><strong>-127.4 164.9</strong></td>
<td><strong>0.46 (SE 0.05)</strong></td>
</tr>
</tbody>
</table>

-99% or ←→ 95% CI

Heterogeneity between 4 trials: $\chi^2_3 = 2.0; P = 0.6$

BCS + RT better | BCS + RT worse

Treatment effect 2P < 0.00001

J Natl Cancer Inst Monogr 2010;2010:162-177

© The Author 2010. Published by Oxford University Press.
Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by age at diagnosis, extent of surgery, and use of tamoxifen (3729 women).
Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by histological grade (1794 women) and nuclear grade (1617 women). Vertical lines indicate 1 SE above or below the 5 and 10 year percentages.
Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 724 women with negative margin status and pathological tumor size 1–20 mm according to nuclear grade: 10-year cumulative risks of any ipsilateral breast event. Vertical lines indicate 1 SE above or below the 5 and 10 year percentages.

Size 1–20 mm, Negative margin status

Low nuclear grade:
- 291 women
- 5-yr gain 13.5 % (SE 4.6)
- 10-yr gain 18.0 % (SE 5.5)
- logrank 2P = 0.002

Intermediate/High nuclear grade:
- 433 women
- 5-yr gain 9.2 % (SE 3.5)
- 10-yr gain 10.3 % (SE 4.2)
- logrank 2P = 0.02
Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 3729 women: 10-year cumulative risks of breast cancer mortality, mortality without a breast event (ie, mortality from causes other than breast cancer in the period before a breast event), and any death.
ECOG DCIS Registry Trial

Inclusion Criteria:
- Low to intermediate grade, 2.5 cm or less
  - Median size = 6 mm
- High grade, 1 cm or less
  - Median size = 5 mm
- Margins 3 mm or greater
- No residual calcifications on post-biopsy mammograms
- 1997-2002
- Median follow-up ~ 6.5 years
Ipsilateral breast events (IBEs) and contralateral breast events (CBEs) in patients with low-or intermediate-grade ductal carcinoma in situ.

Hughes L L et al. JCO 2009;27:5319-5324
Ipsilateral breast events (IBEs) and contralateral breast events (CBEs) in patients with high-grade ductal carcinoma in situ.

Hughes L L et al. JCO 2009;27:5319-5324
ECOG DCIS Registry Trial

Conclusions:
- Patients were selected and rigorously evaluated.
- Low to intermediate grade DCIS with widely negative margins may be candidates for observation after lumpectomy.
- High grade DCIS had an unacceptably high local recurrence rate without radiation.
RTOG 9804: Eligibility: “Good Risk” DCIS

- No symptoms: either mammographic finding or incidental finding in otherwise benign bx
- ONLY low or intermediate grade anywhere
- Size (defined on mammogram if possible) ≤ 2.5 cm
- Margin width ≥ 3 mm
- Stratified by age (+/- 50), size (≤1 cm, >1 cm), margin width (3-9 mm, >1 cm, negative re-exc)
- Randomized post-lumpectomy to Tamoxifen x 5 yrs +/- whole breast RT

McCormick B, RTOG Semi-annual meeting, June 2012
Local Failure Ipsilateral Breast

- **Failed/Total**
  - Observation: 15/298
  - RT: 2/287

Gray's test p-value = 0.0022
HR = 0.14 (0.03, 0.61)

- **5-Years Rates:**
  - Observation: 3.2%
  - RT: 0.4%

- **Patients at Risk**
  - Observation: 298, 272, 232, 147
  - RT: 287, 264, 228, 141

McCormick, RTOG Semi-annual meeting, June 2012
MSKCC Nomogram for predicting local recurrence risk after breast conserving surgery for DCIS

- 1681 DCIS patients treated with BCT
- Ten variables built into nomogram estimating probability of 5 and 10 year local recurrence
- Good calibration and discrimination, concordance index = 0.7
- Largest factors influencing LR include use XRT, use HT, age, margin, number excisions, time period

Rudloff, J Clin Oncol, 2010
Nomogram for predicting 5- and 10-year probability of ipsilateral breast tumor recurrences (IBTR) after breast-conserving surgery for ductal carcinoma in situ.

