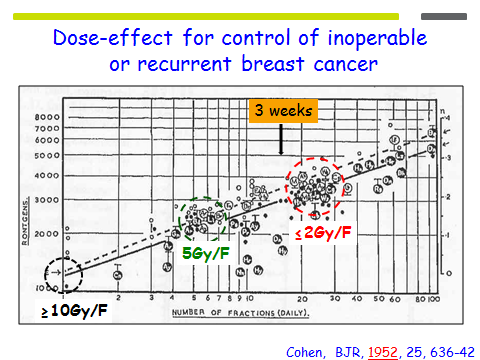
**Changes in radiotherapy fractionation – breast cancer**

**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 trainees like me. Just a few days’ contact with these outstanding teachers did more than anything else to stimulate a lasting interest in clinical radiation biology in the student group. In the years that followed, Jack Fowler became a leading interpreter of the linear-quadratic model developed by Rodney Withers and colleagues (1, 2). The delivery of radiotherapy as a series of dose increments or fractions had been developed by clinicians since the early 20th century using the technologies to hand. 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 The Royal College of Radiologists in 2006 (3).

Interest in hypofractionation applied to primary breast cancer was sparked by a review of superfractionation (fractions <2.0 Gy) by the Canadian radiation biologist Bruce Douglas through the lens of the still-new linear quadratic model (4). On the final page of this 11-page manuscript was a single passing reference to *hypo*fractionation; “For breast cancer, however, the β/α value that can be calculated from published data is about 0.26.” Well, that sentence made me jump, since the reciprocal of 0.26 becomes an α/β 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, see Figure 1.

**Figure 1.** Dose-effect for control of inoperable or recurrent breast cancer, adapted from Cohen (5). Vertical axis is total dose expressed in Roentgens; Vertical position indicates median tumour dose prescribed. Horizontal axis indicates number of daily fractions given 5-times weekly. Large circles represent published series of minimum 30 patients; open large circles describe control in which ≥50% tumour control; closed large circles describe control in which <50% tumour control. Small circles/dots represent individual patients treated by Cohen; open symbol indicates local control, closed symbol indicates local failure. Dashed line represents the median tumour control dose for 61 of Cohen’s patients. Solid line represents median tumour control doses for previously published series



**Randomised trials of adjuvant hypofractionation**

A 2016 systematic overview of fraction size in breast radiotherapy in the Cochrane Database of Systematic Reviews identified 4 trials (3 from UK and 1 Canadian) reporting 10-year outcomes of hypofractionation plus 2 further studies (N=908 and N=47) reporting 3.5-year results (6). The first 4 trials will be summarised briefly, given that they have been published for several (7-13). 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 were 3-arm studies designed to generate direct estimates of α/β for local cancer control and normal tissue responses unconfounded by differences in treatment time (5 weeks), whereas the UK START-B and Ontario 2-arm trials were pragmatic in testing non-inferiority of 15- and 16-fraction regimens (2.7 Gy per fraction) over 3 and 3.2 weeks, respectively, in terms of local tumour control and adverse effects. Patient and treatment characteristics of these 4 trials are summarised in Table 1.

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| --- | --- | --- | --- | --- |
| **Table 1.** Patient and treatment characteristics in 4 randomised trials testing hypofractionated radiotherapy after surgery for early breast cancer | | | | |
|  | START-P (8) | START-A (10) | START-B (11) | 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 ≥T2 (%) | 42.5a | 48.6b | 35.9b | 20.0b |
| 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 |  |  |  |  |

Rates of local tumour relapse in these trials are summarised in Table 2, from which a couple of points can be made. The 2 test dose regimens in START-P were 13-fraction regimens estimated to be iso-effective with 50 Gy in 25 fractions based on α/β values of 6 Gy 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 START-B, the 3.3 Gy (42.9 Gy) dose level was reduced to 3.2 Gy (41.6 Gy) in the START-A trial, corresponding to a schedule iso-effective with 50 Gy in 25 fractions assuming α/β value of 4 Gy.

