Pushing the frontiers of radiobiology: a special feature in memory of Sir Oliver Scott and Professor Jack Fowler: review article

Changes in radiotherapy fractionation—breast cancer

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ABSTRACT

Conventional fractionation for half a century has been justified on the basis that 2.0 Gy fractions spare dose-limiting late-responding normal tissues to a greater degree than cancerous tissues. Early indications that breast cancer responds more strongly to fraction size than many other common cancers were followed several decades of investigation, but there is now reliable Level I evidence that this is the case. Four randomised trials testing fraction sizes in the range 2.7–3.3 Gy have reported 10-year follow up in almost 8000 patients, and they provide robust estimates of $\alpha/\beta$ in the range of 3 Gy. The implication is that there are no advantages in terms of safety or effectiveness of persisting with 2.0 Gy fractions in patients with breast cancer. 15- or 16-fraction schedules are replacing the conventional 25-fraction regimen as a standard of care for adjuvant therapy in an increasing number of countries. A number of concerns relating to the appropriateness of hypofractionation in patient subgroups, including those treated post-mastectomy, advanced local-regional disease and/or to lymphatic pathways are addressed. Meanwhile, hypofractionation can be exploited to modulate dose intensity across the breast according to relapse risk by varying fraction size across the treatment volume. The lower limits of hypofractionation are currently being explored, one approach testing a 5-fraction schedule of local-regional radiotherapy delivered in 1 week.

A BIT OF HISTORY

My first exposure to Jack Fowler and Oliver Scott was at the Gray Laboratories and Mount Vernon Hospital in June 1975, during the very first Royal College of Radiologists 1 week radiobiology teaching course organised by Hugh Thomlinson for first year trainees. A few days’ contact with these individuals did more than anything else to stimulate in our student group a lasting interest in clinical radiation biology. In the years that followed, Jack Fowler became a leading interpreter of the linear–quadratic model developed by Rodney Withers and colleagues.1,2 No better summary exists of the early history of fractionation, including hypofractionation, than that written by Jolian Hendry for a review of UK practices published by the Royal College of Radiologists in 2006.3

Interest in hypofractionation applied to primary breast cancer was sparked by a review of super/hyperfractionation (fractions <2.0 Gy) by the Canadian radiobiologist Bruce Douglas through the lens of the still-new linear quadratic model.4 On the final page of his 11-page manuscript was a single reference to hypofractionation; “For breast cancer, however, the \(\beta/\alpha\) value that can be calculated from published data is about 0.26”. Well, that sentence made me jump, since the reciprocal of 0.26 is an \(\alpha/\beta\)-value of 3.8 Gy. The data to which Douglas referred were published by Lionel Cohen in the British Journal of Radiology in 1952.5 His manuscript combined an analysis of patients treated at the Radiotherapy Department, Johannesburg, with a review of earlier manuscripts describing tumour control in >1000 locally advanced or recurrent breast cancer patients irradiated with a range of fractionation regimens (Figure 1).

Douglas does not describe how he reanalysed Cohen’s data, but he will have controlled for time-related effects by estimating median tumour control doses for subgroups of patients treated to different total doses in daily fractions over similar time periods.

RANDOMISED TRIALS OF ADJUVANT HYPOFRACTIONATION

A 2016 systematic overview of fraction size in breast radiotherapy in the Cochrane Database of Systematic Reviews identified four trials (three from UK and one Canadian) reporting 10 year outcomes of hypofractionation.
plus two further studies \((N = 908\) and 47\) reporting 3.5 year results. These trials will be summarised only briefly, since they have been published for several years. All adopted a control regimen of 50 Gy in 25 fractions following primary surgery, mostly breast conservation surgery, and tested fraction sizes in the range 2.7–3.3 Gy. The UK START-Pilot (-P) and START-A trials were three-arm studies designed to generate direct estimates of \(\alpha/\beta\) for local cancer control and normal tissue responses unconfounded by differences in treatment time (5 weeks), whereas the UK START-B and Ontario trials were pragmatic two-group comparison testing non-inferiority of 15- and 16-fraction regimens (2.7 Gy per fraction) over 3 and 3.2 weeks in terms of local tumour control and adverse effects. Patient and treatment characteristics of these four trials are summarised in Table 1.

