Ultra-hypofractionated whole breast radiotherapy for breast cancer

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Objectives

To review key aspects of breast cancer ultra-hypofractionated radiotherapy including:

- Selection criteria
- Differences between ultra-hypofractionation and more protracted fractionation schemes
- Supporting data and literature
- Practical treatment planning considerations
Case

- 57-year-old female with abnormal screening mammogram
- ECOG: 0; KPS: 100
- PMHx: HTN, depression
- SurgHx: Hernia repair, tonsillectomy
- GYN: G1P1, menarche age 12, menopause age 50
- SocHx: No smoking, alcohol or illicit drug use
- Meds: HCTZ, sertraline
- FMHx: No family history of cancer
- Physical Exam: No palpable breast masses or adenopathy, skin abnormalities, or axillary/supraclavicular adenopathy. No bone tenderness
Case

- Screening MG: suspicious mass in the right breast, upper outer quadrant 3 cm from the nipple
- Diagnostic MG and U/S: confirm spiculated mass measuring 8 mm, no suspicious axillary adenopathy
- Core needle biopsy: invasive ductal carcinoma, ER positive, PR positive, and Her2/neu negative, grade 1
- Breast-conserving surgery and sentinel lymph node bx performed
- Path: IDC measuring 7mm, Grade 1, no associated DCIS, no LVI, 3 SLN negative, all margins negative by >5mm
- Pathologic stage: pT1b N0, IA
Adjuvant radiotherapy after breast-conserving surgery

- Omission in select patients (≥ 70 years of age, ER+, pN0, T1, low grade tumors receiving adjuvant endocrine tx) per PRIME-II, CALGB 9343, ongoing NRG BR007

- Whole breast radiation therapy +/- boost

- Partial breast radiation

Whole breast radiotherapy after breast-conserving surgery

Whole breast RT: 50 Gy in 25 fx

Hypofractionation: 40-42.5 Gy in 15-16 fx

Ultra-hypofractionation: 26-28.5 Gy in 5 fx

1980s

Milan, Gustave-Roussy, NSABP B-06, NCI, EORTC 10801, Danish trials

START A&B

OCOG

FAST

FAST-Forward
Benefits of ultra-hypofractionation radiotherapy

- More convenient for patients translating to improved compliance
- Radiobiologic advantage of ultra-hypofractionation in breast cancer due to low $\alpha/\beta$ ratio

Indications for ultra-hypofractionated whole breast radiotherapy

• NCCN 2021: “For patients who require a more limited number of treatment visits for whole breast radiotherapy (WBRT) delivery, ultra-hypofractionated WBRT of 28.5 Gy in 5 (once-a-week) fractions, may be considered in selected patients age ≥ 50 following breast-conserving surgery with pTis/T1/T2/N0 tumors. However, late toxicity effects beyond 10 years are currently not defined”

• Royal College of Radiologists: “Offer 26 Gy in 5 fractions over one week for whole breast radiotherapy.” “Consider 28.5 Gy in 5 fractions over five weeks instead of 26 Gy in 5 fractions over one week for patients with significant co-morbidities and/or frailty that makes daily radiotherapy difficult”

COVID19 considerations

• 2020 COVID19 pandemic recommendation: “delivery of radiotherapy in five fraction only for all patients requiring radiation therapy with node negative tumors that do not require a boost is recommended”

• The use of 26 Gy in 5 fractions increased from 0.2% in 4/2019 to 60.6% in 4/2020 in the United Kingdom during the COVID19 pandemic

2236 pts, pT1-3a pN0-1 M0 s/p lumpectomy or mastectomy. Chemotherapy and endocrine therapy allowed.

Whole breast radiation:
- START-A: 50 Gy in 25 fx in 5 wks vs 41.6 or **39 Gy in 13 fx** in 5 wks
- START-B: 50 Gy in 25 fx in 5 wks vs **40 Gy in 15 fx** in 3 wks

Conclusion: No difference in locoregional relapse or disease-free survival. Better toxicity outcomes with 39 Gy and 40 Gy, no difference in side effects between 41.6 and 50 Gy

Locoregional tumor relapse rate START-A

Locoregional tumor relapse rate START B

Figure 1: Cumulative risk of local-regional tumour relapse in START-A (A) and START-B (B).
Whelan et al OCOG

1234 pts, pN0 early-stage breast cancer s/p breast-conserving surgery.

