Quality assurance analysis of participating centres' protocol compliance to a UK multicentre hypofractionated breast (FAST) trial

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Objectives: The FAST (FASTER radiotherapy for breast radiotherapy) trial is a UK Phase 2 multicentre randomised clinical trial evaluating a five-fraction schedule of whole-breast radiotherapy following local excision of early breast cancer. The purpose of this quality assurance study was to analyse the radiotherapy planning data in order to confirm compliance with the trial protocol.

Methods: 915 patients were recruited between 2004 and 2007 from 18 centres. The protocol required that all centres should use three-dimensional dose compensations to optimise radiotherapy plans. Planning techniques, maximum dose ($D_{\max}$) and dose–volume histograms from treatment plans were evaluated and compared between centres. The homogeneity of plans was tested by creating a cut-off value of 5% for the percentage of breast volume receiving $>105\%$ of the prescribed dose.

Results: 672 data sets from 15 centres were available. 93% (624/672) of plans were treated using forward-planned multileaf collimator (MLC) segments, 6% with breast compensators and 1% with inverse-planned MLC segments. 94% (635/672) of patients had a $D_{\max} \leq 107\%$ of the prescribed dose. 11% (74/672) of plans delivered $>105\%$ of the prescribed dose to $>5\%$ of the breast volume.

Conclusion: Reviewing the data in this study, 95% of plans submitted by centres complied with the protocol. With the improved breast radiotherapy standards shown in FAST centres, the following recommendations were suggested for future UK breast radiotherapy trials: (i) the minimum, mean and maximum dose to the whole-breast planning target volume (PTV) should be recorded and assessed; (ii) apart from having a $D_{\max} \leq 107\%$ of the prescribed dose, $\leq 5\%$ of PTV should receive dose $>105\%$ of the prescription dose.

Received 1 June 2011
Revised 21 September 2011
Accepted 11 October 2011

DOI: 10.1259/bjr/32249628

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There is recent level I evidence to support the adoption of modest hypofractionation for adjuvant radiotherapy in females with early breast cancer [1–5]. A regimen delivering 40 Gy in 15 fractions over 3 weeks has been recommended by the National Institute for Health and Clinical Excellence (NICE) as standard of care in the UK, but a 15-fraction schedule may not represent the lower limit of what hypofractionation has to offer [6].

To explore hypofractionation further, the UK National Cancer Research Network (NCRN) FAST (FASTER radiotherapy for breast radiotherapy) trial tested a five-fraction regimen delivered as one fraction per week, with defining change in photographic breast appearance as the primary end point. The complex nature of advanced radiotherapy techniques potentially introduces problems in ensuring reproducibility and accuracy of patients' treatment. This is especially true when carried out on a multicentre basis. A quality assurance (QA) programme is "a mandatory prerequisite when aiming at high dose,

high precision radiotherapy" and is an integral component of any radiotherapy trial as defined by the European Organisation for Research and Treatment of Cancer (EORTC) guidelines for trial protocols in radiotherapy [7, 8]. In the FAST trial, the QA programme was based on that developed from previous UK multicentre trials [9, 10]. This was implemented to ensure that technical guidelines within the protocol were understood and implemented correctly by participating centres. This QA analysis of the breast dosimetry data in the FAST trial was carried out to investigate the compliance of participating centres to the trial protocol, in order to ensure that the late tissue complications in the test schedules were not caused by the potential impact of the breast dose inhomogeneity.

Methods and materials

Trial design

Between 2004 and 2007, 915 patients participated in the FAST trial, a prospective randomised clinical trial testing 5 fractions of 6.0 Gy (Test Group 1) and 5.7 Gy (Test Group 2) against the control schedule of 25 fractions of 2.0 Gy (which was the standard fractionation schedule at the time of developing protocol) in terms of late normal

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We acknowledge NHS funding to the National Institute of Health Research Biomedical Research Centre and we thank Cancer Research UK, which provided the core grant for ICR-CTSU (Grant C1491/A9895).

tissue effects and tumour control in females prescribed whole-breast radiotherapy after local excision of early breast cancer. The trial eligibility criteria included (i) age at least 50 years, (ii) invasive carcinoma breast, (iii) pathological tumour diameter <3 cm and (iv) complete microscopic resection with negative axillary node. The exclusion criteria were patients who required (i) mastectomy, (ii) lymphatic radiotherapy, (iii) radiotherapy breast boost or (iv) neoadjuvant or adjuvant cytotoxic therapy. The primary end point was late radiation-induced changes in breast appearance scored on a graded three-point scale (none, mild or marked change) from serial photographs scored by three observers blind to treatment allocation [11]. Other end points included annual clinical assessment of adverse effects, relapse and survival. Assuming an average of 20% of females develop mild or marked change in breast appearance 24 months after the proposed test schedules, randomisation of 900 patients (300 per treatment group) would allow an absolute 10% difference in the probability of a change in breast appearance between the two test dose levels to be detected with 90% power at the 5% significance level (two-sided test).

