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Focus On

Hypofractionated whole breast irradiation

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Abstract The international standard regimen of radiotherapy for women with early breast cancer following mastectomy or local tumour excision involves the delivery of daily doses (fractions) of 2.0 Gy to a total dose of 50 Gy. Recent randomised clinical trials suggest that there is most unlikely to be any disadvantages in terms of local tumour control or late adverse effects, and obvious advantages in terms of convenience, for schedules treating to a lower total dose using a smaller number of larger fractions. Fifteen or 16 fractions of 2.67 Gy are being adopted in some countries, and future research will test the limits of this approach, termed accelerated hypofractionation.

Keywords: Adjuvant therapy; Early breast cancer; Hypofractionation; Radiotherapy

We may be living in an era of fast-moving molecular medicine, but historical influences exert profound, and often justified, effects on everyday practices. Radiotherapy fractionation represents a good example, since dose-limiting toxicities of new radiotherapy regimens take decades to mature, setting limits on the pace of change. Radiotherapy for carcinomas of the head and neck, bronchus, and uterine cervix has been a most important influence on radiotherapy practices as a whole. Squamous carcinomas are, on average, relatively fast-growing neoplasms best treated to high total doses ($>$65 Gy) delivered in multiple fractions $\leqslant$2.0 Gy [1,2]. In an attempt to overcome the compensatory tumour proliferation between schedules delivering five fractions per week over 7 weeks or more, six daily 2.0 Gy fractions per week or twice daily fractions of 1.8 Gy have been tested [3,4]. Post-operative radiotherapy for early breast cancer has also traditionally used fractions of 1.8–2.0 Gy to a total dose of around 50 Gy, albeit without a perceived need to shorten treatment time (so-called accelerated fractionation).

There is no doubt that 50 Gy in 25 fractions of 2.0 Gy is effective in the adjuvant therapy of early breast cancer, current levels of local tumour control after breast conservation surgery or mastectomy being $>$95% at 5 years [5,6]. However, colleagues in the UK and Canada have long believed that a lower total dose delivered in fewer, larger fractions can be at least as safe and effective as this standard schedule [7,8]. For example, the Christie Hospital in Manchester, UK, introduced the use of 40 Gy in 15 fractions of 2.67 Gy over 3 weeks, with satisfactory results in terms of late adverse effects and local tumour control [9].

The responses of normal and malignant tissues to changes in fraction size are non-linear and are well described using a linear quadratic model [10]. Reductions in total dose are needed to take account of the increasing effect of larger fractions on normal tissues. The main controversy focuses on whether a single hypofractionated regimen can be identified that is at least equivalent to 50 Gy in 25 fractions in every clinically relevant respect, including a range of late adverse effects. It is certain that some forms of hypofractionation are unsuitable for treating the axilla and supraclavicular fossa by virtue of the sensitivity of brachial plexus to

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Table 1. Summary of prospective randomised trials in early breast cancer testing radiotherapy fractions larger than 2.0 Gy.

Trial	Number of patients	Control arms Fraction size (Gy) × number of fractions	Test arms Fraction size (Gy) × number of fractions
Ontario [12]	1234	2.0 × 25	2.66 × 16
UK RMH/GOC [16,17]	1410	2.0 × 25	3.0 × 13 3.3 × 13
UK START A [5]	2236	2.0 × 25	3.0 × 13 3.2 × 13
UK START B [6]	2215	2.0 × 25	2.67 × 15

fraction size. However, it appears that schedules using fractions >2.0 Gy can be identified, which are equivalent in all clinically relevant aspects of late normal tissue damage to patients undergoing breast radiotherapy. Assuming this to be the case, the only other uncertainty is whether breast cancer responds to change in fraction size in a similar way to the critical late responding normal tissues. This remains controversial in the view of some experts, given that squamous carcinomas are known to be less responsive to fraction size than the dose-limiting late normal tissue reactions (atrophy and fibrosis) [11].