Rates of local tumour relapse in these trials are summarised in Table 2, from which a couple of points can be made. The two test dose regimens in START-P were 13-fraction regimens estimated to be isoeffective with 50 Gy in 25 fractions based on \(\alpha/\beta\)-values

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**Table 1. Patient and treatment characteristics in four randomised trials testing hypofractionated radiotherapy after surgery for early breast cancer**

|                  | START-P\(^8\) | START-A\(^9\) | START-B\(^10\) | Ontario\(^7\) |
|------------------|---------------|---------------|----------------|---------------|
| Years accrual    | 1986–1998     | 1998–2002     | 1999–2001       | 1993–1996     |
| Total number of patients | 1410          | 2236          | 2215           | 1234          |
| Standard arm (Gy/fr/weeks) | 50/25/5       | 50/25/5       | 50/25/5        | 50/25/5       |
| Test arm A (Gy/fr/weeks)   | 42.9/13/5     | 41.6/13/5     | 40.0/15/5      | 42.5/16/3.1   |
| Test arm B (Gy/fr/weeks)   | 39/13/5       | 39/13/5       | n/a            | n/a           |
| Mean age (years)        | 54.5          | 57.2          | 57.4           | Not reported  |
| Node+ (%)               | 32.7          | 28.8          | 22.8           | 0             |
| Mastectomy (%)          | 0             | 15            | 8              | 0             |
| Tumour size \(\geq T_2\) (%) | 42.5\(^a\)   | 48.6\(^a\)   | 35.9\(^a\)    | 20.0\(^a\)   |
| Boost (%)               | 74.5          | 60.6          | 42.6           | 0             |
| Chemotherapy (%)        | 13.9          | 35.5          | 22.2           | 11            |
| Regional radiotherapy (%) | 20.6          | 14.2          | 7.3            | 0             |

\(^a\)Clinical T- stage.
\(^b\)Pathological stage.
of 6 and 3 Gy respectively, representing the highest and lowest estimates of fractionation sensitivity of the dose-limiting late-reacting normal tissues of the breast/ribcage consistent with the literature in the mid-1980s. Based on the results of the START-P trial, the 3.3 Gy (42.9 Gy) dose level was reduced to 3.2 Gy (41.6 Gy) in START-A, corresponding to a schedule isoeffective with 50 Gy in 25 fractions assuming an $\alpha/\beta$-value of 4 Gy.

A second point to note in Table 2 is that START-B confirmed non-inferiority of the 15-fraction regimen based on an upper 95% confidence interval (CI) for local relapse at 10 years. The results of the Ontario trial were consistent with this result. A recent post hoc evaluation of the better-than-expected 3.8% point estimate for local relapse rate 10 years after 40 Gy in 15 fractions compared to 5.2% after 50 Gy in 25 fractions in START-B raises the possibility of a time effect for local control after adjuvant breast radiotherapy. Better-than-expected because the 3-week schedule is equivalent to 46 Gy in 23 fractions assuming $\alpha/\beta = 3$ Gy, as estimated by START-P and –A trials, in which all patient groups had 5 weeks of radiotherapy. A hypothesis-generating analysis postulates 0.65 Gy wasted dose per day, when 2 Gy fractions are used.14

Table 2. Rates of local tumour relapse in four randomised trials testing hypofractionated radiotherapy after surgery for early breast cancer