Radiotherapy planning

The protocol defined the whole-breast clinical target volume (CTV) as the soft tissues of the whole breast down to the deep fascia, but not including underlying muscle and ribcage or overlying skin and excision scar. It suggested the breast localisation could be performed clinically by using anatomical landmarks or placing radio-opaque wires around breast tissues. Taking account of setup errors, breast swelling and breathing, the trial suggested a typical uniform 10-mm margin to the CTV to generate the whole-breast planning target volume (PTV). The recommended maximum lung and heart distances in the treatment volume were 2 and 1 cm, respectively. The radiotherapy plan consisted of two standard tangential fields with non-divergent posterior field edges for all treatment schedules in the trial as shown in Figure 1.

The dose was prescribed to the standardised prescription point defined in the START (STAndardisation of breast Radio Therapy) trial, half way between the lung surface and the skin surface on the perpendicular bisector of the posterior treatment beam edge [12]. The FAST protocol followed the International Commission on Radiation Units and Measurements (ICRU) report guidelines 50 and 62, and restricted dose variation across the treated volume to be between -5% and 7% of the reference isodose [13, 14]. In practice, small partial volumes (hot spots) received doses outside these limits owing to irregular tissue contours and electron-density inhomogeneity. A standard wedged pair was sufficient for some patients, but others required full-dose compensation. All patients were treated with three-dimensional (3D) dose compensation methods as required in the FAST protocol. Among the participating centres, there were three main 3D dose compensation methods used to improve dose homogeneity: (i) physical breast compensators, (ii) simple forward-planned intensity-modulated radiation therapy (IMRT) multileaf collimator (MLC) segment fields/field-in-field (FIF) technique and (iii) inverse-planned IMRT MLC segment fields [15–18].

Figure 1. Illustration of a breast CT slice planned with two tangential treatment fields.

Data collection

The majority of commercial planning systems were capable of export in either Radiation Therapy Oncology Group or DICOM RT format. When exported in this way, data sent to the FAST QA team included CT scans, treatment plan parameters, details of structures outlined and the radiation dose within the treatment volume computed by the planning system.

Data analysis

The data analysis was performed using the Guinness program (Stefano Gianolini, Royal Marsden Hospital, 2004, personal communication). Guinness was written using the Interactive Data Language, and it provided a graphical display of the radiotherapy dose distributions and allowed for the computation of dose-volume histograms (DVHs) for the patient-related structures that have been outlined. As it was not a mandatory requirement in the FAST trial to outline the treatment volumes, the analysis was performed by exporting the whole dose cube of a patient's plan to obtain the whole patient volume's DVH. The volumes that received >50% of the prescribed dose were used to represent the whole-breast PTV. This is acceptable in analysing breast radiotherapy treatment plans because the geometry of the 50% isodose line approximates the edge of the breast with very little irradiation of normal tissue outside of the 50% isodose line. To ensure protocol compliance of not having plans with hotspots >107% of the prescribed dose, maximum dose ($D_{\max}$) was used in this study for evaluating treatment plans. By the ICRU definitions, $D_{\max}$ is the maximum dose received by a volume with a diameter >15 mm. For this exercise, it was defined as the volume >2 cm³.

Results

Planning technique statistics

The FAST trial recruited 915 patients from 18 UK centres. There were 672 plans with compatible electronic format from 15 centres available for this retrospective

study. There were 219 plans in the control group, 228 plans in Test Group 1 and 225 plans in Test Group 2. The three centres that were unable to provide data in the suitable format for this analysis completed the pre-trial QA questionnaire to demonstrate that they were able to use full-dose compensations for breast treatment. For the 15 centres included in this study, 3 used the treatment planning systems with collapsed cone calculation algorithms, 7 used pencil beam models and 5 used stored beam models.

13 out of 15 centres used the simple forward-planned MLC segment method, which is referred to as FIF technique in other literature, while one centre used physical breast compensators and another used inverse-planned segments. Of the 672 plans analysed, most (93%) were treated using forward-planned MLC segment compensation methods, and the rest were treated with breast compensators (6%) or inverse-planned MLC segments (1%).