Rudloff U et al. JCO 2010;28:3762-3769
Recurrence Score Risk for Predicting DCIS Local Recurrence

Multigene expression test to differentiate between low and high risk DCIS undergoing breast conservation therapy
- Tumor samples from ECOG E5194 of excision alone for DCIS (N=327; Median f/u = 8.8 years)
- Oncotype DX DCIS Score Algorithm (12 genes) tested and validated
- Continuous DCIS Score was associated with 10 Year “in breast events”, adjusted for tamoxifen use
- Low risk score = 12% LR risk
- High risk score = 27% LR risk

Solin, SABCS 2011
DCIS is a highly complex disease

Many management questions require further investigation including the nature of untreated disease

Term “carcinoma” should be eliminated

Outcomes of treatment are excellent

Future research should focus on accurate identification of subsets who may be managed with less intervention without compromising outcomes

Accurate risk stratification methods based on clinicopathologic and biologic features must be developed

- Allegra, JNCI, 2009
II. Adjuvant post-lumpectomy radiation for early stage invasive breast cancer
Adjuvant Post-lumpectomy Radiation for Early Invasive Breast Cancer

Selection criteria for:
- Fractionation for whole breast radiation
- Use of a tumor bed boost
- Whole breast versus partial breast irradiation
- Omission of breast irradiation after lumpectomy
- Neoadjuvant radiation
- Post-mastectomy radiation in early stage disease
1. Patient selection for breast-conserving surgery and breast radiation
Contraindications for Breast Conservation with Breast Irradiation

- Cosmetically unfavorable tumor-to-breast ratio
- Pre-existing Scleroderma or Morphea
- T4 disease
- Diffuse microcalcifications on mammogram
- Gross multicentric disease
- Current pregnancy
- Pacemaker in field
  - Generally must keep pacer dose < 5 Gy (some models < 1 Gy)
  - May attempt to move pacers to contralateral chest
- Patient refuses to undergo indicated breast irradiation
- Prior in-field radiation
  - May be able to safely treat some patients with prior RT for Hodgkin’s Disease or lung & upper GI cancers
  - Breast re-irradiation after local recurrence with APBI under investigation
  - Re-irradiation of chest wall for recurrence after mastectomy seems feasible
Not Contraindications for Breast Irradiation

• Young age
• Non-biopsied MRI findings
• Systemic lupus
• BrCa1 or 2 mutation carrier
• Contralateral breast or chest irradiation
• Node positive disease
• High grade histology
• Triple negative subtype
• T3 disease
• Retroareolar location
Local-regional Recurrence & Molecular Subtypes

Meta-analysis of 15 outcomes studies recording molecular subtype:
- BCT N=7174
- Mastectomy N=5418

Relative risk of LRR for luminal A/B cancers was less after both BCT & MRM than TNBC and Her2+

Her2+ had higher LRR than TNBC after BCT but not MRM
Local-regional Recurrence & Molecular Subtypes

British Columbia Cancer Agency cohort:
- N=2985 with early breast cancer treated with BCT or MRM underwent tissue microarray; Median f/u = 12 years (1986-92); Chemo underused; No trastuzumab used in this era
- Ten-Year Local Relapse Free Survival After Breast-Conserving Surgery by Subtype:

<table>
<thead>
<tr>
<th>Subtype</th>
<th># Patients</th>
<th># Events</th>
<th>10 Y LRFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>587</td>
<td>55</td>
<td>92</td>
</tr>
<tr>
<td>Luminal B</td>
<td>295</td>
<td>27</td>
<td>90</td>
</tr>
<tr>
<td>Luminal-Her2</td>
<td>61</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>Her2+</td>
<td>80</td>
<td>15</td>
<td>79</td>
</tr>
<tr>
<td>Basal-like</td>
<td>134</td>
<td>19</td>
<td>86</td>
</tr>
<tr>
<td>TN-nonbasal</td>
<td>114</td>
<td>9</td>
<td>92</td>
</tr>
</tbody>
</table>

Voduc K D et al. JCO 2010;28:1684-1691
### Ten-Year Local Relapse Free Survival After Mastectomy by Subtype:

<table>
<thead>
<tr>
<th>Subtype</th>
<th># Patients</th>
<th># Events</th>
<th>10 Y LRFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>717</td>
<td>57</td>
<td>92</td>
</tr>
<tr>
<td>Luminal B</td>
<td>418</td>
<td>54</td>
<td>86</td>
</tr>
<tr>
<td>Luminal Her2</td>
<td>124</td>
<td>19</td>
<td>80</td>
</tr>
<tr>
<td>Her2+</td>
<td>147</td>
<td>21</td>
<td>83</td>
</tr>
<tr>
<td>Basal-like</td>
<td>161</td>
<td>26</td>
<td>81</td>
</tr>
<tr>
<td>TN-nonbasal</td>
<td>147</td>
<td>18</td>
<td>87</td>
</tr>
</tbody>
</table>

Voduc K D et al. JCO 2010;28:1684-1691
Univariate analysis of local relapse–free survival in patients treated with BREAST-CONSERVING THERAPY reveals significant differences among breast cancer intrinsic subtypes (log-rank test, $P = .00515$).

