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Original article

Hypofractionated radiotherapy in early breast cancer: Clinical, dosimetric and radio-genomic issues

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Curative radiotherapy is enhanced by partitioning the total dose into daily dose increments, called fractions. Most human cancer types respond to total dose rather than to the size of daily fractions [1]. This is an important point of difference in comparison with the responses of normal tissues responsible for the most important late adverse effects, which are sensitive to fraction size as well as total dose. This difference underpins the historical use of 'small' fractions, classically ≤2.0 Gy, to deliver the highest possible tolerated total dose, thereby, ensuring the highest rate of tumour control. The α/β ratio is an empirical descriptor of fraction size sensitivity, early reacting normal tissues and most cancer types being insensitive (α/β ratio 7–20 Gy) relative to the late reacting (dose limiting) normal tissues with low α/β ratios in the range 0.5–6 Gy [2]. This difference in fractionation sensitivity between cancers and late reacting normal tissues has been challenged in the last 20 years by randomised clinical trials offering high level evidence that breast cancer is an exception in showing comparable sensitivity to fraction size as the normal tissues of the breast and ribcage. The evidence base includes four randomised trials from Canada and the UK [3–7]. The results suggest that there is no disadvantage to hypofractionation in terms of safety and efficacy, and benefits to patients and health services in terms of convenience and cost.

The Ontario trial (N = 1234) compared 42.5 Gy in 16 fractions of 2.7 Gy over 3.2 weeks against 50 Gy in 25 fractions over 5 weeks to the whole breast after breast conserving surgery; patient and treatment characteristics are summarised in Table 1. Ten-year ipsilateral tumour relapse rates were 6.7% after 50 Gy in 25 fractions and 6.2% after 42.5 Gy in 16 fractions (absolute difference in favour of hypofractionation of 0.5%; 95% CI −6.9 to 9.8), see Table 2 [5]. Cosmetic outcome was equally good in both groups, with 71.3% of women after 50 Gy in 25 fractions compared to 69.8% after 42.5 Gy in 16 fractions having good or excellent cosmetic outcome (absolute difference 1.5%; 95% CI −6.9 to 9.8), see Table 3.

Three randomised trials testing whole breast/chest wall hypofractionation were conducted in the UK, starting in 1986, see Tables 1–3 [3,4,6,7]. The START-A (N = 2236) and START–B (N = 2215) trials enrolled women after completely excised invasive breast cancer (pT1-3a, pN0-1, M0) between 1999 and 2002. Patients were randomly assigned after primary surgery with chemotherapy and endocrine treatment prescribed according to local practice. Eligibility criteria included age ≥18 years and no immediate surgical reconstruction. The trial design was informed by the results of the START-pilot trial, and included 2 dose levels of a 13-fraction regimen testing 3.0 Gy fractions (total dose 39.0 Gy) and 3.2 Gy fractions (total dose 41.6 Gy) over 5 weeks against a 50 Gy in 25 fractions control group. At a median follow-up in START-A of 9.3 years, the 10-year rates of ipsilateral local-regional relapse did not differ significantly between the 41.6 Gy and 50 Gy groups (6.3%, 95% CI 4.7–8.5 versus 7.4%, 95% CI 5.5–10.0; hazard ratio [HR] 0.91, 95% CI 0.59–1.38; p = 0.65, nor between the 39 Gy (8.8%, 95% CI 6.7–11.4) and 50 Gy groups (HR 1.18, 95% CI 0.79–1.76; p = 0.41). In START-A, moderate or marked breast induration, telangiectasia, and breast oedema were significantly less common normal tissue effects after 39 Gy group than after 50 Gy group. Late adverse effects did not differ significantly between 41.6 Gy and 50 Gy groups.

Based on a combined total of 278 local-regional tumour relapses in the START-pilot and START-A trials at 10 years follow up, the adjusted α/β value for tumour control was estimated to be 3.5 Gy

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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 [3,38]	START-A [13]	START-B [14]	Ontario [5,39]
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	41.5/13/5	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 (%)	42.5[a]	48.6[b]	35.9[b]	20.0[b]
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.