| Trial     | Randomisation (Gy/fraction) | % 5 year local relapse (95% CI) | % 10 year local relapse (95% CI) |
|-----------|-----------------------------|---------------------------------|----------------------------------|
| START-P9,13 | 50.0/25                     | 7.9 (5.4–10.4)                  | 12.1 (8.8–15.5)                  |
|           | 42.9/13                      | 7.1 (5.4–10.4)                  | 9.6 (6.7–12.6)                   |
|           | 39.0/13                      | 9.1 (6.4–11.7)                  | 14.8 (11.2–18.3)                 |
| START-A10,13 | 50.0/25                     | 3.4 (2.3–5.1)                   | 6.7 (4.9–9.2)                    |
|           | 41.6/13                      | 3.1 (2.0–4.7)                   | 5.6 (4.1–7.8)                    |
|           | 39.0/13                      | 4.4 (3.1–6.2)                   | 8.1 (6.1–10.7)                   |
| START-B11,13 | 50.0/25                     | 3.3 (2.4–4.6)                   | 5.2 (2.7–5.2)                    |
|           | 40.0/15                      | 1.9 (1.2–3.0)                   | 3.8 (2.7–5.2)                    |
| Ontario12 | 50.0/25                      | 3.2$a$                         | 6.7$b$                           |
|           | 42.5/16                      | 2.8$a$                         | 6.2$b$                           |

CI, confidence interval.

*a Absolute difference 0.4% [95% CI (-1.5 to +2.4%)].

*b Absolute difference 0.5% [95% CI (-2.5 to +3.5%)].

Table 3. Clinically assessed moderate or marked adverse effects for patients treated by breast conservation surgery in four randomised trials testing hypofractionated radiotherapy7–13

| Trial      | Randomisation (Gy/fraction) | % breast shrinkage at 10 year (95% CI) | % excellent or good breast cosmesis at 10 year (95% CI) |
|------------|----------------------------|---------------------------------------|--------------------------------------------------------|
| START-pilot | 50.0/25                     | 63.8                                  | 56.8                                                   |
|            | 42.9/13                      | 74.4                                  | 64.2                                                   |
|            | 39.0/13                      | 58.0                                  | 55.0                                                   |
| START-A    | 50.0/25                      | 34.2 (29.8–39.2)                      | 33.4 (28.7–38.1)                                       |
|            | 41.6/13                      | 31.4 (27.2–36.0)                      | 30.6 (26.8–34.4)                                       |
|            | 39.0/13                      | 30.0 (25.7–34.8)                      | 29.5 (25.3–33.7)                                       |
| START-B    | 50.0/25                      | 31.2 (27.9–34.9)                      | 31.2 (27.8–34.9)                                       |
|            | 40.0/15                      | 26.2 (23.1–29.6)                      | 26.2 (23.1–29.6)                                       |
| Ontario    | 50.0/25                      | 71.3$a$                               | 69.8$a$                                                |
|            | 42.5/16                      | 69.8$a$                               | 69.8$a$                                                |

CI, confidence interval.

*a Absolute difference 1.5% [95% CI (−6.9 to +9.8)].

Table 3 summarises secondary end points, including moderate or marked adverse effects of breast shrinkage and cosmesis in the Ontario trial.

Estimates of $\alpha/\beta$ for local tumour control and late adverse effects based on 10 year follow up of 8681 patients in the START-P and START-A/B trials are summarised in Table 4. The estimates are consistent with hypothesis that 2 Gy fractions are as gentle on breast cancer as they are on healthy tissues. This
means there are no advantages to patients in continuing their use in this setting.

Based on the consistency in primary and secondary outcomes of all four randomised trials, an increasing number of countries incorporate 15- or 16-fraction regimens as a standard of care for substantial categories, if not all, of their patients, most commonly the large population of females over 50 years with axillary node negative tumours. Another randomised hypofractionation trial led by Birgitte vrou Offersen, Aarhus, Denmark, is currently conducting a valuable independent test of the START-B schedules viz. comparing 50 Gy in 25 fractions against 40 Gy in 15 fractions in patients prescribed breast radiotherapy. The 15-fraction regimen is also being tested in patients prescribed local-regional radiotherapy in the international randomised Skagen I trial, led by Birgitte vrou Offersen. Meanwhile, a UK consensus statement by the Royal College of Radiologists states “There is no indication to use more than 15 fractions for the breast, chest wall or nodal areas for standard adjuvant treatment.” This schedule is currently standard of care for all UK patients prescribed adjuvant local or local-regional radiotherapy for operable breast cancer. If a tumour bed boost dose is indicated in patients with high risk features, an additional 13.5 Gy in five fractions of 2.7 Gy delivers the equivalent of 14 Gy in seven fractions of 2 Gy, assuming an $\alpha/\beta$ of 3 Gy.

