Emerging Options in Radiation for Breast Cancer

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Outline

- Can RT be omitted as part of BCT?
- What is Accelerated Whole Breast Irradiation?
- What is Partial Breast Irradiation?
- Can Axillary Radiation Replace Completion Axillary Dissection?
- Who Needs to have Axillary Radiation?
Can RT be Omitted in Early Stage Breast Cancer?
IDC: Local Recurrence without RT

- Harvard/Dana Farber Observation Trial
- Sought to enroll 90 “low risk” patients
  - Unicentric
  - Node Negative
  - 1cm margins
  - No EIC or LVSI
- No systemic therapy given

- 87 patients enrolled before stopping boundary was crossed

- Median follow-up 86 months

- 23% local recurrence

- 5 breast cancer related deaths
2011 Oxford Overview

- 10,801 Women in 17 randomized trials 1979-1999
- BCS +/- XRT only
- XRT reduced the risk of any (no just LR) 1st recurrence at 10 years
- XRT reduced the risk of breast cancer and all cause mortality at 15 years
Addition of RT to BCS reduces any recurrence at 10 years by about 50%.

Addition of RT to BCS reduces breast cancer mortality at 15 years by about 1/6th.
CALGB 9343: RT + Tamoxifen vs. Tamoxifen Alone in Older Patients

- N=636, age ≥ 70, Clinical stage I, ER+
- Median Follow-up 10.5 years
- Local Recurrence: 2% vs. 8%
- Local Regional Recurrence: 2% vs. 9%
- No difference in distant mets or overall survival
- All cause mortality 38%

Hughes et. al., SABCS 2006 & ASCO 2010
Can Tamoxifen Substitute for RT?  
5 Published Studies of Tam +/- RT

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up (median)</th>
<th>Tamoxifen</th>
<th>Tamoxifen + RT</th>
<th>5-year Endpoint</th>
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</thead>
<tbody>
<tr>
<td>NSABP B-21</td>
<td>87 months</td>
<td>8.4%</td>
<td>1.1%</td>
<td>LR</td>
</tr>
<tr>
<td>Canadian</td>
<td>67 months</td>
<td>7.7%</td>
<td>0.6%</td>
<td>LR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.2%</td>
<td>1.1%</td>
<td>LRR</td>
</tr>
<tr>
<td>Scottish</td>
<td>67 months</td>
<td>25%</td>
<td>3.1%</td>
<td>LRR</td>
</tr>
<tr>
<td>CALGB 9343</td>
<td>60 months</td>
<td>4%</td>
<td>1.0%</td>
<td>LRR</td>
</tr>
<tr>
<td>Austrian</td>
<td>54 months</td>
<td>5.1%</td>
<td>0.4%</td>
<td>LR</td>
</tr>
</tbody>
</table>

* Results assume patient remains on Tamoxifen for 5 years
1.) Don’t initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early-stage invasive breast cancer without considering shorter treatment schedules.

Whole breast radiotherapy decreases local recurrence and improves survival of women with invasive breast cancer treated with breast conservation therapy. Most studies have utilized "conventionally fractionated" schedules that deliver therapy over 5-6 weeks, often followed by 1-2 weeks of boost therapy. Recent studies, however, have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses of therapy (~4 weeks). Patients and their physicians should review these options to determine the most appropriate course of therapy.
What is Accelerated Whole Breast Irradiation?
Accelerated Whole Breast Radiation

- **BCCA Accelerated Fractionation Trial**
- 1234 patients randomized to:
  - 50Gy/2Gy, 25 fractions over 35 days vs.
  - 42.5Gy/2.66Gy, 16 fraction over 22 days
- **T1-2 tumors**
- **Node Negative**
- Only 11% received chemotherapy as well
- Excluded large breasted women (separation >25cm)
- **No Boost**

Whelan, et al. JNCI 2002
BCCA Accelerated Whole Breast RT

- Median follow-up: 12 years
- No difference in DFS or OS
- 10 year LR: 6.7% Standard vs. 6.2% Accelerated
- No difference in reported excellent/good cosmetic outcome
  - 5-year: 79% Standard vs. 78% Accelerated
  - 10 year: 71% Standard vs. 70% Accelerated

Whelan, et al. NEJM 2010
### Is Accelerated Whole Breast RT Still Investigational?

