Hypofractionated Radiation for Early Stage Breast Cancer

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Disclosures

- None
Objectives

• Conventional Fractionation: Historical Perspective

• What is hypofractionation?

• What are the perceived benefits and risks of shortening breast radiation?

• What data supports the use of shortened radiation treatment schedules for early breast cancer?
Objectives

• Breast Hypofractionation: Clinical assessment and patient selection

• Dosimetric Challenges
  – Including Dose Selection and Boost
  – Heterogeneity

• Acute and Late effects
  – Cosmetic Outcome
Objectives

• Is hypofractionation better?

• Future considerations
STANDARD EARLY BREAST CA MANAGEMENT
Early Stage Breast Cancer

- Lumpectomy
- +/- Chemo
- Radiation
- +/- Anti-estrogen
Lumpectomy + Whole Breast RT

- Lumpectomy + whole breast RT is standard alternative to mastectomy
  - Many randomized trials supporting
Why radiation after lumpectomy?

- Randomized trials support local recurrence reduction with post lumpectomy radiation
- Local benefit can translate into survival benefit
Conventional Whole Breast XRT

• Whole Breast Radiation
  – Tangents
  – 45-50 Gy @ 1.8-2 Gy
• Lumpectomy Cavity Boost (Age<50, High Grade)
  – e- or photons, brachy
  – EBRT: 10-16 Gy @ 2 Gy
Other XRT options

- APBI
  - Brachytherapy or 3DCRT
- Intraoperative radiation
- Observation
  - CALGB
Breast Conservation Goal

- Achieve cancer cure
- Preserve breast anatomy
- Achieve acceptable cosmetic outcome
Trivia Break

• This singer/songwriter calls the Mobile area home and loves cheeseburgers with lettuce and tomato, Heinz 57 and french fry potatoes.
Jimmy Buffett
HYPOFRACTIONATED WHOLE BREAST RADIATION
Practical Benefits of Hypofractionation

• Convenience

• Decreased Treatment Related Cost
  – Payor costs
  – Patient costs (i.e. transportation, work)

• Decreased machine and staff workload

• Increased breast RT utilization?
Frequent Concerns: Hypofractionation

- Achieve Cancer Cure?
  - Is Local Benefit same as CF?

- Tissue effects/Cosmetic outcome?
Major Randomized Trials

- UK START A and B
- Canadian
- UK FAST
- Others including institutional
UK START A and B

- Multicenter randomized European trials of breast hypofractionation
- Two separate trials run concurrently
- Published 1 month apart
UK Trial Demographics

• START A
  - Majority between age 40-70 (allowed >18)
  - Mostly BCS (85%)
  - 70% node-
  - Mostly T1-T2, some T3
  - ~35% chemo, ~80% Tam
  - ~70% medium breasts
  - ~90% small/medium surgical defect
  - 60% Boost

• START B
  - Majority between age 40-70 (allowed >18)
  - Mostly BCS (~90%)
  - 75% node-
  - Mostly T1-T2, some T3
  - ~20% chemo, ~85-90% Tam
  - ~75% medium breasts
  - ~90% small/medium surgical defect
  - 40% Boost
UK START A

- **Hypothesis**: Fewer fractions and lower dose is as safe and effective as standard (50Gy/25)

- **1998-2002**

- **~2200 women (pT1-3apN0-1M0)**

- **50 Gy/25 (5x/week) vs 41.6 Gy/13 or 39 Gy/13 over 5wks (5 tx per fortnight, MWF -> TTh)**
UK START A

• Initial Report (The START Trialists Group, Lancet Oncol, 4/2008)

• Median f/u 5 yrs

• LR(5y)
  – 50Gy: 3.6%
  – 41.6Gy: 3.5%
  – 39Gy: 5.2%
UK START A

- Cosmetic results: Photographic and patient self assessments
- Lower rates of late effects with 39Gy
  - HR for late change in breast appearance (photographic) was 0.69 (SS)
Trivia Break

- FAMOUS BASEBALL PLAYER
- HOMERUN HITTER
- CAREER HOMERUNS: 755 (RECORD BROKEN BY BARRY BONDS)
- HOMETOWN: MOBILE, AL
UK START B

• Test benefits of larger fraction sizes on LR, normal tissue, QOL, economics in postoperative breast radiation
UK START B

• Initial Report (START Trialists Group, Lancet, 3/2008)

• 1999-2001

• ~2200 women

• pT1-3apN0-N1M0 breast cancer

• 23 centres

• **50Gy/25** (2Gy/fx, 5 wks) vs. **40Gy/15** (2.67 per fraction, 3wks)
UK START B