**ANY CONCERNS?**

Arguments against routine adoption of 15- or 16-fraction regimens given Level I evidence of safety and effectiveness are often expressed in terms of underrepresented patient subgroups, begging questions as to where the burden of proof lies in an era of rapid changes in patient management. Subgroups are clearly important for endocrine and biological agents that target cancer-specific mechanisms operative in defined subsets of tumours. Tumour type-specific molecular pathways targeted by endocrine and other systemic agents stand in contrast to a central role for DNA double strand break processing and repair in normal and malignant tissue responses to fractionated radiotherapy, possibly including immune responses. If standard fractionation is prescribed with confidence before, after or alongside new systemic agents, e.g. there is every likelihood of safety if a hypofractionation regimen is used, an expectation that can be prospectively monitored. Funding tariffs for radiotherapy can also be barriers to adoption of hypofractionation, but putting this aside, what other concerns are expressed?

Are the trial patient and tumour characteristics representative of the population?

The Ontario trial population represents the largest single subgroup of females referred for adjuvant radiotherapy, namely females ≥50 years treated by tumour excision for pT1-2pN0M invasive carcinoma, representing at least one-half of all patients prescribed post-operative adjuvant radiotherapy for early breast cancer in many countries. The eligibility criteria for the START trials were broader, only excluding patients having immediate breast reconstruction or prescribed concurrent cytotoxic chemotherapy. Table 5 shows patient and treatment characteristics for the START trials entered in the three START trials, confirming features representative of the contemporary UK population, including the proportion of patients prescribed adjuvant chemoradiotherapy, 1998–2002. The hazard ratios shown in Figure 2 raise no concerns for any particular subgroup, with point estimates <1 for females under 50 years, those treatment by mastectomy, those with node positive tumours or high tumour grade and females prescribed cytotoxic therapy. On this basis, there is no identifiable reason to withhold radiotherapy from any group of patients, and if this policy is maintained for a population with characteristics broadly comparable with those tested in the hypofractionation trials, the overall results will be those of a safe, effective, convenient and even less expensive therapy.

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**Table 4. Unconfounded estimates of $\alpha/\beta$: START-Pilot & START-A Trials**

| Effect                  | Estimate (95% CI)       |
|-------------------------|-------------------------|
| Adverse effects (815 events/2263 pts): $\alpha/\beta = 3.1$ Gy [95% CI (2.0–4.2)] |
| Tumour relapse (349 events/3646 pts): $\alpha/\beta = 3.5$ Gy [95% CI (1.2–5.7)] |

**Table 5. START pilot, A & B (n = 5861): patient and treatment characteristics**

| Age <50 years | 1389 |
| Age ≥ 50 years | 4472 |
| Breast conserving | 5348 |
| Mastectomy | 513 |
| pN– | 4318 |
| pN+ | 1421 |
| Grade 1 | 1213 |
| Grade 2 | 2398 |
| Grade 3 | 1271 |
| No cytotoxics | 4346 |
| Cytotoxics | 1480 |

**Figure 2. Meta analysis of tumour control: START pilot, A and B (n = 5861).** CI, confidence interval.
What about the heart?
No excess of cardiac damage has been suggested after hypofractionation in the START or Ontario trials, although the small number of cardiac events limits the power of formal comparisons. It is easy to model the impact of hypofractionation by assuming different α/β-values for the heart, Table 6, where it is clear that even assuming a sensitivity to fraction size as low as 1.5 Gy, the equivalent total dose delivered in 2 Gy fractions of 40 Gy in 15 fractions is lower than the historical standard of 50 Gy in 25 fractions. In practice, the challenge is to protect the heart regardless of radiotherapy regimen by adopting breath hold or other heart-sparing technique.

The heavy-breasted patient-“triple trouble”?
It is a myth that dose inhomogeneity in the breast poses a risk to patients prescribed hypofractionation. Look at Table 7, where the impact of dose inhomogeneity is illustrated in relation to a partial volume receiving 105%. If 3.2 Gy fractions are used as illustration, 13 fractions deliver the equivalent of 50 Gy in 25 fractions, corresponding to α/β = 3 Gy and consistent with results of the START-A and Ontario trials. Double trouble as described by Withers is a problem, no doubt about that, but modest hypofractionation does not make this worse i.e. there is no “triple trouble”.