**Randomized data supporting Standard Fractionation**

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
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<tbody>
<tr>
<td>IGR</td>
<td>179</td>
</tr>
<tr>
<td>Milan</td>
<td>701</td>
</tr>
<tr>
<td>NSABP</td>
<td>1,262</td>
</tr>
<tr>
<td>NCI</td>
<td>237</td>
</tr>
<tr>
<td>EORTC</td>
<td>879</td>
</tr>
<tr>
<td>DBCG</td>
<td>905</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>4,163</strong></td>
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</table>

**Randomized data supporting Accelerated Hypofractionation**

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian</td>
<td>1,234</td>
</tr>
<tr>
<td>UK Start A</td>
<td>2,236</td>
</tr>
<tr>
<td>UK Start B</td>
<td>2,215</td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>1,140</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7,095</strong></td>
</tr>
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</table>

**Note:**
- Standard Fractionation: BCS + XRT vs. Mastectomy
- Accelerated Hypofractionation: 2Gy vs. 2.7-3.3Gy
Who is a candidate for Accelerated Whole Breast Treatment?

- Most Node Negative Patients
- Patients receiving adjuvant chemotherapy
- Patients with large breasts with $D_{max} < 105\%$

We avoid AWBI in:

- Any patient receiving nodal treatment
- Patients with VERY large breasts
What is Accelerated Partial Breast Irradiation?
Accelerated Partial Breast Irradiation

**Rationale**

- Majority of breast recurrences occur in or adjacent to primary tumor bed (usually within 1 cm)
- RT likely exerts its maximal effect at primary site
- Treatment time can be accelerated to 1 week (b/c of smaller volume)
- Least amount of radiation to normal tissue
PBI – Single Catheter Brachytherapy

- HDR source placed in center of inflatable balloon in lumpectomy cavity (to give uniform distance from center of cavity to skin)
- Requires a single catheter
- Multiple Vendors – Mammosite, SenoRx, SAVI
MammoSite Multilumen

Contura Multi-Lumen Balloon - MLE

MammoSite®
Targeted Radiation Therapy

HOLOGIC®
The Science of Sure
PBI – Single Catheter

- MammoSite applicator placed at time of lumpectomy or within 4-6 weeks under US guidance
- Inflated with saline to fill cavity (4-5 cm)
- RT starts 2-3 days after placement
- 34 Gy: 3.4 Gy/fx, BID x 10 fx via $^{192}$Ir
- Dose prescribed to 1 cm from balloon surface

Edmunson, IJROBP 2002
PBI – MammoSite Efficacy Data

- Multicenter Registry trial of 1149 patients
  - 87% Invasive Ductal Carcinoma
  - 13% DCIS

- 34 Gy, 3.4 Gy/fx BID in 5 days

- Median follow-up 54 months

- 37 in breast failures (5 year actuarial of 3.8%)

- 90.6% - good/excellent cosmesis

Vincini, et al, IJROBP 2011
Catheter-based APBI Exclusion Criteria

- Node + Disease
- Planned chemotherapy
- Balloon to skin distance <8mm
- Poor Balloon/Cavity Conformality (Whole cavity cannot be covered with 1cm expansion of balloon)
External Beam APBI

- Non-coplanar beam arrangement
- 3-5 field external beam RT
- Cover lumpectomy cavity + margin
- Non-invasive
NSABP B-39/RTOG 0413

WBI
- 50 Gy to whole breast
- Optional boost to 60-66.6 Gy
  - Brachytherapy boost not allowed
- Chemotherapy given prior to WBI

PBI – 3 allowable types
- Multi-cath brachy – 34 Gy in 3.4 Gy/fx
- MammoSite – 34 Gy in 3.4 Gy/fx
- 3DCRT – 38.5 Gy in 3.85 Gy/fx
- BID for 10 treatments
- Chemotherapy given after PBI