Fig 1. (A) Univariate analysis of local relapse–free survival in patients treated with breast-conserving therapy reveals significant differences among breast cancer intrinsic subtypes (log-rank test, $P = .00515$). (B) Univariate analysis of regional relapse–free survival among patients treated with breast-conserving therapy reveals statistically significant differences among breast cancer intrinsic subtypes (log-rank test, $P < .001$). Violet line, luminal A; light blue, luminal human epidermal growth factor receptor 2 (HER2); dark blue, luminal B; gold, five-marker negative phenotype; red, basal; beige, HER2 enriched.

Voduc K D et al. JCO 2010;28:1684-1691
(A) Univariate analysis of local relapse–free survival after MASTECTOMY by breast cancer subtypes reveals statistically significant differences (log-rank test, $P < .001$).

Fig 2. (A) Univariate analysis of local relapse–free survival after mastectomy by breast cancer subtypes reveals statistically significant differences (log-rank test, $P < .001$). (B) Univariate analysis of regional relapse–free survival after mastectomy reveals statistically significant differences (log-rank test, $P < .001$). Violet line, luminal A; light blue, luminal human epidermal growth factor receptor 2 (HER2); dark blue, luminal B; gold, five-marker negative phenotype; red, basal; beige, HER2 enriched.
Among all breast cancer subtypes, TNBC has poorer prognosis, including higher local recurrence after BCT and mastectomy, than other subtypes.

Within early stage TNBC, has higher local recurrence with mastectomy alone than with BCT including breast radiation or with PMRT.
### Triple Negative Breast Cancer

**Chinese randomized trial of stage I-II TNBC:**
- 681 women, 2001-2006, underwent mastectomy
- Randomized to chemo alone or chemo + PMRT
- Median f/u = 86 mos

<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>Chemo+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse free survival</td>
<td>75%</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>p=0.02</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>79%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>p=0.03</td>
<td></td>
</tr>
</tbody>
</table>

Wang, J. et al., Radiother Oncol, 100: 200-4, 2011
**Triple Negative Breast Cancer**

Alburta Registry study of TNBC:
- 768 women with TNBC underwent mastectomy or BCT
- Median f/u 7.2 years

<table>
<thead>
<tr>
<th>5 Yr All:</th>
<th>BCT</th>
<th>MRM</th>
<th>MRM+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRR-free survival</td>
<td>94%</td>
<td>85%</td>
<td>87%</td>
</tr>
<tr>
<td>T1-2N0:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRR-free survival</td>
<td>96%</td>
<td>90%</td>
<td>--</td>
</tr>
<tr>
<td>P=0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abdulkarim, et al., JCO, 29: 2852-8, 2011
Her 2+ Breast Cancer

MD Anderson Database
- N= 5683, 2000-2008
- Compared Her2+/HR+ and Her2+/HR- with or without trastuzumab and HR-/Her2- with HR+/Her2-
- 5 Yr Local Regional Recurrence:

<table>
<thead>
<tr>
<th>Subtype</th>
<th>+ trastuzumab</th>
<th>HR</th>
<th>No trastuzumab</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/Her2+</td>
<td>3%</td>
<td>1.24</td>
<td>6%</td>
<td>2.11</td>
</tr>
<tr>
<td>HR-/Her2+</td>
<td>6%</td>
<td>2.01</td>
<td>6%</td>
<td>2.32</td>
</tr>
<tr>
<td>HR-/Her2-</td>
<td>--</td>
<td>--</td>
<td>9%</td>
<td>4.73</td>
</tr>
<tr>
<td>HR+/Her2-</td>
<td>--</td>
<td>--</td>
<td>2%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Oncotype DX and Local-Regional Recurrence**

- **Oncotype DX Recurrence Score (RS)**: a 21-gene panel developed to predict efficacy of adjuvant chemotherapy in ER+, N0 breast cancers.
- RS preformed on tissue from NSABP B14 and B20.
- Tamoxifen treated N=895
- Placebo treated N=355
- Chemo+ tamoxifen treated N=424
- Patients had either mastectomy or BCT

In tamoxifen treated, 10 Y LRR was significantly associated with RS:
- Low RS < 18 = 4%
- Intermediate RS 18-30 = 7%
- High RS > 30 = 16%

Similar associations for chemo+ tam and placebo treated patients.