- Median f/u 5 yrs
- LR (5y)
  - 50Gy: 3.3%
  - 40Gy: 2.2%
UK START B: Local Relapse

A

Percentage of patients with no local-regional relapse

Number at risk

50 Gy 40 Gy

50 Gy (16/1105)

40 Gy (29/1110)

B

Cumulative hazard rate

0.04

0.02

0.01

0.00

0

0 1 2 3 4 5 6 7 8 9 10

Years since randomisation
Photographic and patient self assessments indicated lower rates of late adverse effects after 40 Gy than 50 Gy.
UK START B: Photographic Appearance

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### UK START B: Late Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Kaplan-Meier 5 year event rate (95% CI), %</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast shrinkage since radiotherapy</td>
<td>24.4 (20.3-28.4)</td>
<td>0.89 (0.70-1.12)</td>
</tr>
<tr>
<td>Breast hardness since radiotherapy</td>
<td>42.3 (37.6-46.9)</td>
<td>0.89 (0.73-1.09)</td>
</tr>
<tr>
<td>Change in skin appearance since radiotherapy</td>
<td>27.8 (23.8-31.8)</td>
<td>0.77 (0.61-0.98)</td>
</tr>
<tr>
<td>Swelling in area of affected breast</td>
<td>12.4 (9.5-15.2)</td>
<td>0.93 (0.65-1.33)</td>
</tr>
<tr>
<td>Change in breast appearance since radiotherapy</td>
<td>39.4 (34.8-44.0)</td>
<td>0.86 (0.70-1.05)</td>
</tr>
<tr>
<td>Change in breast appearance (photographic)</td>
<td>42.2 (37.3-47.4)</td>
<td>0.83 (0.66-1.04)</td>
</tr>
</tbody>
</table>

*Breast conserving patients only

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UK START 10 yr update

- Haviland et al, Lancet Oncol, 2013 OCT
- START A
  - LR at 10 y - > No difference
    - 41.6 Gy and 50 Gy: 6.3%; 39 Gy: 8.8%
    - Normal Tissue Effects better 39 Gy, no difference 41.6 Gy and 50 Gy
UK START 10 yr update

- Haviland et al, Lancet Oncol, 2013 OCT
- START B
  - LR at 10 y -> No difference
    - 40 Gy: 4.3% vs. 50 Gy: 5.5%
  - Normal Tissue Effects better 40 Gy
True or False: The breast cosmesis outcome in the UK START Trials was worse for hypofractionated treatment.
FALSE
Canadian Trial

• 10 y update: Whelan et al., *Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer*, NEJM, Feb 2010

• 3 weeks (42.5Gy/16) vs. 5 weeks (50Gy/25)
Canadian Trial: Demographics

- All BCS
- All T1-T2 N0
- Max breast width <25 cm
- 75% > age 50
- 70% ER+
- 10% chemotherapy (CMF most common)
- 40% Tam
- No Boost

Canadian Trial: 10 y update

Canadian Trial: 10 y update

Canadian Trial: 10 y update

<table>
<thead>
<tr>
<th>Site and Grade</th>
<th>Standard Regimen (N=424)</th>
<th>Hypofractionated Regimen (N=449)</th>
<th>Standard Regimen (N=220)</th>
<th>Hypofractionated Regimen (N=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 Yr</td>
<td></td>
<td>10 Yr</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>percent of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0†</td>
<td>82.3</td>
<td>86.1</td>
<td>70.5</td>
<td>66.8</td>
</tr>
<tr>
<td>1</td>
<td>14.4</td>
<td>10.7</td>
<td>21.8</td>
<td>24.3</td>
</tr>
<tr>
<td>2</td>
<td>2.6</td>
<td>2.5</td>
<td>5.0</td>
<td>6.4</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>0.7</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0‡</td>
<td>61.4</td>
<td>66.8</td>
<td>45.3</td>
<td>48.1</td>
</tr>
<tr>
<td>1</td>
<td>32.5</td>
<td>29.5</td>
<td>44.3</td>
<td>40.0</td>
</tr>
<tr>
<td>2</td>
<td>5.2</td>
<td>3.8</td>
<td>6.8</td>
<td>9.4</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
<td>3.6</td>
<td>2.5</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).
### Table 2. Global Cosmetic Outcome, Assessed At 10 Yr