Maximum dose analysis

The $D_{\max}$ values of the 672 patients are shown in Figure 2. Nearly 95% (635/672) of patients had a $D_{\max} \leq 107\%$ in this study, which complied with the FAST protocol. For the plans with $D_{\max} > 107\%$, there were 14 in the control group, 12 in Test Group 1 and 11 in Test Group 2.

Figure 3 shows the $D_{\max}$ for each patient in all participating centres. The 37 plans with a $D_{\max} > 107\%$ were from nine different centres. Reviewing the dose compensation methods of those plans, 0 out of 9 plans with inverse-planned IMRT MLC segments had a $D_{\max} > 107\%$, compared with 21 out of 625 (3%) plans with forward-planned MLC segments and 16 out of 38 (42%) for physical compensators.

Dose-volume histogram evaluations

The DVH data were normalised using total volume between isodose bins of 50% to $>107\%$ with the assumption of the cumulative volumes receiving 50% isodose

representing the whole-breast treatment volumes. The normalised mean DVH data with the isodose bin starting from 90% to 107% are shown in Figure 4. The figure was used for assessing the trends of the mean DVH curve for all centres. During evaluation it was found that the data from centre H included only isodose bins of $\geq 90\%$. Thus, this centre was excluded in the mean DVH curve plot.

Analysis of "hotspots" in treatment plans

In order to compare the volumes of high-dose areas in plans among centres, a measure of homogeneity was defined as the percentage of the breast volume receiving a dosage of $>105\%$ of the prescribed dose. An arbitrary cut-off value of 5% of the volume was chosen, and the percentages of plans from each centre exceeding this value were compared in Table 1. 74 out of 672 plans (11%) where $>5\%$ of the volume received $>105\%$ of the prescribed dose.

Discussion

The level of trial protocol compliance of radiotherapy plans submitted in the FAST trial was very high. Based on the results of this study, nearly 95% of the plans delivered a $D_{\max} \leq 107\%$ of the prescribed dose. All participating centres used 3D dose compensations in their breast planning as required in the FAST protocol, and forward-planned treatments using MLC segments were the most common technique used. In agreement with conclusions of previous studies, this compensation method is an efficient and effective way of achieving uniform dose distribution throughout the breast [19–23]. 37 out of 672 plans (6%) failed to fulfil the maximum dose requirement. All of these plans used 6-MV X-rays. As stated in the study by Winfield et al [24], a higher energy can help with large-breasted patients to give a better dose distribution if it is available in the centre. However, the use of higher energy is limited by machine availability and therefore some large-breasted patients might be treated using 6 MV with a less homogeneous

Figure 2. Maximum dose ($D_{\max}$) distribution for all plans.

Figure 3. Maximum dose (D_{max}) distributions according to centre.

treatment plan. 16 (42%) out of 38 plans delivered using physical compensators were associated with a hotspot $>107\%$, and only centre H, where only 6MV of photon energy was available at the time of trial recruitment, used this compensation technique. Evans et al [25] and

Wilks and Bliss [15] showed a significant improvement in dose homogeneity using breast compensators. However, this is a less flexible compensation method than the FIF technique; it is more expensive and it takes longer to produce individualised physical compensators.

Figure 4. Normalised mean differential dose-volume histogram (DVH) plot for the 14 centres.

Table 1. Percentage of plans from each centre where >5% of the volumes received >105% of the prescribed dose

Centre ID	Number of patients	Number (%) of plans with >5% breast volume receiving >105% prescribed dose
A	61	1 (2)
B	13	4 (31)
C	9	1 (11)
D	32	0 (0)
E	107	23 (22)
F	110	0 (0)
G	62	14 (23)
H	38	22 (58)
I	19	3 (16)
J	10	0 (0)
K	43	2 (5)
L	22	2 (9)
M	49	2 (4)
N	4	0 (0)
O	93	0 (0)
Total	672	74 (11)

Donovan et al [21] commented on the limitation of averaging DVH data owing to the loss of spatial information. This study used only the mean DVH data in Figure 4 to illustrate a typical DVH curve from each FAST centre, in order to compare the trend of the DVH curves between centres. The similarity in trends' shapes of the mean DVH curves from the FAST centres shown in Figure 4 indicated that the participating centres normalised and prescribed the treatment plans in the same way as suggested in the protocol.

An earlier study suggested a significant volume effect for breast induration, so that the volumes of hotspots are as important as the $D_{\max}$ [26]. A threshold value of 5% of the whole-breast volume receiving >105% of the prescribed dose was established to investigate the size of the hotspots. Only 11% of the plans were above this threshold, as shown in Table 1. The mean percentage of the breast volume receiving >105% of the prescribed dose at all centres (apart from centre 10) was <5%. During the data analysis period, it was found that one centre provided the DVH data starting from a dose bin of 90% because of the limitations of its in-house planning system. An overestimation of the mean percentage of the volume receiving a dose >105% at this centre might be due to the data loss at the isodose bin boundary. Apart from having a $D_{\max} \leq 107\%$ of the prescribed dose, a dose homogeneity criterion of $\leq 5\%$ of the treatment volume receiving a dose >105% of the prescription dose is considered practical with the current dose compensation methods in the UK.