RS was an independent predictor of LRR on MVA.

Mamounas E. et al, JCO, 2010
2. Use of a Tumor Bed Boost After Whole Breast Irradiation
EORTC Boost Trial

5318 women with stage I or II breast cancer randomized from 1989 to 1996
- Lumpectomy and axillary dissection
- Negative pathologic margins
- Randomization:
  - 50 Gy/25 fractions to the breast only
  - 50 Gy/25 fractions to the breast + 16 Gy boost to tumor bed
- Median follow-up = 10.8 years
- Bartelink, JCO, 2007
EORTC Boost vs. No Boost Trial

Bartelink, JCO, 2007
EORTC Boost Vs. No Boost Trial

A. < 40 yo

B. 41-50 yo

C. 51-60 yo

D. > 60 yo
10 year local recurrence:
- No Boost 10.2%
- Boost 6.2%
  \( P < 0.0001 \)
  \( \text{Hazard ratio} = 0.59 \)

No significant interaction per age group
- Risk reduction largest in < 40 years old
  \( 24\% \text{ vs. } 13.5\% \)

Severe fibrosis increased in boost arm
- 1.6\% vs 4.4\%, \( P < 0.001 \)
  \( \text{Bartelink, JCO, 2007} \)
Selection of Patients for Tumor Bed Boost

Include Boost:
- Age < 40 and/or premenopausal
- High grade histology
- Close margins (< 2 mm), especially if > 1 focus
- Triple negative subtype
- Her2 + subtypes
- T2-T3 tumor size
- Extensive LVI or PNI or EIC

Consider omitting boost after whole breast RT:
- T1 tumor size
- Grade 1-2
- Negative margins (> 2 mm)
- ER+/ Her2 -
- Age > 60
- No LVI or EIC
3. Whole breast hypofractionation
Canadian Randomized Trial of RT Fractionation

- 50 Gy in 25 fractions of 200 cGy vs.
- 42.5 Gy in 16 fractions of 265 cGy
  - 1993-1996
  - N=1234
  - Median f/u = 69 months
  - Opposed 2D tangents + wedges, no CT planning
    - Homogeneity +/- 7% at single plane central axis
    - 4-6 MV or cobalt-60
  - Chemotherapy in 11%; Tamoxifen in 41%
  - Exclusion Criteria:
    - Positive margins
    - No axillary dissection performed
    - Size > 5 cm or T4; Multicentric disease
    - Breast separation > 25 cm due to inhomogeneity
      - Whelan, JNCI, 2002; NEJM 2010
Canadian Randomized Trial of RT Fractionation

- 10 Year OS and DFS > 90% both arms, no statistical difference
  - 10 Year Local Recurrence
    - 50 Gy = 6.7%
    - 42.5 Gy = 6.2%
- Cosmesis good/excellent:
  - 50 Gy = 71%
  - 42.5 Gy = 70%
  - Whelan, NEJM, 2010
Outcomes in Patients with Breast Cancer Who Received a Hypofractionated Regimen of Radiation Therapy as Compared with Patients Who Received the Standard Regimen

### Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 yr</td>
<td>1.02 (0.62–1.70)</td>
<td>0.67</td>
</tr>
<tr>
<td>&lt;50 yr</td>
<td>0.77 (0.35–1.70)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 cm</td>
<td>0.99 (0.49–1.98)</td>
<td>0.90</td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>0.95 (0.55–1.64)</td>
<td></td>
</tr>
<tr>
<td><strong>Estrogen-receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.71 (0.41–1.23)</td>
<td>0.36</td>
</tr>
<tr>
<td>Negative</td>
<td>1.32 (0.62–2.82)</td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td>1.30 (0.22–7.81)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.70 (0.31–1.58)</td>
<td>0.01</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.57 (0.29–1.12)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3.08 (1.22–7.76)</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.86 (0.48–1.55)</td>
<td>0.65</td>
</tr>
<tr>
<td>Yes</td>
<td>1.06 (0.58–1.97)</td>
<td></td>
</tr>
</tbody>
</table>

### Late Toxic Effects of Radiation, Assessed According to the RTOG-EORTC Late Radiation Morbidity Scoring Scheme

**Table 1. Late Toxic Effects of Radiation, Assessed According to the RTOG–EORTC Late Radiation Morbidity Scoring Scheme.**

