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Phase III randomised trial

Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation

Joanne S. Haviland [a,c], Søren M. Bentzen [b], Judith M. Bliss [c], John R. Yarnold [d,*], On behalf of the START Trial Management Group

[a] Faculty of Health Sciences, University of Southampton, UK; [b] Department of Epidemiology and Public Health and Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, USA; [c] ICR-CTSU, Division of Clinical Studies; and [d] Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK

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ABSTRACT

Background: Tests of tumour treatment time effect in patients prescribed post-operative radiotherapy for early breast cancer have focussed on time to start of radiotherapy rather than overall treatment time. The START randomised trials of radiotherapy fractionation provide an opportunity to directly estimate the effect of treatment acceleration.

Methods: Between 1986 and 2002, a total of 5861 women with early breast cancer were recruited into the UK START pilot (START-P), START-A and START-B randomised trials. START-P and START-A tested 13 fractions of 3.0–3.3 Gy against 25 fractions of 2.0 Gy with a fixed treatment duration of 5 weeks for all schedules; START-B tested 15 fractions of 2.67 Gy in 3 weeks against 25 fractions of 2.0 Gy over 5 weeks. Estimates of the effect of length of treatment for local–regional relapse and for a measure of late normal tissue effects (change in photographic breast appearance, for patients following breast conserving surgery) were obtained from Cox proportional hazards regression analyses stratified according to trial.

Results: At a median follow-up of 10 years, 444/5831 (7.6%) patients with data available had a local–regional relapse, and 1135/3185 (35.6%) had mild or marked change in photographic breast appearance by 5 years. Adjusting for prognostic factors, the estimate of the overall treatment time effect for local–regional relapse was 0.60 Gy/day (95%CI 0.10 to 1.18 Gy/day, $p = 0.02$), and 0.14 Gy/day (95%CI −0.09 to 0.34 Gy/day, $p = 0.29$) for change in photographic breast appearance.

Conclusions: Combined analysis of the START trials generates the hypothesis that overall treatment time is a significant determinant of local cancer control after adjuvant whole breast radiotherapy, with approximately 0.6 Gy per day 'wasted' in compensating for tumour cell proliferation.

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Convincing evidence for a time-factor in radiotherapy exists for squamous carcinomas of the head and neck, where at least 0.6 Gy per day of treatment is required to compensate for tumour cell repopulation between fractions, including week-end breaks [1–5]. There are no comparable tests of treatment time in patients prescribed adjuvant radiotherapy following primary surgery for early breast cancer, where studies are limited to exploring the impact of treatment delay. Such sources include randomised trials comparing concomitant versus sequential adjuvant chemo-radiotherapy, representing a difference in time from surgery to radiotherapy of 4 months or so (reviewed in [6]). One of three studies reported better local control after concomitant chemo-radiotherapy, but an excess of late telangiectasia after concomitant therapy suggests a time-independent effect may have contributed to the difference in outcome [7]. The only randomised trial testing sequence of chemotherapy and radiotherapy directly had limited power ($N = 244$) and reported no dependency of long-term local relapse in irradiated breast on whether CMF chemotherapy or breast radiotherapy was given first [8]. The evidence for an impact of delay is not all negative, since a large retrospective cohort analysis of the Surveillance, Epidemiology, and End Results (SEER) Program studied >18000 US women with early stage breast cancer aged >65 years treated 1991–2002 with breast conserving surgery, radiotherapy but no chemotherapy, and this study reported a continuous association between the interval from breast conserving surgery to radiotherapy and local recurrence risk [8–11].

* Corresponding author at: Division of Radiotherapy and Imaging, The Royal Marsden, Downs Road, Sutton SM2 5PT, UK.
E-mail address: john.yarnold@icr.ac.uk (J.R. Yarnold).

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Two randomised trials testing hypofractionation in early breast cancer, the Ontario and START-B trials of adjuvant whole breast radiotherapy, tested schedules delivered in shorter overall treatment time than the international standard of 50 Gy in 25 fractions over 5 weeks [12,13]. The START-P and START-A trials were designed to generate direct estimates of α/β for tumour control and normal tissue effects while controlling overall treatment time, and can be used to adjust for differences in dose-fractionation between randomised groups in the START-B trial [12,14,15]. We have used all three START trials to generate a crude estimate of the effect of overall treatment time for tumour (local control) [15–17]. Since there would be no expected time factor for late adverse effects in schedules extending over 6–8 weeks, the photographic assessments of change in photographic breast appearance were also tested using the same methods as for tumour control, to act as a control [18].