Whole breast radiation:
- 50 Gy in 25 fx over 5 wks
- 42.5 Gy in 16 fx over 4 wks

Conclusion: No difference in oncologic or toxicity outcomes with hypofractionation

Whelan et al. NEJM 2010.
Local recurrence (%)

Survival (%)

Time in years

No. at Risk
Standard regimen: 612, 605, 594, 583, 573, 559, 535, 519, 505, 487, 453, 355, 242
Hypofractionated regimen: 622, 617, 605, 592, 576, 562, 539, 517, 495, 482, 455, 369, 241

Years since Randomization:
0 1 2 3 4 5 6 7 8 9 10 11 12

Standard regimen
Hypofractionated regimen
UK FAST (CRUKE/04015)

915 pts >= 50 yo, pT1-2 pN0, s/p breast-conserving surgery. No pts received chemo.
Whole breast radiation:
- 50 Gy in 25 fractions – control group
- **28 Gy** or 30 Gy **in 5 fractions** once a week over 5 weeks

Conclusion: No difference in oncologic outcomes or toxicity between arms although 30 Gy in 5 fx resulted in a higher rate of normal tissue effects up to 10 years (not 28 Gy in 5 fx)

<table>
<thead>
<tr>
<th>Fractionation Schedule (Gy)</th>
<th>None No. (%)</th>
<th>Mild No. (%)</th>
<th>Marked No. (%)</th>
<th>None No. (%)</th>
<th>Mild No. (%)</th>
<th>Marked No. (%)</th>
<th>OR for Mild/Marked Change (95%CI)</th>
<th>Comparison With 50 Gy, ( P^a )</th>
<th>Comparison Between 30 Gy and 28.5 Gy, ( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>217 (90.4)</td>
<td>20 (8.3)</td>
<td>3 (1.3)</td>
<td>163 (82.3)</td>
<td>31 (15.7)</td>
<td>4 (2.0)</td>
<td>1</td>
<td>.019</td>
<td>.686</td>
</tr>
<tr>
<td>30</td>
<td>205 (82.7)</td>
<td>36 (14.5)</td>
<td>7 (2.8)</td>
<td>160 (75.5)</td>
<td>44 (20.8)</td>
<td>8 (3.8)</td>
<td>1.64 (1.08 to 2.49)</td>
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<tr>
<td>28.5</td>
<td>215 (88.1)</td>
<td>27 (11.1)</td>
<td>2 (0.8)</td>
<td>166 (81.0)</td>
<td>34 (16.6)</td>
<td>5 (2.4)</td>
<td>1.10 (0.70 to 1.71)</td>
<td>.052</td>
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January 15, 2022

Brunt et al. JCO 2020.
<table>
<thead>
<tr>
<th>Event</th>
<th>Fractionation Schedule</th>
<th>Total (N = 915)</th>
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<tr>
<td></td>
<td>50 Gy (n = 302)</td>
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</tr>
<tr>
<td></td>
<td>30 Gy (n = 308)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.5 Gy (n = 305)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
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<tr>
<td>Local (breast skin or parenchyma)</td>
<td>3 (1.0)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td></td>
<td>4 (1.3)</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>Regional (axilla or supraclavicular fossa)</td>
<td>2 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3 (1.0)</td>
<td>5 (0.5)</td>
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<tr>
<td>Distant</td>
<td>17 (5.6)</td>
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<td>15 (4.9)</td>
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<td>Second primary cancer</td>
<td>23 (7.6)</td>
<td>21 (6.8)</td>
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<td>25 (8.2)</td>
<td>69 (7.5)</td>
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<td>Deaths</td>
<td>30 (9.9)</td>
<td>33 (10.7)</td>
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<td></td>
<td>33 (10.8)</td>
<td>96 (10.5)</td>
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<td>Breast cancer</td>
<td>7 (2.3)</td>
<td>8 (2.6)</td>
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<td></td>
<td>10 (3.3)</td>
<td>25 (2.7)</td>
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<td>Other cause</td>
<td>23 (7.6)</td>
<td>25 (8.1)</td>
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<tr>
<td></td>
<td>23 (7.5)</td>
<td>71 (7.8)</td>
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<tr>
<td>Second cancer</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>27</td>
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<td>Cardiovascular</td>
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<td>Pulmonary</td>
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<td>2</td>
<td>12</td>
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<td>Other</td>
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<td>6</td>
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<tr>
<td></td>
<td>6</td>
<td>18</td>
</tr>
</tbody>
</table>
4096 pts, pT1-3 pN0-1, s/p breast-conservation surgery or mastectomy. Chemo allowed.