<table>
<thead>
<tr>
<th>Site and Grade</th>
<th>5 Yr</th>
<th>10 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Regimen (N = 424)</td>
<td>Hypofractionated Regimen (N = 449)</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>82.3</td>
<td>86.1</td>
</tr>
<tr>
<td>1</td>
<td>14.4</td>
<td>10.7</td>
</tr>
<tr>
<td>2</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Subcutaneous tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>61.4</td>
<td>66.8</td>
</tr>
<tr>
<td>1</td>
<td>32.5</td>
<td>29.5</td>
</tr>
<tr>
<td>2</td>
<td>5.2</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* Effects of radiation therapy on skin and subcutaneous tissue were graded on a scale of 0 to 4 (with 0 indicating no toxic effects and grade 4 indicating skin ulceration or soft-tissue necrosis). RTOG–EORTC denotes the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.

† The absolute difference at 5 years was −3.8 percentage points (95% confidence interval [CI], −8.7 to 1.0), and at 10 years the absolute difference was 3.7 percentage points (95% CI, −4.9 to 12.1).

‡ The absolute difference at 5 years was −5.4 percentage points (−11.9 to 0.9), and at 10 years the absolute difference was −2.8 percentage points (−11.7 to 6.5).

Global Cosmetic Outcome, Assessed According to the EORTC Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Baseline</th>
<th>Absolute Difference (95% CI)</th>
<th>5 Yr</th>
<th>Absolute Difference (95% CI)</th>
<th>10 Yr</th>
<th>Absolute Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Regimen (N = 604)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>46.3</td>
<td>46.8</td>
<td>-1.2</td>
<td>(-5.4 to 3.1)</td>
<td>34.3</td>
<td>36.4</td>
</tr>
<tr>
<td>Good</td>
<td>36.3</td>
<td>37.0</td>
<td>44.9</td>
<td>41.5</td>
<td>43.5</td>
<td>39.2</td>
</tr>
<tr>
<td>Fair</td>
<td>15.1</td>
<td>14.6</td>
<td>17.3</td>
<td>19.0</td>
<td>25.5</td>
<td>25.4</td>
</tr>
<tr>
<td>Poor</td>
<td>2.3</td>
<td>1.6</td>
<td>3.5</td>
<td>3.1</td>
<td>3.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Excellent or good</td>
<td>82.6</td>
<td>83.8</td>
<td>79.2</td>
<td>77.9</td>
<td>71.3</td>
<td>69.8</td>
</tr>
</tbody>
</table>

* Absolute differences were calculated as the value in the group that received the standard regimen minus the value in the group that received the hypofractionated regimen. EORTC denotes European Organization for Research and Treatment of Cancer.

Predictors of an Excellent or Good EORTC Global Cosmetic Rating

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (hypofractionated regimen vs. standard regimen) †</td>
<td>1.00 (0.81–1.25)</td>
<td>0.94</td>
</tr>
<tr>
<td>Time from randomization (per yr)</td>
<td>0.93 (0.90–0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (&lt;50 yr vs. ≥50 yr)</td>
<td>1.64 (1.26–21.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor size (&lt;2 cm vs. ≥2 cm)</td>
<td>1.26 (0.99–1.62)</td>
<td>0.07</td>
</tr>
<tr>
<td>Systemic therapy (yes vs. no)</td>
<td>0.89 (0.70–1.12)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* Data are based on a repeated-measures logistic-regression analysis. EORTC denotes European Organization for Research and Treatment of Cancer.
† There were no first-order interactions of treatment with time from randomization, age, tumor size, or systemic therapy.

UK START A Randomized Trial

- pT1-3aN0-1M0, N= 2236, 1998-2002
- Median f/u = 5.1 years
- Lumpectomy (85%) or mastectomy (15%)
- Randomized to:
  - 50 Gy/25 fx/2 Gy per fx vs.
  - 41.6 Gy/13 fx/3.2 Gy per fx vs.
  - 39 Gy/13 fx3.2/3 Gy per fx
- Node positive allowed (29%)
  - Nodal fields used in 14%
  - Breast boost (10 Gy in 5 fx) given in 61%
  - Large breast size in 14%
- 2D planning used:
  - +/- 5% homogeneity at central axis reference point
  - Strict radiotherapy central quality assurance performed
- Chemotherapy in 35%, Tamoxifen only in 54%
UK START A Randomized Trial