<table>
<thead>
<tr>
<th>Rating</th>
<th>Standard Regimen (N=604)</th>
<th>Hypofractionated Regimen (N=616)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent of patients</td>
<td>percent of patients</td>
</tr>
<tr>
<td>Excellent</td>
<td>46.3</td>
<td>46.8</td>
</tr>
<tr>
<td>Good</td>
<td>36.3</td>
<td>37.0</td>
</tr>
<tr>
<td>Fair</td>
<td>15.1</td>
<td>14.6</td>
</tr>
<tr>
<td>Poor</td>
<td>2.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Excellent or good</td>
<td>82.6</td>
<td>83.8</td>
</tr>
</tbody>
</table>

## Table 3. 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>
TRIVIA BREAK

True or False: Recurrence rates in the Canadian trial were no different for HFRT and CFRT
UK FAST

- >50, node negative
- 50Gy/25 vs. 28.5 Gy/5 (5.7Gy/fx) OR 30 Gy/5 (6Gy/fx)
- Higher rates of adverse effects w 30 Gy approach
- 3 yrs: 28.5 Gy seemed comparable to 50 Gy
Canadian Trial: Dosimetric Technique

- Canadian
  - Supine
  - Opposed Tangents, 4-6 MV OR COBALT
  - Clinical setup (skin/bone landmarks)
  - Limit lung to 3 cm at central plane
  - Prescribed point midway along central plane, 2/3 distance from skin to base of tangent
  - Tx volume uniformly to dose +/- 7%
  - No LN coverage or Boost

UK Trials: Dosimetric Technique

- UK
  - Supine
  - 1 cm margin on palpable breast tissue
  - Some received regional xrt as well
  - 6MV or higher or Cobalt
  - Doses rx to international reference points
  - Some central review
  - Allowed 95%-105% dose variation at reference point on central axis
  - <2 cm lung preferable
Predictors for adverse outcomes

• Breast size?
  – UK START: small N for large breasts
  – UK FAST outside analysis*: Large breasts independent predictor of poor cosmetic outcome

• Time

• Dosimetric Techniques
  – Inhomogeneity

• Chemotherapy?
  – **Acute effects greater if HFRT started <20 days after chemo

• Others?

*Goldsmith, C. Radiother Oncol. 2011 Aug;100(2):236-40  
TRIVIA BREAK

True or False: The Canadian and UK Trials required a segment weighted technique to reduce hot spots.
FALSE
Cardiac Risk with HFRT?

• Tjessem et al.
  – Evaluated two cohorts treated with HFRT, 1975-1991
  – The degree of hypofractionation and parasternal photon beams contributed to increased cardiac mortality
  – Became evident at 12-15 yrs

• Canadian Group (Aleman)
  – Retrospective ~5300 pts, 1990-1998
  – No increased cardiac risk with HF or CF

Oct 1;87(2):337-43
Aleman et al. Ned Tijdschr Geneeskd. 2015
Hypofractionation Utilization and Clinical Pathway

• After publication seminal HF-WBI trial
  – HF utilization increased 6.5% to 33.8%
    • Academic:
      – HR 3.6 with publication
      – HR 10.6 with pathway
    • Community:
      – No change after pub
      – HR 21 with pathway

• Increased utilization with pathway saved ~$154k annually within their network

Rajagopalan et al. Practical Radiation Oncology. 2015 Mar-Apr;5(2):63-9
Other Thoughts

• Is HFRT better than CFRT?
  – Breast ca $\alpha/\beta$

• Prone technique
  – *improved dose coverage, better homogeneity, reduced dermatitis, lower mean heart/ips lung dose with prone IMRT for large breasted patients

• DCIS?

HFRT vs. APBI

• Rapid Trial
  – APBI (3DCRT) vs. WBI (CFRT or HFRT)
  – Higher rates adverse effects with 3DCRT APBI

Olivotto et al. JCO. July 8, 2013,
Future directions

• NRG/RTOG 1005 (GOOD REFERENCE FOR DOSIMETRY)
  – A PHASE III TRIAL OF ACCELERATED WHOLE BREAST IRRADIATION WITH HYPOFRACTIONATION PLUS CONCURRENT BOOST VERSUS STANDARD WHOLE BREAST IRRADIATION PLUS SEQUENTIAL BOOST FOR EARLY-STAGE BREAST CANCER
• Extreme Hypofractionation
  – UK Fast
  – Univ. of Louisville
• PMRT?
• Regional Radiation Therapy
Conclusions

• HFRT is accepted approach to whole breast radiation as a component of breast conservation after lumpectomy
• ASTRO Guidelines provide recommendations for patient selection
• Dosimetric endpoints including heterogeneity and heart dose very important
• Can expect increased utilization with time