Several prospective randomised trials have compared 50 Gy in 25 fractions with a lower total dose delivered in fewer, larger fractions, a practice referred to as hypofractionation (see Table 1). In the recently published UK Start Trial A, 2236 women with early breast cancer at 17 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy (749 women) or 41.6 Gy in 13 fractions of 3.2 Gy (750 women) or 39 Gy in 13 fractions of 3.0 Gy (737 women) [5]. All regimens were given over 5 weeks, and women were eligible if they were aged over 18, did not have immediate surgical reconstruction, and were available for follow-up. The end-points of the trial were tumour relapse, defined as the reappearance of cancer at irradiated sites, the effect of the regimen on normal tissues, and quality of life. At a median follow-up of 5.1 years, rates of tumour relapse at 5 years were very similar in all treatment groups: 3.6% after 50 Gy, 3.5% after 41.6 Gy, and 5.2% after 39 Gy. Photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than after 50 Gy. The conclusions were that 41.6 Gy in 13 fractions over 5 weeks offers similar rates of tumour control and normal tissue damage as the international standard fractionation schedule of 50 Gy in 25 fractions. These results are entirely consistent with the hypothesis under test viz. that breast cancer is as sensitive to fraction size as the late reacting normal tissues (if as insensitive as squamous carcinomas, the larger reduction in total dose, from 50 to 41.6 Gy, would lead to higher local tumour relapse rates with this 13-fraction schedule).

In Start Trial B, 2215 women with early breast cancer at 23 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2 · 0 Gy over 5 weeks (1105 women) or 40 Gy in 15 fractions of 2.67 Gy over 3 weeks (1110 women) [6]. The eligibility for the trial and its measured end-points were the same as for Start Trial A. At a median follow-up of 6.0 years, the rate of tumour relapse at five years was very similar in both groups: 2.2% after 40 Gy and 3.3% after 50 Gy. Both photographic and patient self-assessments suggested lower rates of late adverse effects after 40 Gy than after 50 Gy. The conclusions were that after surgery for early breast cancer, a radiotherapy schedule delivering 40 Gy in 15 fractions over 3 weeks appears to offer local regional tumour control and rates of late normal tissue effects at least as good as the accepted international standard of 50 Gy in 25 fractions over 5 weeks. The 5-year results of a Canadian trial evaluating a 16-fraction regimen are entirely consistent with those of the START Trials [12].

The outcomes of >7000 women participating in well-designed randomised trials testing hypofractionation in early breast cancer are strongly supportive of the hypothesis that hypofractionation can be both safe and effective for breast cancer. Residual uncertainties focus on the period of follow-up required before comparisons of late adverse effects and local tumour control are reliable enough to change practice. Some commentators argue for longer follow-up, on the basis that the very late-onset damage to the heart, for example, may be more sensitive to changes in fraction size than other late-reacting healthy tissues [13]. Such concerns are likely to be misplaced, although it is true that 20+ years of follow-up will be needed to establish this. There is no evidence that the fractionation sensitivity of tissues change in the decades

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Table 2. Schema of UK FAST Trial ($N = 900$; in follow-up phase).

Trial arms	Total dose (Gy)	Number of fractions	Fraction size (Gy)	Time (weeks)
Control	50	25	2.0	5
Test 1	30	5	6.0	5
Test 2	28.5	5	5.7	5

following radiotherapy, most systematically studied in human skin, for example [14]. Meanwhile, heart exposure is undesirable whatever fractionation schedule is used, and this organ should be shielded whenever possible.