Whole breast radiation (WBI):
- 40 Gy in 15 fractions
- 27 Gy in 5 fractions in one week
- **26 Gy in 5 fractions in one week**

Conclusion: No difference in oncologic outcomes up to **5 years**
Ipsilateral Breast Tumor Relapse

40 Gy in 15 fractions
27 Gy in 5 fractions
26 Gy in 5 fractions

Time in years

**Figure 2: Cumulative risk of ipsilateral breast tumour relapse by fractionation schedule**

**ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY**
27 Gy led to significantly more adverse breast / chest wall events than 40 Gy

26 Gy was equivalent to 40 Gy in all measures of toxicity except for:
1) Breast induration: 0.8% vs 1.6% (p = 0.013 for 26 Gy)
2) Telangiectasias: 1% vs 1.6% (p = 0.07 for 26 Gy - NS)
3) Breast edema: 1.5% vs 2.4% (p = 0.032 for 26 Gy)

How clinically meaningful are these differences?

Prospective single-arm trial
- 158 pts, stage 0-II, s/p breast conserving surgery
- 10% node positive
- 31% received CHT
- 11% received tumor bed boost

1) **28.5 Gy in 5 fx** WBI – half of pts (2013-2015)
2) 30 Gy in 5 fx WBI (2011-2013)

Conclusion: no difference in oncologic outcomes.
Patient-reported outcomes: mild-moderate cosmetic changes

Reshko et al. IJROBP 2022 and Eldredge-Hindy et al. IJROBP 2020
Retrospective

- 367 pts s/p breast conserving surgery
- age ≥70
- 24% node positive
- 17% positive margins

1) 50 Gy in 25 fx WBI
2) 32.5 Gy in 5 fx WBI

Conclusion: no difference in oncologic outcomes

Kirova et al. IJROBP 2009
IBTR: 2.3% with a median follow-up of 5.4 years

Retrospective.

- 150 pts
- 28.5% mastectomy, rest: BCS
- 34% node positive
- 3% received chemotherapy
- 32.5 Gy in 5 fx WBI

Conclusion: mild early reactions and acceptable late toxicity, good long-term local control
Returning to our case

Would have qualified for START A&B, OCOG, FAST, and FAST-Forward trials. Considered suitable for APBI

WBI radiotherapy options: conventionally fractionated, hypofractionated, and ultra-hypofractionated radiotherapy

Patient was treated with ultra-hypofractionated WBI on an institutional protocol
Technical considerations

- Field-based 3D planning is utilized for whole breast radiotherapy – same as with hypofractionation
- Target localization: lumpectomy cavity clips

<table>
<thead>
<tr>
<th></th>
<th>CTV</th>
<th>PTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Breast (WB)</td>
<td>$CTV_{WB} = \text{Soft tissues of the whole breast, 5 mm below the skin surface}$</td>
<td>$PTV_{WB} = CTV_{WB} + 10 \text{ mm margin}$</td>
</tr>
<tr>
<td>Chest Wall (CW)</td>
<td>$CTV_{CW} = \text{Skin flaps and soft tissues}$</td>
<td>$PTV_{CW} = CTV_{CW} + 10 \text{ mm margin}$</td>
</tr>
<tr>
<td>Boost</td>
<td>$CTV_{TB} = \text{tumour bed}$</td>
<td>$PTV_{TB} = CTV_{TB} + 10 \text{ mm margin}$</td>
</tr>
</tbody>
</table>

