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

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SUMMARY

Background
Standard curative schedules of radiotherapy to the breast deliver 25 doses (fractions) of 2.0Gy treating 5 times per week. The hypothesis under test is that fewer, larger fractions are as safe as, and more effective than, regimens based on 2.0Gy fractions. If confirmed, curative radiotherapy in early breast cancer could be greatly simplified for the benefit of patients and health services.

Aim
To test the effects of radiotherapy fractions >2.0Gy on local tumour control and dose-limiting normal tissues of the breast after tumour excision and radiotherapy for early breast cancer. The primary endpoint of normal tissue effects has been published elsewhere.

Methods
1410 women with T1-3 N0-1 M0 invasive breast cancer were randomised between 1986-98 to receive one of three radiotherapy regimens after local tumour excision of early stage breast cancer; 50Gy in 25 fractions versus two dose levels of a test schedule giving 39Gy or 42.9Gy in 13 fractions over 5 weeks. Fraction sizes were 2.0Gy, 3.0Gy and 3.3Gy, respectively. The primary endpoint was late change in breast appearance. Secondary endpoints included ipsilateral tumour relapse, which is now reported for the first time.

Results
After a median follow up of 9.7 years (IQR 7.8-11.8) in the survivors, the current estimate of 10-year risk of ipsilateral tumour relapse was 12.1% (95% CI 8.8-15.5%) after 50Gy in 25F and demonstrated a clear dose-response in the test arms: 14.8% (95% CI 11.2-18.3%) and 9.6% (95% CI 6.7-12.6%) after 39Gy and 42.9Gy in 13 fractions, respectively. The sensitivity
of breast cancer to dose per fraction was quantified by the $\alpha/\beta$ value of a linear-quadratic model and estimated to be 4.0Gy (95% CI 1.0–7.8). This result is comparable to that estimated for the late normal tissue adverse effects of breast radiotherapy.

**Conclusion**

It is likely that breast cancer is, on average, just as sensitive to fraction size as the dose-limiting normal tissues. If confirmed, radiotherapy schedules can be greatly simplified by the delivery of fewer larger fractions without compromising efficacy or safety, and possibly improving both.
INTRODUCTION

The use of 2.0Gy fractions in breast cancer radiotherapy is strongly influenced by reliable data for carcinomas of the bronchus, cervix uteri and head and neck \(^1\), where the rate of tumour control increases more slowly than late complication risk as fraction size increases above 2.0Gy \(^1\). The justification for testing fractions >2.0Gy (hypofractionation) in primary breast cancer is based on data suggesting that breast adenocarcinoma may be more sensitive to fraction size than squamous carcinomas and comparable in fractionation sensitivity to the dose-limiting normal tissue exposed during treatment, including skin, subcutaneous tissues, muscle and ribs \(^2,3\). The data for recurrent or inoperable breast cancer suggest greater sensitivity to fraction size than hitherto assumed, represented by an \(\alpha/\beta\) value (3–5Gy) comparable to that for late normal tissue injuries in a commonly-used empirical model of clinical response \(^4,5\). If breast cancer is, on average, as sensitive to fraction size as the late reacting healthy tissues of the breast, muscle and underlying ribcage, this has clear implications for the optimal choice of radiotherapy regimen. Fewer, larger fractions would be at least as effective as standard 2.0Gy fractions and would offer convenience and cost savings for patients and health services. Against this background, a randomised clinical trial was started in 1986 to test the effects of modest increases in fraction size above 2.0Gy, with normal tissue effects and tumour control as the primary and secondary endpoints, respectively. The trial was controlled for overall treatment time, and generated reliable estimates of \(\alpha/\beta\) 3.6Gy (95% CI 1.8-5.4) for late change in breast appearance and 3.1Gy (95% CI 1.8-4.4) for moderate/marked breast induration \(^6\). The early results informed the design of the UK National Cancer Research Institute (NCRI) Standardisation of Radiotherapy (START) trial launched in January 1999, which was designed to have sufficient statistical power to assess tumour control as the primary endpoint \(^7\). A meta-analysis of the tumour control data from both trials will be performed when the START trial data mature. This manuscript reports on local tumour control in the first trial.
METHODS

Patients
Details of the patient characteristics have been previously described\(^6\). Briefly, between January 1986 and March 1998, 1410 patients were enrolled in a clinical trial of radiotherapy dose schedules at the Royal Marsden Hospital, Sutton and the Gloucestershire Oncology Centre, Cheltenham, UK. Patients with operable invasive breast cancer (T1-3 N0-1 M0) requiring radiotherapy were eligible for the trial provided they were under 75 years at presentation, and had had breast preserving surgery and complete macroscopic resection of invasive carcinoma.