Materials and methods

Design, methods and results of the START pilot, A and B trials have been published elsewhere [12,14–17]. The START pilot (N = 1410) and START A trials (N = 2236) tested 3.0–3.3 Gy against 2.0 Gy fractions with overall treatment time fixed at 5 weeks, allowing direct estimates of the fractionation sensitivity of breast cancer. A meta-analysis of the START pilot and START A trials with those of the START B trial (N = 2215) testing 15 fractions of 2.67 Gy in 3 weeks against 25 fractions of 2.0 Gy over 5 weeks allowed estimation of the possible change in treatment effect for a 3-week versus a 5-week schedule for local–regional relapse and for the normal tissue effects endpoint of any change in photographic breast appearance. Only patients who had breast conserving surgery were eligible for the photographic assessments, which scored change in breast appearance annually up to 5 years and then at 10 years in START-P and at 2 and 5 years in START A and B compared with a post-surgery baseline photograph taken prior to start of radiotherapy treatment [19].

Statistical methods

Cox proportional hazards (PH) regression analyses of time to local–regional relapse and time to any change in photographic breast appearance were stratified by trial to allow for differences in case mix among trials. Crude estimates of the proliferation effect for each endpoint was obtained from separate Cox PH regression models including terms for total dose (β_{Dose}), total dose x dose per fraction (β_{Dxd}) and a dummy variable for treatment time (β_{time}), where 0 represents 5 weeks and 1 represents 3 weeks. The actual length of radiotherapy treatment for each patient according to reported start and finish dates was not used in the analysis, although very few had major delays [16,17]. Parameter estimates obtained from the Cox PH regression were then used in the following formula to estimate the dose recovered per day due to proliferation (in 2.0 Gy equivalent fractions), assuming a 14-day time difference between the 2 schedules in START trial B:

$$D_{prolif} = \frac{\beta_{time}/14}{\beta_{Dose} + 2\beta_{Dxd}}$$

Non-parametric bootstrap resampling was used to obtain bias-corrected 95% confidence intervals (CI) of the D_{prolif} estimate. Known prognostic factors were included in the Cox PH regression models: age, type of primary surgery, radiotherapy to axilla or supraclavicular fossa, tumour bed boost, adjuvant chemotherapy, tamoxifen, pathological tumour size for local–regional relapse; age, adjuvant chemotherapy, tamoxifen, radiotherapy to axilla or supraclavicular fossa, breast size and surgical deficit for any change in photographic breast appearance. Tumour grade and nodal status were not included in the model for local–regional relapse due to the number of patients for which these variables were unknown.

Results

Post-randomisation data were available for 5831 of the 5861 patients entered into the START pilot, START A and B trials, of whom 444 were reported to have had a local–regional relapse (402/4730 (8.5%) for all 5-week schedules combined and 42/1101 (3.8%) for the 3-week schedule); median follow-up was 10 years overall. Scores for any change in photographic breast appearance at 2 and/or 5 years were available for 3185 patients, of whom 1135 were scored as mild or marked change. Patient clinical and treatment characteristics for the analysis dataset are shown in Table 1 for the 5-week schedules versus the 3-week schedule. There were some differences due to varying case mix between the three START trials. The crude (unadjusted) estimate of D_{prolif} for local–regional relapse was 0.65 Gy/day (95%CI 0.12 to 1.66 Gy/day). Adjusting for prognostic factors for local–regional relapse (type of primary surgery, radiotherapy to axilla or supraclavicular fossa, tumour bed boost, adjuvant chemotherapy, tamoxifen, pathological tumour size) in 5613 patients with data available for all variables in the Cox PH regression model gave an adjusted estimate of D_{prolif} for local–regional relapse of 0.60 Gy/day (95%CI 0.10 to 1.18 Gy/day) (Table 2). Thus, the effect of overall treatment time on local–regional control is statistically significant (p = 0.02). Corresponding estimates of D_{prolif} for any change in photographic breast appearance were 0.17 Gy/day (95%CI −0.10 to 0.36 Gy/day) for the crude estimate, and 0.14 Gy/day (95%CI −0.09 to 0.34 Gy/day) adjusted for age, radiotherapy to axilla or supraclavicular fossa, adjuvant chemotherapy, tamoxifen, breast size and surgical deficit (Table 2). The effect of overall treatment time on change in photographic breast appearance is not statistically significant (p = 0.29 for the adjusted estimate).