Fifteen or 16 fractions is unlikely to represent the limits of hypofractionation. The UK FAST Trial is testing two dose levels of a five-fraction regimen delivered in 5 weeks against 50 Gy in 25 fractions with 900 women in follow-up (see Table 2). Meanwhile, a pilot trial ($N = 30$) testing 30 Gy in five fractions over 15 days in terms of early and late adverse effects is also in follow-up phase, with favourable results at 2 years [15]. Future proposals include testing a five-fraction schedule delivered over 5 days, which we consider a realisable research objective. At the time of writing, discussion focuses on whether 50 Gy in 25 fractions or 40 Gy in 15 fractions should represent the control comparator schedule. In conclusion, evidence is building that modest degrees of hypofractionation are both safe and effective for women with early breast cancer. There appear to be no disadvantages to this approach, which is simpler for the patient and health services. Future trials evaluating shortened treatment times may reveal advantages for tumour control. Meanwhile, research into the molecular determinants of fractionation sensitivity focuses on differences in DNA repair processes in slowly and rapidly proliferating tissues. The goals of this research are two-fold: first, to identify biomarkers that predict tumour sensitivity to fraction size; and second, to identify molecular targets for interventions that selectively modulate fractionation sensitivity and enhance treatment outcome. In conclusion, after decades of resistance to hypofractionation in curative radiotherapy, this approach is gaining rapid acceptance in selected tumour types, including breast cancer.

References

1. Stuschke M, Thames HD. Fractionation sensitivities and dose–control relations of head and neck carcinomas: analysis of the randomized hyperfractionation trials. *Radiother Oncol* 1999; **51**: 113–121.
2. Overgaard J, Hansen HS, Specht L, *et al*. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003; **362**: 933–940.
3. Beck-Bornholdt HP, Dubben HH, Liertz-Petersen C, *et al*. Hyperfractionation: where do we stand? *Radiother Oncol* 1997; **43**: 1–21.
4. Bourhis J, Overgaard J, Audry H, *et al*. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006; **368**: 843–854.
5. Bentzen SM, Agrawal RK, Aird EG, *et al*. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; **9**: 331–341.
6. Bentzen SM, Agrawal RK, Aird EG, *et al*. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; **371**: 1098–1107.
7. Patterson R. *The Treatment of Malignant Disease by Radium and X-rays*, 1st edition. London: Edward Arnold; 1948.
8. Peters MV. Carcinoma of the breast. Stage II – radiation range. Wedge resection and irradiation. An effective treatment in early breast cancer. *JAMA* 1967; **200**: 134–135.
9. Magee B, Stewart AL, Swindell R. Outcome of radiotherapy after breast conserving surgery in screen detected breast cancers. *Clin Oncol (R Coll Radiol)* 1999; **11**: 40–45.
10. Jones B, Dale RG, Deehan C, *et al*. The role of biologically effective dose (BED) in clinical oncology. *Clin Oncol (R Coll Radiol)* 2001; **13**: 71–81.
11. Bentzen SM, Ruifrok AC, Thames HD. Repair capacity and kinetics for human mucosa and epithelial tumors in the head and neck: clinical data on the effect of changing the time interval between multiple fractions per day in radiotherapy. *Radiother Oncol* 1996; **38**: 89–101.
12. Whelan T, MacKenzie R, Julian J, *et al*. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002; **94**: 1143–1150.
13. Bartelink H, Arriagada R. Hypofractionation in radiotherapy for breast cancer. *Lancet* 2008; **371**: 1050–1052.
14. Turesson I. The progression rate of late radiation effects in normal tissue and its impact on dose-response relationships. *Radiother Oncol* 1989; **15**: 217–226.
15. Martin S, Mannino M, Rostom A. Acute toxicity and two-year adverse effects of 30 Ggy in 5 fractions over 15 days to whole breast after local excision of early breast cancer. *Clin Oncol*; Published online 13 June 2008 (Epub ahead of print).

https://doi.org/10.1017/S1470903108007694 Published online by Cambridge University Press

16. Owen JR, Ashton A, Bliss JM, *et al*. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006; **7**: 467–471.

17. Yarnold J, Ashton A, Bliss J, *et al*. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005; **75**: 9–17.

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