Trial design, entry procedure and follow up
Patients were randomised to 3 alternative dose schedules delivered over 5 weeks at an allocation ratio of 1:1:1. The control arm of 50Gy in 25 fractions over 5 weeks was compared with 2 dose levels of a test schedule delivering 13 fractions over 5 weeks. Fraction sizes of 3.0 and 3.3Gy were selected corresponding to schedules iso-effective with 50Gy in 25 fractions assuming \(\alpha/\beta\) values of 1.8Gy and 6.0Gy, respectively.

Randomisation was achieved by a telephone call to the Clinical Trials and Statistics Unit (ICR-CTSU) at the Institute of Cancer Research, Sutton, after obtaining informed consent. Patients were stratified by treatment centre and by whether microscopic foci of invasive or intraduct disease were present at or close (<3mm) to the nearest surgical margin. In patients with a complete microscopic resection, when the clinician felt it was appropriate and the patient consented, a sub-randomisation to tumour bed boost versus no boost was performed. This sub-randomisation closed in July 1997, and thereafter, all patients were offered an
elective boost. Patients were reviewed 3-monthly to 3 years, 6-monthly to 5 years and
annually thereafter.

**Radiotherapy**

Radiotherapy technique has been previously described. Patients were simulated and treated
in the same supine position. Megavoltage photons (6MV x-rays) were used, except for a
minority of small-sized patients treated with Co\(^{60}\) \(\gamma\)-rays or 4MV x-rays, and large-sized
patients treated with 10MV x-rays. Wedge tissue compensators were used in all patients, with
the wedge angles estimated from a single transverse external contour through the central
plane. The reference point for tangential fields was in the centre of the breast, midway
between the skin entry points of the tangential fields and midway between a perpendicular
line from the skin surface to the lung/chest wall interface. When delivered, lymphatic
radiotherapy comprised an anterior field to the supraclavicular fossa prescribed as an applied
dose. If the axilla was included, an equally weighted posterior axillary field was treated with
every fraction to ensure that 100\% of the prescribed dose was delivered to the axillary
midline.

In all patients allocated to receive a boost, this was delivered by electrons to the tumour bed to
a dose of 14Gy to the 90\% iso-dose (15.5Gy to 100\%) in 7 daily fractions. The proportion of
patients who received a boost was almost identical in the three arms; 74.0\% for 50Gy, 74.7\%
for 42.9Gy and 74.0\% of the patients randomised to receive 39Gy.

**Definition and assessment of endpoint**

Local relapse was defined as any malignancy occurring in ipsilateral breast parenchyma or
overlying skin.
**Statistical methods**

The original sample size was estimated on the basis of not increasing the incidence of moderate or severe late radiation effects on normal tissues above 10% (assuming <5% in the 50Gy control arm), which was the primary endpoint. Mid trial, it was decided to extend the trial to allow a reliable comparison of relapse rates. It was estimated that for 90% power and a 5% significance level, 2250 patients would be needed to detect a 5% absolute increase in the risk of relapse in either experimental arm compared to an expected 5-year local relapse rate of 10% in the control arm (50Gy). Accrual into this trial was terminated before the target was reached, as this local initiative was superseded by the START trial, the corresponding national trial, which has tumour control as its primary endpoint.

The time from randomisation to first relapse or date last seen was calculated. The probability of no local relapse was depicted over the follow up period on a Kaplan-Meier survival curve, and pairs of fractionation schedules compared using the Logrank test. Kaplan-Meier (KM) estimates of the probability of no local relapse at 5 and 10 years were obtained, with 95% confidence intervals (CI). Cox proportional hazards (PH) regression was used to estimate the hazard ratios (with 95% CI) for local relapse for each fractionation schedule. Since point estimates of differences in event rates can, by chance, be atypical of the overall pattern of differences, smoothed estimates of absolute differences in relapse rates at 5 and 10 years were obtained using the hazard ratios obtained from the Cox model and the KM estimate of local relapse in the control arm. In order to obtain direct estimates (with 95% CI) of the α/β ratios for local relapse, a Cox PH regression model was fitted including a term for total dose and another term for total dose multiplied by dose per fraction. Analysis included all randomised patients on an intention-to-treat basis.
RESULTS

Patients and follow up

A total of 1410 patients were recruited, as shown in Figure 1. Median follow up in those still alive was 9.7 years with an inter-quartile range (IQR) of 7.8 to 11.8 years and a maximum of 18.4 years. Eighteen patients (1.3%) were lost to follow up (median follow up 4.9 years, IQR 2.5-8.3). The trial protocol was to discharge patients at 10 years: 172 (12.2% of the total) were discharged at a median follow-up time of 12.8 years (IQR 10.1-14.9) and 36 (2.5% of the total) were discharged early at a median of 7.8 years (IQR 7.0-8.9). At the time of analysis, 838 patients (59.4%) were alive and without local relapse, 46 (3.3%) were alive with local relapse (but no distant relapse or contralateral breast cancer), 46 (3.3%) were alive with distant relapse (including 10 with local relapse and 5 with contralateral breast cancer), 35 (2.5%) were alive with a second primary cancer in the contralateral breast (including 3 with local relapse) and 445 (31.6%) had died (99 of the patients who died had a local relapse).