Discussion

This is a hypothesis-generating study suggesting that treatment time influences local outcome of adjuvant radiotherapy in breast cancer. The literature referred to in the Introduction yields conflicting results, most commonly based on the analysis of treatment delay. Our investigation was prompted by a suggestion of lower local–regional relapse rates after 40 Gy in 15 fractions over 3 weeks compared with 50 Gy in 25 fractions over 5 weeks reported in START-B (estimate of absolute difference −1·2%, 95% CI −2·6% to 1·0%). The START-B trial was powered for non-inferiority and the observed effect was not statistically significant, but the 95% confidence interval was more suggestive of lower local–regional relapse rates (by up to 2.6%) than of a higher rate for the 3-week schedule. This prompted further examination on the grounds that the local–regional relapse rate was expected to be higher after 40 Gy in 15 fractions than after 50 Gy in 25 fractions, for the following reason. The α/β point estimate of 3.5 Gy for local–regional tumour control in the START-P and START-A trials applied to the START-B 40 Gy in 15 fractions schedule generates an equivalent total dose delivered in 2.0 Gy fractions (EQD2 Gy) that is closer to 45 Gy than 50 Gy, assuming no impact of treatment time. The slope of the dose–response for local control rates >90% is very shallow, so a large difference in local control could not be expected, even for an EQD2 Gy 5 Gy lower than the Control group receives. Assuming the slope of the dose–response curve at the 95% level of local control is described by a gamma value 0.1–0.2 (ten times shallower than at 50% levels of local control), the expected absolute inferiority in local control would be 1 to 2%. So, the

Table 1
Characteristics of the 5831 patients included in the analyses for the 5-week schedules from all 3 START trials combined and the 3-week schedule from START trial B.

	5-Week schedules *N* = 4730 (%)[+]	3-Week schedule N = 1101 (%)[+]	Total *N* = 5831 (%)[+]
Age (years)			
Mean (SD)	56.3 (10.4)	57.8 (9.5)	56.6 (10.2)
[range]	[23.3–86.8]	[30.9–82.9]	[23.3–86.8]
Pathological tumour size (cm)			
Mean (SD)	2.2 (1.6)	1.8 (1.0)	2.1 (1.5)
Tumour grade			
1	898 (23.8)	309 (28.6)	1207 (24.9)
2	1853 (49.1)	527 (48.7)	2380 (49.0)
3	1020 (27.0)	246 (22.7)	1266 (26.1)
Unknown	959	19	978
Nodal status			
Negative	2924 (71.7)	797 (75.1)	3721 (72.4)
Positive	1152 (28.3)	264 (24.9)	1416 (27.6)
Unknown	654	40	694
Type of primary surgery			
Breast conserving surgery	4310 (91.1)	1009 (91.6)	5319 (91.2)
Mastectomy	420 (8.9)	92 (8.4)	512 (8.8)
Tumour bed radiotherapy boost			
No	2089 (44.4)	652 (59.5)	2741 (47.2)
Yes	2618 (55.6)	444 (40.5)	3062 (52.8)
Unknown	23	5	28
Radiotherapy to axilla or supraclavicular fossa			
No	4022 (85.4)	1015 (92.6)	5037 (86.8)
Yes	686 (14.6)	81 (7.4)	767 (13.2)
Unknown	21	5	26
Adjuvant chemotherapy			
No	3469 (73.6)	864 (78.9)	4333 (74.6)
Yes	1245 (26.4)	231 (21.1)	1476 (25.4)
Unknown	16	6	22
Adjuvant tamoxifen			
No	928 (19.7)	135 (12.3)	1063 (18.3)
Yes	3786 (80.3)	960 (87.7)	4746 (81.7)
Unknown	16	6	22
Breast size from baseline photograph[*]			
Small	344/2847 (12.1)	37/454 (8.1)	381/3301 (11.5)
Medium	2068/2847 (72.6)	344/454 (75.8)	2412/3301 (73.1)
Large	435/2847 (15.3)	73/454 (16.1)	508/3301 (15.4)
Surgical deficit from baseline photograph[*]			
Small	1701/2838 (59.9)	247/454 (54.4)	1948/3296 (59.1)
Medium	909/2838 (32.0)	162/454 (35.7)	1071/3296 (32.5)
Large	228/2838 (8.0)	45/454 (9.9)	273/3296 (8.3)
Unknown	9	0	9

[+] %s calculated excluding unknowns.
[*] Baseline photographs available for 3301 of the 3185 patients who were in the photographic assessments sub-studies of the trials.

Table 2
Crude and adjusted bootstrap estimates of the proliferation parameter for local–regional relapse and change in photographic breast appearance (dose recovered per day in 2.0 Gy equivalent fractions).

	Crude estimate (95%CI), Gy/day	Adjusted estimate (95%CI),Gy/day
Local–regional relapse	0.65 (0.12 to 1.66)	0.60 (0.10 to 1.18)[a]
Any change in photographic breast appearance[c]	0.17 (−0.10 to 0.36)	0.14 (−0.09 to 0.34)[b]

[a] Adjusted for age, type of primary surgery, radiotherapy to axilla or supraclavicular fossa, tumour bed boost, adjuvant chemotherapy, tamoxifen, pathological tumour size.
[b] Adjusted for age, radiotherapy to axilla or supraclavicular fossa, adjuvant chemotherapy, tamoxifen, breast size, surgical deficit.
[c] Any change in photographic breast appearance includes mild or marked change (compared with pre-radiotherapy baseline).

observed 4.3% 10-year local–regional relapse rate after 40 Gy in 15 fractions is about 2.2 to 3.2 percentage points lower than predicted, assuming no time effect. This is how the observed non-inferiority of tumour control in START B raises the possibility of a treatment time effect on tumour control, which our results estimate to be 0.6 Gy per day (95%CI 0.10 to 1.18 Gy per day).