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| **Table 2.** Rates of local tumour relapse in 4 randomised trials testing hypofractionated radiotherapy after surgery for early breast cancer | | | |
| Trial | Randomisation (Gy/fraction) | Percent 5 yr local relapse (95% CI) | % 10 yr local relapse (95% CI) |
| START-P (9, 13) | 50.0/25  42.9/13  39.0/13 | 7.9 (5.4-10.4)  7.1 (4.6-9.5)  9.1 (6.4-11.7) | 12.1 (8.8-15.5)  9.6 (6.7-12.6)  14.8 (11.2-18.3) |
| START-A (10, 13) | 50.0/25  41.6/13  39.0/13 | 3.4 (2.3-5.1)  3.1 (2.0-4.7)  4.4 (3.1-6.2) | 6.7 (4.9-9.2)  5.6 (4.1-7.8)  8.1 (6.1-10.7) |
| START-B (11, 13) | 50.0/25  40.0/15 | 3.3 (2.4-4.6)  1.9 (1.2-3.0) | 5.2 (3.9-6.9)  3.8 (2.7-5.2) |
| Ontario (12) | 50.0/25  42.5/16 | 3.2a  2.8a | 6.7b  6.2b |
| a Absolute difference 0.4% (95% CI –1.5 to +2.4%)  b Absolute difference 0.5% (95% CI –2.5 to +3.5%) | | | |

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 (5.2%) at 10 years that was <5% above the 3.9% lower 95% CI for local relapse after 50 Gy in 25 fractions. 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 α/β=3 Gy, as estimated by START-P and -A. A hypothesis-generating analysis, assuming these are accurate estimates of effect, postulates 0.65 Gy wasted dose per day when 2 Gy fractions are used (14). Table 3 summarises secondary endpoints, including moderate or marked adverse effects of breast shrinkage and cosmesis in the Ontario trial.

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| **Table 3.** Clinically assessed moderate or marked adverse effects for patients treated by breast conservation surgery in four randomised trials testing hypofractionated radiotherapy (7-13) | | | |
| Trial | Randomisation (Gy/fraction) | Percent breast shrinkage at 10 yr (95% CI) | Percent excellent or good breast cosmesis at 10 yr (95% CI) |
| START-pilot | 50.0/25  42.9/13  39.0/13 | 63.8  74.4  58.0 |  |
| START-A | 50.0/25  41.6/13  39.0/13 | 34.2 (29.8-39.2)  31.4 (27.2-36.0)  30.0 (25.7-34.8) |  |
| START-B | 50.0/25  40.0/15 | 31.2 (27.9-34.9)  26.2 (23.1–29.6) |  |
| Ontario | 50.0/25  42.5/16 |  | 71.3a  69.8a |
| a Absolute difference 1.5% (95% CI -6.9 to +9.8) | | | |

Estimates of α/β for local tumour control and late adverse effects based on 10-year follow up of 5861 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, and that there are no advantages in continuing their use in this setting.

**Table 4.** Unconfounded estimates of α/β: START-Pilot & START-A Trials (13)

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| --- |
| Adverse effects (815 events/2263 pts): α/β = 3.1 Gy (95% CI 2.0-4.2) |
| Tumour relapse (349 events/3646 pts): α/β = 3.5 Gy (95% CI 1.2-5.7 |

Based on the consistency in primary and secondary outcomes of all 4 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 women 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 is prescribed breast radiotherapy. The 15-fraction regimen is also being tested in patients prescribed local-regional radiotherapy in the international randomised Skagen I trial, also 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” (15). 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 5 fractions of 2.7 Gy delivers the equivalent of 14 Gy in 7 fractions of 2 Gy, assuming an α/β 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 under-represented 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 cell and molecular mechanisms operative in defined subsets of tumours. Multiple tumour-specific molecular pathways of therapeutic action contrast to the central role for DNA double strand break processing and repair in a large majority of normal and malignant tissue responses to radiotherapy, including response to fraction size (16). If standard fractionation is prescribed with confidence before, after or alongside new systemic agents, for example, there is a every likelihood of safety if a standard hypofractionation regimens are used, an expectation that can be prospectively monitored. Apart from clinical concerns, funding tariffs for fractionated radiotherapy can also be barriers to adoption. Putting these influences aside, what concerns are most commonly expressed?

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

The Ontario trial population represents the largest single ‘subgroup’ of women referred for adjuvant radiotherapy, namely women ≥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 5a shows patient and treatment characteristics for the 5861 patients entered in the 3 START trials, showing features representative of the contemporary UK population, including the proportion of patients prescribed adjuvant chemotherapy, 1998-2002. Table 5b suggests no treatment effects disfavouring hypofractionation, with point estimates <1 for women <50 years, those treatment by mastectomy, with node positive tumours, high tumour grade or treatment including 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 confirm safety and non-inferiority.

