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Original Article

Modern Hypofractionation Schedules for Tangential Whole Breast Irradiation Decrease the Fraction Size-corrected Dose to the Heart

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Abstract

Aims: Hypofractionation of postoperative radiotherapy for breast cancer has been evaluated in a number of large randomised clinical trials, but concerns remain over the late cardiac toxicity. In this study, we examined the predictions of the linear quadratic model on the estimated fraction size-corrected dose to the heart for four evidence-based hypofractionation regimens.

Materials and methods: Dose plans for 60 left-sided breast cancer patients were analysed. All patients were planned with tangential fields for whole breast irradiation. Dose distributions were corrected to the equivalent dose in 2 Gy fractions (EQD_2) using the linear quadratic model for five different fractionation schedules (50 Gy/25 fractions and four hypofractionation regimens) and for a range of α/β values (0–5 Gy). The mean EQD_2 to the heart ($D_{mean}^{EQD_2}$) and the volume receiving 40 Gy ($V_{40\ Gy}^{EQD_2}$), both as calculated from the EQD_2 dose distributions, were compared between schedules.

Results: For $\alpha/\beta = 3$ Gy, $V_{40\ Gy}^{EQD_2}$ favours hypofractionation for 40 Gy/15 fractions, 39 Gy/13 fractions and 42.5 Gy/16 fractions, but not for 41.6 Gy/13 fractions. All of the hypofractionation schedules result in lower $D_{mean}^{EQD_2}$ compared with normofractionation. These results hold as long as $\alpha/\beta \gtrsim 1.5$ Gy. If the heart is blocked from the treatment beam, the fraction size-corrected dose is lower for the first three hypofractionation schedules, compared with normofractionation, even for $\alpha/\beta = \sim 1$ Gy.

Conclusion: For standard tangential field whole breast irradiation, most of the examined hypofractionation schedules are estimated to spare the heart when compared with normofractionation. The dose to the heart, adjusted for fraction size using the linear quadratic model, will generally be lower after hypofractionated compared with normofractionated schedules, even for very low values of α/β.

Key words: Breast; heart; hypofractionation; late cardiac toxicity; linear quadratic model

Introduction

Postoperative whole breast irradiation for breast cancer patients both reduces the risk of local recurrence and improves overall survival [1]. Although a normofractionated schedule of 50 Gy in 25 fractions has been the standard treatment in most countries, moderate hypofractionation is now being introduced in many places.

Over 7000 patients have been enrolled in large, randomised clinical trials comparing hypofractionated with normofractionated radiotherapy [2–6]. The results suggest that α/β of breast cancer is in the range of 3–5 Gy [4,5,7]. As a result, several hypofractionation regimens have been identified, with disease control rates and toxicity profiles comparable with those seen with normofractionated whole breast irradiation after breast-conserving surgery [8,9].

Still, concerns are nonetheless being raised over the safety of hypofractionation in terms of long-term toxicity [10], especially concerning mortality from radiation-induced heart disease, the sceptics arguing that the follow-up is still insufficient to judge the incidence of cardiac toxicity [11]. After a follow-up of 10 years, however, the Ontario Clinical Oncology Group trial [2] saw no difference in death due to cardiac disease between hypo- and normofractionated whole

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breast irradiation (nine and 12 deaths, respectively). This is consistent with the results of the British START A [5] and START B [6] trials, although the median follow-up was shorter (5.1 and 6.0 years).

Theoretical estimates of the cardiac toxicity after hypofractionation as compared with normofractionation depend on the fractionation sensitivity of the heart, quantified by the α/β ratio of the linear-quadratic model. Generally, a generic 'late tissue damage' α/β ratio of 3 Gy has been assumed, corresponding to relatively high fractionation sensitivity. There have, however, been suggestions of an even lower α/β for the heart, possibly as low as 1 Gy, although the data arguably are not very strong [12].