![Kaplan-Meier plot (A) and Nelson-Aalen cumulative hazard plot (B) of local-regional tumour relapse in 2236 patients]

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>5Y LRR</th>
<th>5 Yr Distant Relapse</th>
<th>5 Yr Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy/2 Gy fx</td>
<td>3.6%</td>
<td>9.8%</td>
<td>88.9%</td>
</tr>
<tr>
<td>41.6 Gy/3.2 Gy fx</td>
<td>3.5%</td>
<td>9.5%</td>
<td>88.7%</td>
</tr>
<tr>
<td>39 Gy/3 Gy fx</td>
<td>5.2%</td>
<td>11.9%</td>
<td>89.3%</td>
</tr>
</tbody>
</table>

P-value: NS NS NS

UK START A Randomized Trial

Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 1055 patients with breast conserving surgery.

UK START B Hypofractionation Trial

- pT1-3apN0-1M0
- N= 2215; 1999-2001
- Median f/u= 6.1 years
- Lumpectomy (92%) or mastectomy (8%)
- Randomized to 50 Gy/25 fx vs. 40 Gy/15 fx
- 2D planning used:
  - +/- 5% homogeneity at central axis reference point
  - Regional nodal RT allowed (7.5%)
  - Tumor bed boost (10 Gy/5 fx) allowed (43%)
  - Large breast size in 17%

START Trialists’ Group, Lancet 371: 2008
# START B Hypofractionation Trial

![Kaplan-Meier plot](image-a.png) and Nelson-Aalen cumulative hazard plot (B) of local-regional tumour relapse in 2215 patients

<table>
<thead>
<tr>
<th>Tx Arm</th>
<th>5 Yr LRR</th>
<th>5Yr Distant Relapse</th>
<th>5 Yr Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy/25 fx</td>
<td>3.3%</td>
<td>10.2%</td>
<td>89%</td>
</tr>
<tr>
<td>40 Gy/15 fix</td>
<td>2.2%</td>
<td>7.6%</td>
<td>92%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.21</td>
<td>0.01</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Kaplan-Meier plot (A) and Nelson-Aalen cumulative hazard plot (B) of local-regional tumour relapse in 2215 patients

START TrialistsôGroup, Lancet 371: 2008
Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 patients with breast conserving surgery.
When to Offer Hypofractionation?

- Early stage invasive cancer
- Node negative, or nodal fields not planned (1-2 +LN, micromets)
- ER+
- Grade 1-2
- Age > 50 years

Caveats:
- Hypofractionation LC WORSE if grade 3 or ER-
- Larger breasted patients?
  - Not excluded from START Trials
  - Canadian study is 2D planning, so OK if homogeneous?
- Not studied in DCIS
- Toxicity when using boost or nodal fields not reported
  - Boost allowed in START trials but no subgroup analysis
4. Patient selection and techniques for accelerated partial breast irradiation
Accelerated Partial Breast Irradiation (APBI)

Brachytherapy
IORT

3D CRT
ASTRO APBI Consensus Statement

Process: ASTRO Board commissioned task force of recognized breast cancer experts (academic and private practice radonc, surgeons, physicists, residents represented)

Tasked to provide guidance on which patients are suitable candidates for APBI OFF-PROTOCOL based on available literature as of May 2008

Task group used evidence-based approach using systematic literature review to identify:
- 4 randomized trials
- 38 prospective single arm studies
- Minimum 4 years follow-up required
Suitable Category: Treatment with APBI is an acceptable option outside a clinical trial

All criteria must be present:
- Age $\geq 60$
- Pathologic factors: Tumor size $\leq 2$ cm; T1; any grade; Margins $> 2$ mm; No LVSI; ER+; Unicentric; Clinically unifocal $\leq 2$ cm; Invasive ductal or other favorable subtype
- Nodal factors: pN0 (i-,i+); SNBx or ALND required
- No DCIS or EIC allowed; LCIS allowed
- Other: No neoadjuvant chemotherapy; No BrCa mutation

Cautionary Criteria: Caution in using APBI off-protocol should be used due to limited data.