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| **Table 5a.** START pilot, A & B (n=5861): patient and treatment characteristics (13). | **Table 5b.** Metanalysis of tumour control: START pilot, A and B (n=5861) (13). |
| |  |  | | --- | --- | |  | Number patients | | Age <50yrs | 1389 | | Age ≥50yrs | 4472 | | Breast conserving | 5348 | | Mastectomy | 513 | | pN- | 4318 | | pN+ | 1421 | | Grade 1 | 1213 | | Grade 2 | 2398 | | Grade 3 | 1271 | | No cytotoxics | 4346 | | Cytotoxics | 1480 | |  |
|  |  |

*What about the heart?*

No excess of cardiac damage has been suggested after hypofractionation in the START or Ontario trials, although a 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, see Table 6, where it is clear that even assuming a sensitivity to fraction size as low as 1.5 Gy, the equivalent total dose (EQD) delivered in 2 G fractions of 40 Gy in 15 fractions is *lower* than the historical standard of 50 Gy in 25 fraction (17). In practice, the challenge is to protect the heart regardless of radiotherapy regimen by adopting breath hold or other heart-sparing technique (18).

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| **Table 6.** Current whole breast hypofractionation is likely less damaging to the heart (17). | | | | |
|  | **α/β value** | **Equivalent Total /Dose in 2 Gy fractions** | |
|  |  | |
|  | 50 Gy/25F | 40Gy/15F |
|  | 3.0 Gy | 50.0 | 45.5 |
|  | 1.5 Gy | 50.0 | 48.0 |

*The heavy-breasted patient - “triple trouble”?*

It is a myth that dose inhomogeneity 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% (19). 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”.

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| **Table 7.** ‘Triple trouble’ in heavy-breasted patients is not a concern, either (19) | | |
| **Breast dose inhomogeneity** | **Total equivalent dose (Gy) in α/β = 3 Gy &**  **you use fraction sizes of** | |
| 2 Gy | 4 Gy |
| 100% | 50.0 | 50.0 |
| 105% | 53.6 | 54.0 |
|  | ‘double trouble’ | ‘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% confidence intervals for selected patient-reported outcomes in START-A in Table suggest no cause for concern (20). 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 Gy, 40 Gy in 15 fractions is expected to generate milder late adverse effects than 50 Gy in 25 fractions.

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| **Table 8.** Patient-reported outcomes for breast conservation and mastectomy patients enrolled in START-A trial (20) | | |
|  | Type of primary surgery |  |
|  | Breast conserving surgery (n=848) | Mastectomy (n=232) |
| **Change in skin appearance since radiotherapy** | | |
| 50 Gy | 1 | 1 |
| 41.6 Gy | 0.92 (0.68-1.25) | 0.53 (0.28-0.99) |
| 39 Gy | 0.63 (0.45-0.88) | 0.64 (0.34-1.17) |
| **Skin problems on or in area of affected breast** | | |
| 50 Gy | 1 | 1 |
| 41.6 Gy | 1.02 (0.70-1.50) | 0.90 (0.39-2.10) |
| 39 Gy | 0.87 (0.58-1.30) | 1.07 (0.48-2.38) |
| **Pain in area of affected breast** | | |
| 50 Gy | 1 | 1 |
| 41.6 Gy | 1.29 (0.92-1.82) | 0.82 (0.42-1.61) |
| 39 Gy | 1.01 (0.70-1.45) | 0.87 (0.45-1.69) |

*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 (13). A retrospective analysis 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 α/β=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 exploiting improved planning and treatment techniques is introduced, the risk of “triple trouble” is as insignificant for brachial plexus as “triple trouble” 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 α/β value of 3.8 Gy, which is comparable with that generated by randomised trials in the adjuvant setting. Bulky prostatic carcinomas are 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 well 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-inferior to standard sequential boost techniques, see Figure 2a (22). All patients were treated using megavoltage x-rays using forward or inverse planned intensity modulated radiotherapy (IMRT) localised using image-guidance to visualise titanium ligaclips inserted in the tumour bed. Target volumes for whole breast and boost volumes were defined prior to randomisation. The boost dose intensity in Test 1 was chosen on the basis that it was expected to be iso-effective with Control assuming α/β = 3 Gy, whereas the dose intensity to whole breast in Test 1 was reduced to reflect the lower tumour burden and low recurrence risk outside the boost volume. The dose spared in Test 1 was ‘moved’ into the boost volume in Test 2, which received approximately the same integral total breast dose as Control, see Figure 2b. It is hoped that patient reported outcomes and clinical evaluations of adverse effects and local tumour control will inform more effective distributions of breast dose leading to further improvement in therapeutic ratio.

