Hypofractionation in Breast Cancer Radiotherapy

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Outline – Hypofractionation in Breast Carcinoma Radiotherapy

• What is hypofractionation?
• Why might this be useful?
• What is the benefit in breast cancer?
• What are the concerns regarding hypofractionation?
• Future directions of hypofractionation / unanswered questions?
What is hypofractionation?

• Standard radiotherapy - dose per fraction in the adjuvant or curative setting is 2 Gy per fraction

• Hypofractionation uses doses of >2 Gy per fraction

• Overall treatment dosage is reduced - compensates for the increased dose per fraction

• Reduced treatment time - may avoid re-population.
Linear Quadratic Model

- Linear component of DNA damage
  - Analogous to a double strand DNA break caused by a single photon

- Quadratic component of DNA damage
  - Analogous to 2 separate single strand DNA breaks caused by 2 independent photons

\[ \ln S = (\alpha D + \beta D^2) \]
Biologically Equivalent Dose

• Take LQ model and divide both sides by $\alpha$

$$\ln S = (\alpha D + \beta D^2)$$

$$\text{BED} = Nd \left[ 1 + \frac{d}{(\alpha/\beta)} \right]$$

Assumptions for $\alpha/\beta$:

- Tumour and early reacting tissues = 10
- Normal and late reacting tissues = 2-3
Why consider hypofractionation as treatment option?

- Evidence that α/β may be lower for some tumours (≈1.5 for prostate and 3-4 for breast carcinoma)

- Patient convinence and increasing demand for radiotherapy treatment

- Lower cost of treatment

- Evidence of clinical effectiveness in clinical trials
Why might the LQ model fail to predict at higher dose per fraction?

- Tissue response may actually be linear with higher dose per fraction
- ? increased vascular damage and hypoxia
- ? enhanced immune response
- ? Increased cell kill / apoptosis.
Non-randomised evidence of benefit of hypoFx for breast ca

• Manchester dose fractionation of 40 Gy in 15 Fractions over 3 week – established practice over many decades¹

• Prior French Study²
  – 7 x 6.5 Gy per week in elderly patients
  – Acceptable cosmesis and local control

## Summary of Randomised trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose per fraction (Gy)</th>
<th>Total Dose (Gy)</th>
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<tbody>
<tr>
<td>START P</td>
<td>3/3.3</td>
<td>39/42.9</td>
</tr>
<tr>
<td>START A</td>
<td>3/3.2</td>
<td>39/41.6</td>
</tr>
<tr>
<td>START B</td>
<td>2.67</td>
<td>40.0</td>
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<tr>
<td>FAST</td>
<td>5.7</td>
<td>28.5</td>
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<tr>
<td>Canadian Trial</td>
<td>2.66</td>
<td>42.5</td>
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Canadian Study

50 Gy in 25 Fx vs 42.5 Gy in 16 Fx over 22 days

Whelan TJ, et al. NEJM, 2010, 362; 513-520
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START Studies

Women with completely excised invasive breast cancer, T1-3 N0-1 M0

**Trial A**
- N=2236

- 50Gy in 25 # (2.0Gy) 5 wks N=749
- 39.0Gy in 13 # (3.0Gy) 5 wks N=750
- 41.6Gy in 13 # (3.2Gy) 5 wks N=737

**Trial B**
- N=2215

- 50Gy in 25 # (2.0Gy) 5 wks N=1105
- 40Gy in 15 # (2.67Gy) 3 wks N=1110

**Primary Endpoint**
- Loco-regional relapse

**Secondary Endpoints**
- Normal tissue effects
- Disease free survival
- Overall Survival

**Median Follow-Up**
- START A – 9.3 months
- START B – 9.9 months

START A - Loco-regional tumour relapse

START B - Loco-regional tumour relapse

START B – Disease Free Survival

Normal tissue effects

START Trial A


START Trial B
\( \frac{\alpha}{\beta} \) Ratio estimate from START A

Adverse effects:
\[ \frac{\alpha}{\beta} = 3.4 \text{ Gy} \ (95\% \text{CI} \ 2.3-4.5) \]

Tumour relapse:
\[ \frac{\alpha}{\beta} = 4.6 \text{ Gy} \ (95\% \text{CI} \ 1.1-8.1) \]

Hence smaller doses per fractions have the same effect on the tumour as normal tissue and are equally as sparing

Conclusions of the START studies

• Breast cancer & the dose limiting normal tissues respond similarly to fraction size; no advantage to 2Gy fractions

• Patients can be safely & effectively treated to a lower total dose with fewer fractions

• No detrimental effects of hypofractionation are identified in the subgroups studied

• Results support 40Gy in 15 fractions as UK standard for all patients with invasive disease (NICE 2009)
The FAST Trialists group. Radiotherapy and Oncology 2011;100:93-100.

UK FAST Trial

FAST Trial
N=915

50Gy 25Fr
5 weeks
N= 302

30Gy 5FR
5 weeks
N= 308
α/β=4

28.5 Gy 5FR
5 weeks
N= 305
α/β=3

Inclusion criteria
• Woman ≥ 50 year
• Invasive breast carcinoma
• Tumour < 3.0cm
• Node negative
FAST study - moderate/marked breast shrinkage as assessed by a physician

3 year rates (95% CI):
- 50 Gy: 6.8% (4.3% - 10.6%)
- 30 Gy: 11.8% (8.5% - 16.3%)
- 28.5 Gy: 7.1% (4.6% - 11.0%)

Pairwise logrank tests:
- 50 Gy vs. 30 Gy: p=0.002
- 50 Gy vs. 28.5 Gy: p=0.455
- 30 Gy vs. 28.5 Gy: p=0.016

The FAST Trialists group. Radiotherapy and Oncology 2011;100:93-100.
FAST-Forward Study

N=4000

40Gy 15Fr
3 weeks

27Gy 5Fr
1 week

26Gy 5Fr
1 week

Pre-randomisation decision to boost or no boost (16 Gy in 8 Fr or 10 Gy in 5 Fr)
TROG DCIS – BIG 3-07 Study

Phase III RCT of radiation dose and fractionation schedules in DCIS

Patient Population
- women with completely excised non low-risk DCIS by BCS
- Suitable for adjuvant whole breast radiotherapy

Stratification factors-
- Age- <50, ≥ 50
- Endocrine therapy

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<tr>
<td>50 Gy in 25 Fractions / 35 days vs 42.5 Gy in 16 Fractions / 22 days</td>
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<tr>
<td>Boost 16 Gy in 8 Fractions / 10 days vs No Boost</td>
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Does breast hypofractionation increase cardiac morbidity?

• Linear quadratic model indicates that most fractionation regimens spare the heart as long as $\alpha/\beta \geq 1.5\text{Gy}$ assuming late cardiac effects are not sensitive to overall treatment time\(^1\)

• Canadian population based study with a median follow-up of 12 years demonstrated no worsening of cardiac disease in those patients with hypofractionated treatments\(^2\)

Conclusions

Hypofractionation provides a convenient and cost effective alternative to standard 2 Gy fractionation.

There is evidence of improved cosmesis and no evidence of undesirable late effects such as cardiac damage.

Proof of effectiveness in non-invasive disease is lacking - current research is awaited.

Hypofractionation in breast cancer radiotherapy is safe and effective.