After mastectomy?
Why some people worry that removing the breast might alter the fractionation sensitivity of overlying skin and underlying ribcage is unclear, but this is an occasional concern expressed at conferences. Several hundred mastectomy patients (N = 513) were entered in the START trials, and comparisons were not powered for statistical analysis. However, just looking at the hazard ratios and 95% CIs for selected patient-reported outcomes in START-A in Table 8 raise no cause for concern. The hypofractionation trials were conducted before the current era of oncoplastic surgery, but there are no identifiable reasons to avoid hypofractionation in this subgroup either. As emphasised above, even assuming α/β of 1.5, 40 Gy in 15 fractions is expected to generate milder late adverse effects than 50 Gy in 25 fractions.

Is there any reason to avoid the lymphatics?
Only 470 patients were prescribed lymphatic radiotherapy in the START trials, most commonly to supraclavicular fossa, and extending to upper axillary levels in a small minority. Variable volumes of Level I/II axilla would have been included the tangential beams to the breast, despite Level I/II surgical dissection in >90% patients. There was no suggestion of enhanced shoulder stiffness or arm oedema associated with hypofractionation in the 10-year START assessments, but these included all patients regardless of lymphatic radiotherapy.

Table 6. Current whole breast hypofractionation is likely less damaging to the heart

| α/β-value | Equivalent total /dose in 2 Gy fractions |
|-----------|----------------------------------------|
|           | 50 Gy/25F | 40 Gy/15F |
| 3.0 Gy    | 50.0      | 45.5      |
| 1.5 Gy    | 50.0      | 48.0      |

Table 7. ‘Triple trouble’ in heavy-breasted patients is not a concern, either

| Breast dose inhomogeneity | Total equivalent dose (Gy) if α/β = 3 Gy for fraction sizes of |
|---------------------------|---------------------------------------------------------------|
|                           | 2 Gy                           | 4 Gy                           |
| 100%                      | 50.0                           | 50.0                           |
| ↓                         | ↓                              | ↓                              |
| 105%                      | 53.6                           | 54.0                           |

‘double trouble’ ‘triple trouble’

Table 8. Patient-reported outcomes for breast conservation and mastectomy patients enrolled in START-A trial

| Change in skin appearance since radiotherapy | Type of primary surgery |
|---------------------------------------------|-------------------------|
|                                             | Breast conserving surgery (n = 848) | Mastectomy (n = 232) |
| Change in skin appearance since radiotherapy | 50 Gy | 41.6 Gy | 39 Gy | 50 Gy | 41.6 Gy | 39 Gy |
|                                             | 1 | 0.92 (0.68–1.25) | 0.63 (0.45–0.88) | 0.53 (0.28–0.99) | 0.64 (0.34–1.17) |
| Skin problems on or in area of affected breast | 50 Gy | 41.6 Gy | 39 Gy | 50 Gy | 41.6 Gy | 39 Gy |
|                                             | 1 | 1.02 (0.70–1.50) | 0.87 (0.58–1.30) | 0.90 (0.39–2.10) | 1.07 (0.48–2.38) |
| Pain in area of affected breast              | 50 Gy | 41.6 Gy | 39 Gy | 50 Gy | 41.6 Gy | 39 Gy |
|                                             | 1 | 1.29 (0.92–1.82) | 1.01 (0.70–1.45) | 0.82 (0.42–1.61) | 0.87 (0.45–1.69) |
of patient-reported outcomes in those prescribed lymphatic radiotherapy raises no suggestion of enhanced arm or shoulder dysfunction associated with hypofractionation (Haviland, in press). With regard to the brachial plexus, no cases were recorded after 40 Gy in 15 fractions in the START-B trial, and modelling the expected impact of this schedule assuming a very low value of $\alpha/\beta = 1.5$ Gy (as in Table 6 for heart), suggests that this regimen should be gentler on the brachial plexus than 50 Gy in 25 fractions. As comprehensive lymphatic radiotherapy is introduced that exploits improved planning and treatment techniques, the risk of "triple trouble" is as insignificant for brachial plexus as it is for heavy-breasted patients. In other words, if oncologists are confident in prescribing 50 Gy in 25 fractions to contemporary lymphatic treatment volumes, they should be confident to prescribe 40 Gy in 15 fractions.