Local relapse

At the time of the analysis, there were 158 local relapses out of the 1410 patients randomised (11.2%). Local relapse rates were highest between years three and five and 67% of all events occurred within five years of follow-up. Table 1 and Figure 2 show the results of the survival analysis of local relapse, comparing the fractionation schedules. A significant dose-response relationship was demonstrated for local relapse: when the 42.9Gy and 39Gy arms were compared, the logrank test was statistically significant ($\chi^2 = 4.9$, degrees of freedom (df) = 1, $p = 0.027$).

In Figure 2 there was evidence of divergence in the relapse-free survival curves for the fractionation schedules after five years of follow-up, whereas this did not appear to be the
case in the first five years. Splitting the follow-up at five years and fitting separate Cox PH regression models for the two time periods supported this observation, as the hazard ratios in the first five years were closer to 1, compared with larger relative effects from five years onwards. In the first five years, the hazard ratios (95% CI) compared with 50Gy were 0.90 (0.55-1.46) for 42.9Gy and 1.14 (0.72-1.79) for 39Gy. From five years onwards, the hazard ratios (95% CI) compared with 50Gy for 42.9Gy and 39Gy were 0.77 (0.36-1.69) and 1.81 (0.96-3.41), respectively. However, the test of the proportional hazards assumption was not statistically significant (p = 0.1), indicating that the apparent differences between the two time periods were not substantial.

**Alpha-beta value, equivalent dose in 2.0Gy fractions and dose-response**

From the Cox PH regression, the direct estimate of the $\alpha/\beta$ ratios for local relapse is 4.0Gy (95% CI 1.0-7.8). Applying this value to estimate the equivalent total doses in 2.0Gy fractions, 39Gy in 3.0Gy fractions is equivalent to 46Gy in 2.0Gy fractions, and 42.9Gy in 3.3Gy fractions over 5 weeks is iso-effective with 52Gy in 2.0Gy fractions. By interpolation, 50Gy in 25 fractions is iso-effective with 41.6Gy in 13 fractions of 3.2Gy over 5 weeks. These iso-effect doses allow estimation of the local steepness of the dose-response curve, the normalised dose-response gradient ($\gamma$-value), corresponding to a 0.5% increase in local control probability for a 1% increase in total dose. Thus, a 2% absolute improvement in local control rate is the consequence of a 2Gy increment in total dose.

**DISCUSSION**

Based on an analysis of 158 ipsilateral local tumour relapse events, an estimated $\alpha/\beta$ value of 4.0Gy (95% CI 1.0-7.8) compares closely with 3.6Gy (95% CI 1.8–5.4) for any change in breast appearance, and with 3.1Gy (95% CI 1.8–4.4) for moderate/marked induration reported
in the same trial\textsuperscript{6}. This is to the best of our knowledge the first direct estimate of fractionation sensitivity of human breast cancer. An important observation from the present trial is the significant dose-response relationship for local tumour control. A $\gamma$-value around 0.5 may appear low, but in the adjuvant situation the dose-response curve does not range from 0\% to 100\% control, since 70\% or so of the patients are locally controlled by surgery alone\textsuperscript{8}. The outcome of the present trial is consistent with recent modelling based on the results of the EORTC radiotherapy breast boost trial\textsuperscript{9}.

Assuming linearity between the two test dose levels, 41.6Gy in 13 fractions of 3.2Gy over 5 weeks is equivalent to 50Gy in 25 fractions in terms of tumour control, although the confidence intervals remain wide. Reliable estimates of the fractionation sensitivity of breast cancer await the results of the UK START Trial A (n = 2236), which includes randomised comparisons of 41.6Gy in 13 fractions and 39.0Gy in 13 fractions over 5 weeks against a control arm of 50Gy in 25 fractions. A recently reported Canadian randomised trial of 1234 patients reported no difference in ipsilateral tumour relapse rates, based on 44 tumour events, following 50Gy in 25 fractions over 35 days and 42.5Gy in 16 fractions over 22 days to the whole breast following microscopic tumour excision\textsuperscript{10}. A comparison based on 44 events is necessarily very imprecise, but if the 25- and 16-fraction schedules are truly iso-effective for tumour control, and assuming no difference in tumour cell repopulation between schedules, the $\alpha/\beta$ value for tumour response could be as low 3.0Gy, which is consistent with the fractionation sensitivity of the dose-limiting normal tissue responses developing years later. Meanwhile, the results of the UK START Trial B, which randomised 2215 women to 40Gy in 15 fractions over 3 weeks or 50Gy in 25 fractions over 5 weeks, will strengthen the interpretation of the Canadian schedule.
The clinical implications for breast cancer patients and health services will be profound if it is reliably demonstrated that the fractionation sensitivity of breast cancer is comparable to that of the dose-limiting normal tissues of the breast, including underlying pectoral muscle and ribcage. Although the data do not apply to treatment of the lymphatic pathways, where the brachial plexus is known to be highly sensitive to fraction size, there would be no reason to prefer 2.0Gy fractions for the majority of women requiring radiotherapy to the conserved breast or post-mastectomy chest wall. The challenge will be to determine the useful limits of hypofractionation. Current initiatives in this area include the randomised UK FAST Trial, which compares two dose levels (5.7Gy and 6.0Gy) of a 5-fraction regimen over 5 weeks against 50Gy in 25 fractions delivered using 3D dose-compensated whole breast radiotherapy. It should be stressed that although our trial results are consistent with the hypothesis under test, they are not sufficiently reliable on their own to justify hypofractionation outside the context of well designed randomised trials.