Any criteria invokes caution:
- Age 50-59
- Pathologic factors: 2.1-3.0 cm; T0 or T2; Close margins < 2 mm; Focal LVSI; ER-; Clinically unifocal 2.1-3.0 span
- Invasive lobular
- Pure DCIS ≤ 3 cm; EIC ≤ 3 cm
ASTRO APBI Consensus Statement

Unsuitable category: APBI is generally not advisable outside a clinical trial

Any criteria present:
- Age < 50
- Pathologic factors: > 3 cm; T3-4; Positive margins; Extensive LVSI; Multicentric or multifocal > 3 cm span
- Nodal factors: pN1,2,3; No nodal surgery performed
- Pure DCIS > 3 cm; EIC > 3 cm
- Other: Neoadjuvant chemotherapy used; BrCa ½ mutation present
Low risk (may have APBI off-protocol): Age ≥ 50; unicentric, unifocal, ≤ 3 cm; pT1-2; pN0, non-invasive lobular; No EIC or LVSI, Negative margins > 2 mm

High risk (APBI is contraindicated): age ≤ 40; Positive margin; Multicentric; size > 3 cm; EIC+; LVSI present; ≥ 4 positive nodes or pNx

Intermediate risk (APBI should be used only on protocol): Criteria not met in other two groups - Polgar et al., Radioth Oncol, 2012
ASBS Consensus Statement on APBI

Selection criteria for considering APBI for treatment as sole form of radiotherapy:
- Age ≥ 45 invasive cancer; Age ≥ 50 for DCIS
- Invasive carcinoma or DCIS
- Total tumor size ≤ 3 cm
- Negative margins
- Sentinel node negative

Board of Directors, ASBS, August 2011
11 references given to support statement
Inclusion Criteria for APBI:
- Age ≥ 50
- Invasive ductal cancer, T1 or T2 ≤ 3 cm; N0

Exclusion Criteria:

Absolute:
- Multicentric disease, positive margins
- Autoimmune disorders
- Distant metastases

Relative:
- EIC; Multifocal disease

Uncertain:
- Age ≤ 45; DCIS; 1-3 positive nodes
Issues:
- Further data have emerged since June 2008, including two large randomized trials of APBI with IORT and numerous prospective single arm trials with maturing data
- Impact of Her2 status is not addressed
- Differences among different statements
- Long term outcomes still lacking
- No data to guide selection of APBI technique
Selection of Patients for APBI

- Develop a consistent approach based on one of the published consensus statements
- Inform patients of ongoing clinical trials and lack of long term outcomes or randomized data for any form of APBI
- Ensure proficiency among providers in all techniques used for APBI
- Have stringent quality assurance and follow-up procedures in place
5. Contouring of the breast and lumpectomy targets for radiation treatment planning
Definitions for Breast

6.4.2.2 Breast volumes:

6.4.2.2.1. Breast CTV. Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation (see section 6.3), the apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders, and the Lumpectomy CTV from the breast cancer atlas (section 6.4.2.1). The breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratus anterior muscle excluding chestwall, boney thorax and lung. In general, the pectoralis and/or serratus anterior muscles are excluded from the breast CTV unless clinically warranted by the patient’s pathology. The breast CTV should generally follow consensus guidelines


6.4.2.2.2. Breast PTV: Breast CTV + 7 mm 3D expansion (exclude heart and do not cross midline).

6.4.2.2.3. Breast PTV Eval: Since a substantial part of the Breast PTV often extends outside the patient, the Breast PTV is then copied to a Breast PTV Eval which is edited. This Breast PTV Eval is limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and posteriorly is limited no deeper to the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV Eval is the structure used for DVH constraints and analysis. This Breast PTV Eval cannot be used for beam aperture generation.

Thank you Dr. Freedman for these slides!
RTOG 1005: Breast CTV and PTV

Breast Planning Target Volume (PTV)

Breast Clinical Target Volume (CTV)

External marker for clinical breast extent

7 mm expansion

External marker for clinical breast extent
Breast Planning Target Volume for evaluation (PTV-eval)

- excludes boney thorax from anterior rib surface
- extends within 5 mm of skin

Breast Clinical Target Volume (CTV)
Definitions for Lumpectomy Cavity

6.4.2.1 Lumpectomy volumes:
6.4.2.1.1 Lumpectomy GTV: Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended). Patients without a clearly identifiable lumpectomy bed are not eligible for protocol participation.

6.4.2.1.2 Lumpectomy CTV: Lumpectomy GTV + 1 cm, 3D expansion. Limit the CTV posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin and should not cross midline. In general, the pectoralis and/or serratus anterior muscles are excluded from the lumpectomy CTV unless clinically warranted by the patient’s pathology.