Trials tested only adjuvant hypofractionation

Oxygen status, proliferative kinetics and other parameters change according to disease bulk, raising a question about hypofractionation in patients with clinical disease. There are no randomised data, but the starting point of this manuscript was an analysis of $>1000$ patients with locally advanced or locally recurrent disease treated with a wide range of fractionation regimens deriving an $\alpha/\beta$-value of 3.8 Gy, which is comparable with that generated by randomised trials in the adjuvant setting. Bulky prostatic carcinomas are also sensitive to fraction size, so on balance it seems very likely that breast cancer is too, but it would certainly be beneficial to put this hypothesis to test in randomised trials.21

**HYPOFRACTIONATION AND DOSE INTENSITY MODULATION**

Since hypofractionation to the whole breast/chest wall is a standard of care in an increasing number of countries, it carries implications for how a tumour bed boost doses should be delivered. There seems little point in retaining fraction sizes of 2.0 Gy, if modulation of fraction size can achieve the same outcomes. The UK IMPORT HIGH trial ($N = 2,658$) tests the hypothesis that concomitant boost is as safe and non-
The UK FAST trial tested two total doses (30 & 28.5 Gy) of a 5-fraction regimen (3.0 & 5.7 Gy per fraction) delivering one fraction per week against 50 Gy in 2.0 Gy fractions to whole breast in 915 females ≥50 years following complete microscopic local resection of pT1-2pN0M0 disease. Median 3 year analyses of adverse effects (primary end point) were consistent with $\alpha/\beta$ of 3 Gy; as reported by the START trials, although the point estimate was slightly lower at 2.6 Gy [95% CI (1.4–3.7)]. If a point estimate of 2.6 Gy is assumed, it may reflect the much lower rate of moist desquamation (11% after 50 Gy vs 2% after 28.5 Gy) and reduced risk of consequential late effects, particularly telangiectasia in the inframammary fold. Consequential late effects share the same high $\alpha/\beta$-value as the epidermal depletion that causes them and if present will tend to increase the estimate of $\alpha/\beta$-value. At the time of last reporting (median 3 years), only two local relapses had been recorded.

The early results of the FAST trial informed the design of the UK FAST-Forward trial ($N = 4000$) testing two dose levels of a 5-fraction regimen delivered in 3 days against the current UK standard of 40 Gy in 15 fractions in patients prescribed whole breast or post-mastectomy irradiation after primary surgery (Figure 9). The trial recruited between 2012 and 2014 and remains in follow up. A lymphatic subprotocol is currently recruiting with arm swelling and shoulder mobility as primary endpoints.

**THE FUTURE?**

Figure 5 shows the timeline of the UK adjuvant breast radiotherapy trials referred to in this review.

A possible outcome is a 1 week schedule of dose intensity modulated whole or partial breast radiotherapy that not only improves the balance of local cancer control and adverse effects but also reduces the physical, emotional and economic burdens of classical treatment schedules. The trials discussed here, and many other radiotherapy trials worldwide, undoubtedly owe a debt to the inspiration and encouragement offered by Jack Fowler and Oliver Scott to many generations of radiation oncologists.

Table 9

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**Table 9. Fast forward ($N = 4000$): local RT after breast conservation surgery or mastectomy**

| Group | Total dose (Gy) | Fraction size (Gy) | Number fractions | Time (weeks) |
|-------|----------------|-------------------|-----------------|-------------|
| Control | 40.0 | 2.7 | 15 | 3 |
| Test 1° | 27.0 | 5.4 | 5 | 1 |
| Te | 26.0 | 5.2 | 5 | 1 |

RT, radiotherapy.

°Equivalent to control assuming $\alpha/\beta = 3$ Gy and no time effect.
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