The main strength of this study is that it is based on data collected systematically and prospectively in randomised trials that pre-specified and quality-assured the delivery of radiotherapy and ensured high compliance with collection of post-treatment outcome data. The main weakness is that the estimate for a treatment time effect is based on a single trial (START-B), given that the duration of treatment was 5 weeks for all schedules in the START-P and START-A trials. In addition, although randomisation is the most effective way of balancing prognostic variables between treatment groups, small imbalances are inevitable, even in a trial of >2000 patients. Whether or not the above factors apply here, it is noteworthy that the Ontario trial testing 42.5 Gy in 16 fractions of 2.7 Gy in 3.2 weeks whole breast radiotherapy against 50 Gy in 25 fractions did not detect any differences in long-term outcome between schedules, either in terms of local tumour control (absolute difference, 1.5 percentage points; 95% CI −6.9 to 9.8) or breast cosmesis (absolute difference, 0.5 percentage points; 95% CI −2.5 to 3.5) [13]. It took only 19 days to deliver 15 fractions

in START-B when treatment started on a Monday and was uninterrupted, but on average, most patients started on another week-day resulting in a treatment duration of 21 days compared with the 22 days needed to deliver 16 fractions in the Ontario trial. In other words, the difference in treatment time between these two trials could be closer to 1 day than 3 days. The different outcomes in the START B and Ontario trials could possibly be due to differences in the tumour characteristics of the populations tested in the two trials, particularly tumour grade, or simply be a factor of the imprecision in the tumour control estimates.

If a treatment time effect for breast cancer is real and of the magnitude estimated in this analysis, the implications are significant. For patient populations suffering local relapse risks >10% following conventionally fractionated radiotherapy, the absolute gains in local control from adopting a 3-week schedule are likely to be clinically worthwhile, even without considering the lower adverse event rates (e.g. HR 0.8, 95% CI 0.67 to 0.96 for breast shrinkage) associated with this regimen in the START-B trial [12]. The implications for tumour bed boost dose regimens would be that synchronous/concomitant boost would be more effective than sequential boost techniques; this is the hypothesis tested in the UK IMPORT HIGH and RTOG 1005 trials. For patient populations experiencing local relapse risks <<10% after conventional fractionation, the main benefit would be the reduced rate of late adverse events reported after 40 Gy in 15 fractions, as described above [12].

The final point of discussion relates to the adjusted estimate of 0.14 Gy/day (95%CI −0.09 to 0.34 Gy/day) as the time factor for late change in photographic breast appearance. Assuming this is a real effect (it is not statistically significantly different from zero, $p = 0.286$), the difference between the estimates for local control and for late effects still means that a therapeutic gain can be achieved from shortening overall treatment time. In fact, testing the one-sided hypothesis that the treatment time effect for subclinical breast cancer exceeds that for late effects (measured by photographic breast appearance in this analysis) yields a statistically significant p-value of $p = 0.03$. If there is a small, effect of overall treatment time it could be explained by the distinction between a 'true' late effect, which might not be expected to show a time effect, from a 'consequential' late effect that is a result (direct consequence) of healing by secondary intention of a severe early effect, usually moist desquamation in inframammary and other skin folds [20]. Telangiectasia is the most visible manifestation in the irradiated breast, but severe cases can be accompanied by subcutaneous induration and atrophy impacting on breast appearance. Numbers of events were too small to allow testing of association between a time factor and breast size as a surrogate for moist desquamation risk in the START-B trial. In the existing literature, a time factor for telangiectasia has been reported by Turesson, attributed to slow repair rather than repopulation [21]. More recently, two large randomised trials of radiotherapy in head and neck cancer testing 60 Gy in 30 fractions delivered in 5 or in 6 weeks reported no significant time factor for late adverse effects despite significantly higher rates of both early adverse effects and local tumour control [1,2]. In conclusion, we consider the time factor for late effects in START-B to represent a reasonable negative control for our analysis.

Conclusions

A meta-analysis of the START trials generates the hypothesis that overall treatment time is a significant determinant of local cancer control after adjuvant whole breast radiotherapy, with approximately 0.6 Gy per day 'wasted' in compensating for tumour cell proliferation. Independent replication is needed before this observation can be used in support of accelerated schedules of hypofractionated radiotherapy in breast cancer.

Conflict of interest statement

The authors declare no conflict of interest.

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