ACKNOWLEDGEMENTS

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REFERENCES


Figure 1: Flow of patients through the Breast Fractionation Trial

Number randomised

Fractionation schedule

50Gy 25Fr 5 weeks  
\( n=470 \)

42.9Gy 13Fr 5 weeks  
\( n=466 \)

39Gy 13Fr 5 weeks  
\( n=474 \)

Received allocated treatment

\( n=465 \)

Reasons why allocated treatment not received:
- 3 received boost although randomised to no boost (1 local relapse before RT; 1 prescription error; 1 narrow margins);
- 1 received 46Gy total dose (3cm lung in field);
- 1 received 60Gy total dose (multifocal disease).

\( n=456 \)

Reasons why allocated treatment not received:
- 1 received boost although randomised to no boost (prescription error);
- 3 withdrew from study;
- 1 randomisation error;
- 1 bone mets;
- 1 local relapse during RT;
- 1 refused trial allocation;
- 1 reason not known.

\( n=459 \)

Reasons why allocated treatment not received:
- 9 randomised to receive 41.6Gy before protocol amendment;
- 2 error in RT delivery;
- 2 died during RT;
- 1 refused trial allocation;
- 1 declined to finish.

Lost to follow-up

\( n=8 \)

Reasons:
- 7 moved (2 emigrated);
- 1 DNA appointments and was then discharged.

\( n=8 \)

Reasons:
- 4 moved;
- 4 unable to be traced.

\( n=2 \)

Reasons:
- 1 emigrated;
- 1 unable to be traced.

Number analysed

\( n=470 \)

\( n=466 \)

\( n=474 \)
Figure 2: Local relapse in the breast according to fractionation schedule (n=1410)

Number of events / Number at risk for each yearly interval:

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<th>0</th>
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<th>3</th>
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<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
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<tbody>
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<td>50Gy</td>
<td>4/470</td>
<td>9/459</td>
<td>13/443</td>
<td>3/410</td>
<td>6/397</td>
<td>2/377</td>
<td>1/364</td>
<td>6/323</td>
<td>3/262</td>
<td>1/206</td>
<td>0/146</td>
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<td>0/82</td>
<td>0/59</td>
<td>0/42</td>
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<tr>
<td>42.9Gy</td>
<td>5/466</td>
<td>7/451</td>
<td>10/437</td>
<td>7/407</td>
<td>2/386</td>
<td>3/371</td>
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### Table 1: Survival analysis of local relapse according to fractionation schedule (n=1410)

<table>
<thead>
<tr>
<th>Fractionation schedule</th>
<th>No of local relapses / pyrs</th>
<th>Crude hazard ratio (95%CI)</th>
<th>KM estimate of local relapse rate (%) (95%CI) at:</th>
<th>Smoothed estimate of absolute difference* in local relapse rate compared with 50Gy (%) (95%CI) at:</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5 years</td>
<td>10 years</td>
</tr>
<tr>
<td>50Gy</td>
<td>50/3965</td>
<td>1</td>
<td>7.9 (5.4 - 10.4)</td>
<td>12.1 (8.8 - 15.5)</td>
</tr>
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<td>42.9Gy</td>
<td>42/3840</td>
<td>0.86 (0.57 - 1.30)</td>
<td>7.1 (4.6 - 9.5)</td>
<td>9.6 (6.7 - 12.6)</td>
</tr>
<tr>
<td>39Gy</td>
<td>66/3890</td>
<td>1.33 (0.92 - 1.92)</td>
<td>9.1 (6.4 - 11.7)</td>
<td>14.8 (11.2 - 18.3)</td>
</tr>
</tbody>
</table>

pyrs = person-years
95%CI = 95% confidence interval
KM = Kaplan-Meier
* -ve difference means relapse rate lower than in 50Gy arm