CT simulation was performed in a supine position, arms up in a breast board if tolerated (this pt could not elevate the left arm)
Opposed tangential fields were used, field-in-field dose modulation with MLC-shaped segments, mixed energies (6 and 18 MV)
Green color: prescription isodose line, red: lumpectomy bed, blue and brown: lower dose isodose lines
Contouring

Whole breast
- Breast CTV: include glandular tissue; exclude chest wall
- Upper – bottom of clavicular head
- Inferior – 2cm below breast
- Lateral – 2cm beyond breast
- Medial – should not cross midline

Tumor bed
- Seroma and surgical clips

Heart
- Contouring atlas: Feng et al. IJROBP 2011
• Tangent field beam’s eye view (BEV)
• Yellow rectangle: radiation field modulated by MLC’s posteriorly
• Dark blue: 26 Gy dose, green: 28.5 Gy dose, red: lumpectomy bed
Dose constraints from FAST

Table 2: Upper and lower dose limits for whole breast PTV

<table>
<thead>
<tr>
<th></th>
<th>Mandatory</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limit</td>
<td>V95% ≥ 90%</td>
<td>V95% ≥ 95%</td>
</tr>
<tr>
<td>Upper limit</td>
<td>V105% ≤ 7%</td>
<td>V105% ≤ 5%</td>
</tr>
<tr>
<td></td>
<td>V107% ≤ 2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{\text{max}}$ ≤ 110%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Dose constraints for organs at risk for whole breast and chest wall irradiation

<table>
<thead>
<tr>
<th></th>
<th>Mandatory</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral lung</td>
<td>V30% ≤ 17%</td>
<td>V30% ≤ 15%</td>
</tr>
<tr>
<td>Heart</td>
<td>V25% ≤ 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V5% ≤ 22%</td>
<td></td>
</tr>
</tbody>
</table>
DVH

CTV breast

Lumpectomy CVT

Heart

Right lung

Left lung
Treatment planning

• This patient did not undergo a boost as her risk of local recurrence was deemed sufficiently low
• Lumpectomy bed boost to 10-16 Gy in 2-Gy fractions sequentially was done in 25.1% of patients in FAST-FORWARD but none of the patients in FAST received a boost
• Deep-inspiration breath hold scan (DIBH) may be obtained to reduce the heart dose in left-sided tumors
• Daily portal imaging is used for treatment verification
Post-treatment considerations

- Same as for conventionally-fractionated
- Follow-up: H&P 1-4/year x 5 years, then annually
- Mammography every 12 months
- Medical Oncology follow-up for endocrine therapy / chemotherapy
- Lifestyle considerations: active lifestyle, healthy diet, limited alcohol intake, and achieving and maintaining a BMI of 20-25
- Survivorship clinic
Additional considerations

Ongoing randomized trials comparing ultra-hypofractionation to hypofractionated WBI:

- NCT03788213 in India (26 Gy in 5 fx vs 40 Gy in 15 fx)
- NCT04434677 in Egypt (26 Gy in 5 fx vs 40.05 Gy in 15 fx)
Conclusions

• Ultra-hypofractionated WBI is a viable treatment modality for select early-stage breast cancers and is endorsed by NCCN, RMR, and COVID19 pandemic guidelines
• Ultra-hypofractionation offers equivalent oncologic and toxicity outcomes, superior patient convenience, improves radiotherapy compliance, and takes advantage of the low $\alpha/\beta$ ratio of breast cancer
• Lack of 10-year follow-up in FAST-FORWARD is a limitation of this technique
Beyond the scope of this ARROcase: accelerated partial breast irradiation, lumpectomy bed boost indications, dose and fractionation in the setting of ultra-hypofractionation, regional nodal irradiation for central/medial tumors or tumors > 2 cm with extensive LVI or young age, and how the Oncotype score factors into radiation therapy decision-making.
References


References