6.4.2.1.3 Lumpectomy PTV: Lumpectomy CTV + 7 mm 3D expansion (excludes heart).

6.4.2.1.4 Lumpectomy PTV Eval: Since a substantial part of the Lumpectomy PTV often extends outside the patient (especially for superficial cavities), the Lumpectomy PTV is then copied to a Lumpectomy PTV Eval which is edited. This Lumpectomy PTV Eval is limited to exclude the part outside the ipsilateral breast and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and excluding the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung) when pertinent. The lumpectomy PTV should not cross midline. This Lumpectomy PTV Eval is the structure used for DVH constraints and analysis. This Lumpectomy PTV Eval cannot be used for beam aperture generation.
RTOG 1005: Boost CTV

- **Lumpectomy**
- **Clinical Target Volume (CTV)**
- 5 mm inside skin
- 10 mm expansion
- Excludes pectoralis muscle, chestwall
RTOG 1005: Boost PTV
RTOG 1005: Boost PTV Eval

Planning Target Volume for evaluation (PTV-eval)
- excludes chestwall/pectoralis muscles
- extends within 5 mm of skin

Planning Target Volume (PTV)

Clinical Target Volume (CTV)

Excludes pectoralis muscle, chestwall

5 mm inside skin
6. Omission of radiation in certain patients with early stage invasive breast cancer
NSABP B-21

- T1N0, ≤ 1 cm invasive cancers
  - ER negative or unknown in ~45%

- N= 1009 randomized after lumpectomy to XRT+placebo, XRT + tamoxifen or tamoxifen alone

- Compared to Tam alone:
  - XRT+ placebo reduced IBTR 49%
  - XRT + Tam by 81%

- Compared to XRT+ placebo:
  - XRT+ Tam reduced IBTR by 63%

- 8 Yr IBTR:
  - Tam alone 16.5%
  - XRT+placebo 9.3%
  - XRT+Tam 2.8%

- Fisher B. et al., JCO, 2002
NSABP B-21 In-Breast Tumor Recurrence

Fisher, JCO 2002

Fig 1. Cumulative incidence of IBTR after treatment with TAM, XRT and placebo, or XRT and TAM. Pairwise comparisons: TAM v XRT + placebo: \( P = .008 \); TAM v XRT + TAM: \( P < .0001 \); XRT + placebo v XRT + TAM: \( P = .01 \).
Lumpectomy + Tam +/- RT CALGB Randomized Trial
T1N0, Age ≥ 70 years, ER positive

8 Year Local Recurrence Tam = 9% vs TamRT = 2%; p=0.015

Hughes, NEJM, 2004; ASCO 2010
Lumpectomy + Tamoxifen +/- RT British Columbia Randomized Trial
T1-2N0, Age ≥ 50 years

Overall LF 12.2% vs. 4.1% at 8 years

Fyles, IJROBP 2006
Lumpectomy + Tamoxifen +/- RT British Columbia Randomized Trial
T1-2N0, Age > 50 years

Favorable T1 ER positive, 9.9% vs. 4.4% at 8 years

Fyles, IJROBP, 2006
CAVEATS FROM RANDOMIZED STUDIES FOR OLDER WOMEN

5 year median follow-up underestimates the value of radiation for local control
Studies powered for local control, not survival
EBCTGC Overview of randomized trials demonstrates the value of local control in reducing the rate of breast cancer deaths
Life expectancy in U.S. is 15 years at age 70 and 9 years at age 80
Consider if T1N0M0, ER+, Her2 negative, grade 1-2, with “negative margins”
- Probably wider than “tumor on ink”, 2-3 mm minimum

Consider if significant co-morbidities limit life expectancy compared to breast cancer prognosis
2. Which of the following cardiac dose constraints for a left sided breast cancer patient should be selected when prescribing 50 Gy at 2 Gy per fraction?

a) Whole heart V20 Gy < 10%
b) Whole heart V20 Gy < 5%
c) Whole heart V20 < 15%
d) Mean heart dose < 10 Gy
e) Mean heart dose < 5 Gy
3. For a 66 year old healthy patient with a T1bN0M0 right breast grade 1 invasive ductal cancer, ER/PR+/Her2-, status post lumpectomy with negative margins, what would you choose as your external beam fractionation scheme to treat the breast based on available evidence?

a) 50 Gy in 2 Gy fractions whole breast  
b) 50 Gy whole breast + 10 Gy boost in 2 Gy fractions  
c) 42.56 Gy whole breast in 2.66 Gy fractions  
d) 42.56 Gy whole breast in 2.66 Gy fractions + 10 Gy boost  
e) 38.5 Gy in 3.85 Gy fractions to right partial breast target volume
Thank you!