Table 2
Rates of local tumour relapse in five 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 [3,38]	50.0/25	7.9 (5.4–10.4)	12.1 (8.8–15.5)
	42.9/13	7.1 (4.6–9.5)	9.6 (6.7–12.6)
	39.0/13	9.1 (6.4–11.7)	14.8 (11.2–18.3)
START-A [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-B [14]	50.0/25	3.3 (2.4–4.6)	5.2 (3.9–6.9)
	40.0/15	1.9 (1.2–3.0)	3.8 (2.7–5.2)
Ontario [5,39]	50.0/25	3.2[a]	6.7[b]
	42.5/16	2.8[a]	6.2[b]

[a] Absolute difference 0.4% (95% CI −1.5 to +2.4%).
[b] Absolute difference 0.5% (95% CI −2.5 to +3.5).

(95% CI 1.2–5.7), comparable to 3.5 Gy (95% CI 0.7–6.4) for clinically assessed breast shrinkage and 4.7 Gy (95% CI 2.4–7.0) for breast induration. The results were, therefore, consistent with the hypothesis that breast cancer is as sensitive to fractionation size as surrounding normal tissues and that a 13-fraction regimen delivered over 5 weeks can be as safe and effective as 50 Gy in 25 fractions in the adjuvant breast cancer setting.

Whereas the START-pilot and START-A trials have high explanatory power, 13 fraction regimens delivered over 5 weeks are not convenient in the routine treatment setting, in which the results of START-B are more relevant [7]. This pragmatic trial compared 40 Gy in 15 fractions of 2.7 Gy in 3 weeks against 50 Gy in 25 fractions over 5 weeks to the control group. At a median follow-up of 9.3 years, 10-year rates of ipsilateral local-regional relapse did not differ significantly between the 40 Gy (4.3%, 95% CI 3.2–5.9) and the 50 Gy groups (5.5%, 95% CI 4.2–7.2; HR 0.77, 95% CI 0.51–1.16; $p = 0.21$). Breast shrinkage, telangiectasia, and breast oedema were significantly less common in the 40 Gy group, a benefit consistent with prospective patient self-reported 5-year assessments of a range of adverse effects [8]. Turning to the primary endpoint of local-regional control in START-B, residual imprecision indicated by the upper and lower 95% CI limits for the absolute difference between 40 Gy in 15 fractions and the control schedule in START-B suggests that local-regional tumour relapse is very unlikely (≤2.5%) to be more than 1% higher, and perhaps 1% or 2% lower, than after 50.0 Gy in 25 fractions. The START-B schedule of 40.0 Gy in 15 fractions was adopted as the UK standard of care in 2009 for women prescribed adjuvant radiotherapy for early breast cancer [9]. In the most recent nation-wide audit, conducted during a 2-week period in November 2011, 88% of all dose prescriptions for women with early breast cancer used this schedule (Imogen Locke, personal communication).

Table 3
Clinically assessed moderate or marked adverse effects for patients treated by breast conservation surgery in five randomised trials testing hypofractionated radiotherapy.

Trial	Randomisation (Gy/fractions)	Percent breast shrinkage at 10 yr (95% CI)	Percent excellent or good breast cosmesis at 10 yr (95% CI)
START-pilot [3]	50.0/25	63.8	
	42.9/13	74.4	
	39.0/13	58.0	
START-A [7]	50.0/25	34.2 (29.8–39.2)	
	41.6/13	31.4 (27.2–36.0)	
	39.0/13	30.0 (25.7–34.8)	
START-B [14]	50.0/25	31.2 (27.9–34.9)	
	40.0/15	26.2 (23.1–29.6)	
Ontario [5]	50.0/25		71.3[a]
	42.5/16		69.8[a]

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

Are there any residual concerns?

Patient subgroups

The patient and tumour characteristics of the three START trials appear representative of patients with early breast cancer treated in the UK prior to 2002, although patients enrolled post-mastectomy are under-represented (n = 513). There is no suggestion of inconsistency in treatment effects for tumour control in any of the subgroups recorded in the START Trials, including patients with high grade tumours, see Fig. 1.

Length of follow up

Adverse effects of radiotherapy evolve over the life-time of the patient, so an important question is whether the hazard ratios (HR) for dose-limiting adverse effects in experimental and control groups at early time-points are reliable indicators for the same adverse effects at later time-points. Comparisons of HR at 5 and 10 years for a range of adverse effects scored in the START trials are consistent with the predictive value of the 5-year time-point. In fact, the 10-year relationships between treatment groups are established by year 3 [7].