Trial Closed April 2013 – Awaiting Data!
External Beam
APBI Exclusion Criteria

- Node + Disease
- Planned chemotherapy
- Treatment Volume: Whole Breast Volume > 1/3
- Poorly defined lumpectomy target
- Cautionary - Treatment Volume > 500mL
- Cautionary - Lumpectomy cavity close to skin
Intraoperative PBI

- Multiple Vendors
  - Ziess Intrabeam
  - XOFT (VM)
  - Novac7

- Typically use low energy (short range) x-rays or electrons

- Single Dose – typically 20Gy prescribed to the surface of the applicator

- Dose given over 20-30 minutes

- Lumpectomy is then closed after applicator is removed.
Can Axillary Radiation Replace Completion Axillary Dissection?
ACOSOG Z-11

- Study limited by power
- 27% of patients receiving cALND had additional involved lymph nodes
- Median follow-up 6.3 years
- Local recurrence
  - SLNB only – 1.8%
  - SLNB + ALND – 3.6%
- Regional recurrence
  - SLNB only – 0.9%
  - SLNB + ALND – 0.5%

Giuliano et. al, Ann of Surg, 2010
Randomize to ALND vs. Radiation if sentinel node+

~ 700 patients randomized to each arm

60% received adjuvant chemotherapy

80% received adjuvant endocrine therapy

~ 75 had only 1+ sentinel node

5 year medial follow-up

Clinical Lymphedema –
23% ALND vs. 11% AxRT
NCIC-CTG MA-20

- 1832 Patients (median age 53 years)

- Randomization
  - RT to breast alone
  - RT to breast and regional nodes (SCF, Axilla, IM)

- Eligibility
  - 1-3 + Axillary nodes
  - Tumor >2cm
  - <10 nodes dissected
  - Node negative with ≥ 1 of following
    - Grade 3 histology
    - ER-negative disease
    - Lymphovascular space invasion
### NCIC-CTG MA-20

- Median follow-up 62 months

<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>WBI + RNI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Control</td>
<td>94.5%</td>
<td>96.8%</td>
<td>0.020</td>
</tr>
<tr>
<td>DFS</td>
<td>84%</td>
<td>90%</td>
<td>0.003</td>
</tr>
<tr>
<td>Distant DFS</td>
<td>87%</td>
<td>92.4%</td>
<td>0.002</td>
</tr>
<tr>
<td>OS</td>
<td>90.7%</td>
<td>92.3%</td>
<td>0.070</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>4.1%</td>
<td>7.3%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

- 67% of regional recurrences were in axilla
- Single isolated IMN recurrence

Abstract only
Summary of Ax Dissection vs. AxRT

- Replacing ALND with AxRT appears to be safe in patients with clinically negative axilla and positive sentinel nodes.

- Patients with 1-3 involved nodes after ALND should consider AxRT.

- Patients with a clinically involved axilla prior to surgery should probably have ALND.

- What about neoadjuvant chemo?

- What about patients with extensive involvement/extracapsular extension at SNB?
What about the heart?

- NEJM 2013 Article details increased risk of heart disease in women treated with radiation for left side breast cancer.

- Data based on old techniques 1977-2000.

- Beginning around 2000 almost all women receiving breast radiation were planned using a CT data set.

- More modern data show markedly reduced cardiac risk for left sided breast cancer patients based CT planning b/c the heart can effectively be blocked from the radiation field most of the time.
What if the heart cannot be blocked?

RPM Gated Deep Inspiration Breath Hold DIBH

Intensity modulate radiation therapy (IMRT)

Consider Partial Breast Irradiation (ABPI)
Summary

- RT as a component of BCS has a survival benefit similar to the benefit of chemotherapy in hormone positive breast cancer
- Accelerated whole breast RT offers a promising alternative to standard fractionation RT, with excellent phase 3 data
- PBI offers a promising alternative to standard fractionation RT, with no phase 3 data
- AxRT can replace ALND in many SN+ patients
- Cardiac avoidance has been emphasized in modern radiation technique and has eliminated the increased risk of cardiac toxicity in left sided breast cancer