"Hotspots" cause more tissue damage than expected owing to the "double trouble effect", which describes the significance of a higher total dose and a higher dose per fraction, and this effect might be more important in a hypofractionated schedule, so-called "triple trouble" [27]. Turesson and Thames [28] suggested that the α/β for skin telangiectasia in breast radiotherapy was 2.8–4.3 Gy. This is comparable with the results for subcutaneous breast tissue in the START A trial, where the α/β value for late change in breast appearance was estimated as 3.4 Gy [4]. Applying this 3.4 Gy α/β estimate to the reference (100%) isodose, a linear quadratic equivalent

dose at 2 Gy (LQED₂) of 50 Gy delivered to the control group of the FAST trial compares with 52.2 Gy₂ (equivalent dose in 2 Gy fractions) in Test Group 1 and 46.3 Gy₂ in Test Group 2 [29]. The LQED₂ delivered to the 107% hotspots in the control group and Test Groups 1 and 2 were calculated as 54.9 Gy₂, 58.4 Gy₂ and 53.6 Gy₂, respectively.

Compared with the control schedule at the 100% prescribed dose level, Test Group 1 (LQED₂ of 52.2 Gy₂) would have a dose enhancement effect of 4.4%. Reviewing the 107% hotspots, the 1% of breast volume receiving >107% of the prescribed dose in Test Group 1 receives an LQED₂ of 3.5 Gy (6.4%) higher than the control group. Yarnold et al [30] commented that the extra dose to such a small volume would not be expected to be clinically detectable. There is currently insufficient follow-up in the FAST trial to test this empirically. However, this study analysed the dosimetry parameters in the FAST treatment plans and indicated the protocol compliance rates in the trial. As suggested by Ibbott et al [31], the quality of the trial would be reduced with an elevated number of deviations and this would become a barrier for interpretations of the trial outcomes. The 5% of plans that did not meet the $D_{\max}$ criteria in this study could be counted as trial deviations and should be analysed with the clinical follow-up results separately.

Recently, great advances have been made in the delivery of breast radiotherapy with IMRT. In IMRT, the use of dose constraints is widely implemented and the constraints could be used with a simple forward-planned IMRT technique as used in the FAST trial. This involves a change in the ways in which plans are assessed and prescribed. Instead of recording the dose to a point, minimum, mean and maximum doses received by the PTV can also be included in the prescription [32–34]. Apart from assessing hotspots in the plans, it is essential to ensure that the whole-breast volumes are treated with the prescription dose. A minimum dose constraint should be applied to the treatment volume [13, 14]. In order to carry out all these steps, breast radiotherapy plans are required to have the whole-breast PTV contoured. Not having a treatment volume outlined in FAST patients made DVH analysis challenging. This study used the volumes which received >50% of the prescribed dose to represent the whole-breast PTV. The major limitation of using this treatment volume surrogate is the inclusion of lung and heart volumes within the 50% isodose, although this effect should be minimised by the trial's recommendations of maximum lung and heart distances in the treatment volume to be <2 and 1 cm, respectively.

Conclusions

With few exceptions, all plans submitted by participating centres complied with the FAST trial protocol. Using the 3D dose compensation techniques described, all centres were able to deliver homogeneous plans. Changing from field- to volume-based breast planning will provide the QA team with relevant information for plan assessment. With the improved breast radiotherapy standards shown in FAST centres, the following recommendations were suggested for future UK breast radiotherapy trials:

(i) the minimum, mean and maximum dose to the whole-breast PTV should be recorded and assessed; (ii) apart from having a $D_{\max} \leq 107\%$ of the prescribed dose, no more than 5% of the treatment volume should receive a dose $>105\%$ of the prescription dose. 3D dosimetry does not abolish dose gradients across the breast, which introduces spatial variations in biological dose intensity, which is not likely to be clinically significant. Nevertheless, further work should be carried out to investigate the radiobiological effect of dose inhomogeneities introduced by larger fraction sizes.

Acknowledgments

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We thank all the patients who participated in this study, and the doctors, nurses, radiographers, physicists and data managers at the participating centres. We acknowledge the support of The Royal College of Radiologists (UK). The Cancer Research UK number for the FAST Trial is CRUKE/04/015.

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