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| **Figure 2a.** UK IMPORT High Trial schema (n=2568) (22). | **Figure 2b.** Comparisons of IMPORT HIGH trial total doses *as if* delivered using 2.0 Gy fractions (α/β = 3 Gy) |
|  |  |

Hypofractionation has also been applied in testing dose intensity reduction in women judged at low risk of local relapse after breast conservation surgery see Figures 3a & b. In the recently published IMPORT LOW trial, non-inferiority for local control was confirmed and fewer adverse effects were reported in Test group 2 compared to Group 1 or whole breast radiotherapy (23).

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| --- | --- |
| **Figure 3a.** UK IMPORT Low Trial schema n=2018) radiotherapy (23). | **Figure 3b.** Comparisons of total doses *as if* delivered using 2.0 Gy fractions (α/β = 3 Gy) |
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**What are the limits of whole breast hypofractionation?**

In principle, since the fractionation sensitivity of breast cancer is comparable to that of the dose-limiting normal tissues, it is reasonable to consider if a single fraction is the logical endpoint of hypofractionation in breast cancer, at least in the adjuvant setting where reoxygenation may not need to be exploited. Single high dose-rate intra-operative irradiation of the tumour bed by megavoltage electrons or orthovoltage x-rays as tested in the ELIOT and TARGIT trials represent limited examples of this approach, but the results are difficult to interpret in term, given the impact of total dose, uncertain dosimetry and variable treatment volumes (24, 25).

The UK FAST trial tested 2 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 women ≥50 years following complete microscopic local resection of pT1-2pN0M0 disease (26). Median 3-year analysis of adverse effects (primary endpoint) was consistent with α/β 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 the point estimate of 2.6 Gy is true, 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 α/β value as the epidermal depletion that causes them and if present will tend to increase the estimate of α/β value. At the time of last reporting (median 3 years), only 2 local relapses had been recorded.

The early results of the FAST trial informed the design of the UK FAST Forward trial (N=4000) testing 2 dose levels of a 5-fraction regimen delivered in 5 days against the current UK standard of 40 Gy in 15 fractions in patients prescribed whole breast or post-mastectomy irradiation after primary surgery, see Figure 9 (27). The trial recruited between 2012 and 2014 and remains in follow up. A lymphatic sub-protocol is currently recruiting with arm swelling and shoulder mobility as primary endpoints.

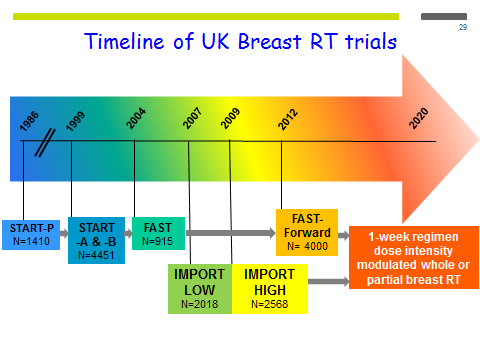
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 9**. Fast Forward (N=4000): Local RT after breast conservation surgery or mastectomy (27). | | | | |
| Group | Total dose (Gy) | Fraction size (Gy) | Number fractions | Time (weeks) |
| Control | 40.0 | 2.7 | 15 | 3 |
| \*Test 1 | 27.0 | 5.4 | 5 | 1 |
| Test 2 | 26.0 | 5.2 | 5 | 1 |

\*Equivalent to Control assuming α/β=3 Gy and no time effect

**The future?**

Figure 4 shows the timeline of the UK adjuvant breast radiotherapy trials referred to in this review.

**Figure 4.** Timeline of UK Beast RT Trials



A possible outcome is a 1-week schedule of dose intensity modulated whole or partial breast radiotherapy relevant to patients 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 several generations of radiation oncologists.

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