In this study, we compared fraction size-corrected dose distributions to the heart for four hypofractionation schedules with the normofractionated schedule of 50 Gy in 25 fractions, for a range of α/β values. The four schedules were those tested in three large, multi-institutional, randomised trials of hypofractionation: the British START A [5] and START B [6] trials and the Ontario Clinical Oncology Group trial of 42.5 Gy in 16 fractions [2].

Materials and Methods

Dose plans for 60 left-sided breast cancer patients treated with postoperative radiotherapy in a single institution in 2010 were analysed. The patients represented an unselected consecutive series of patients referred for irradiation of the residual breast (without regional lymph node irradiation) after breast-conserving surgery. All patients were prescribed 50 Gy in 25 fractions to the mammary tissue. Treatment plans were created in Oncentra MasterPlan® (Nucletron, an Elekta Company, Veenendaal, Netherlands) using tangential fields with a forward planning intensity modulation technique, combining 6 and 18 MV photon beams. Dose distributions were calculated with a collapsed cone algorithm. The dose to the planning target volume was optimised to cover the target by the 93% isodose line with a dose maximum not exceeding 107% of the prescribed dose. Dose distribution homogeneity was improved using hard beam wedges and additional top up fields. For the purpose of the treatment planning process and according to institutional guidelines, $V_{20\ Gy}^{phys}$ (relative volume receiving more than 20 Gy in physical dose) for the heart was kept below 10%, $V_{40\ Gy}^{phys}$ below 5%. If necessary, target coverage was compromised to meet these normal tissue constraints.

Dose distributions for the heart were extracted, and dose volume histograms (DVHs) were renormalised corresponding to the five different dose and fractionation schedules shown in Table 1. All dose distributions were adjusted for fraction size, converting each dose level, D, to the equivalent dose delivered in 2 Gy fractions (EQD_2) [13]

$$EQD_2 = D \cdot \frac{D/n + \alpha/\beta}{2 + \alpha/\beta}$$

Accordingly, five EQD_2 dose distributions were calculated for each patient (one for each of the five schedules in Table 1). All dose metrics mentioned below refer to the EQD_2 dose distributions, unless otherwise noted.

The mean fraction size-corrected dose to the heart, $D_{mean}^{EQD_2}$, and the relative volume receiving more than 40 Gy, $V_{40\ Gy}^{EQD_2}$, were calculated from the EQD_2-corrected DVHs and compared between schedules. The differences between the normo- and hypofractionation schedules,

$$\Delta D_{mean}^{EQD_2} = D_{mean,normo}^{EQD_2} - D_{mean,hypo}^{EQD_2}$$

and

$$\Delta V_{40\ Gy}^{EQD_2} = V_{40\ Gy,normo}^{EQD_2} - V_{40\ Gy,hypo}^{EQD_2}$$

were calculated for each patient and median values of $\Delta D_{mean}^{EQD_2}$ and $\Delta V_{40\ Gy}^{EQD_2}$ for the entire patient cohort were determined. Positive values of $\Delta D_{mean}^{EQD_2}$ and $\Delta V_{40\ Gy}^{EQD_2}$ imply that the hypofractionated regimens were 'colder' than the normofractionated regimen. The calculation was carried out for α/β values ranging between 0 and 5 Gy. All DVH calculations were carried out in MATLAB® (2010b, The MathWorks Inc, Natick, MA, USA). Ninety-five per cent confidence intervals for median values were estimated using a bootstrap procedure drawing 2×10^5 random samples with replacement from the original dataset.

For comparison purposes, EQD_2 doses as a function of the relative dose levels (i.e. percentage of the prescribed dose) were plotted for all five schedules assuming two different α/β values, $\alpha/\beta = 1$ Gy and $\alpha/\beta = 3$ Gy.

Results

Figure 1 shows the physical dose distribution for a randomly chosen patient (for a 50 Gy prescribed dose), as well as the fraction size-corrected DVH for the heart for

Table 1
Fractionation schedules

Schedule	Reference	EQD_2, $\alpha/\beta = 3$	EQD_2, $\alpha/\beta = 1$	Overall treatment time (weeks)
50 Gy/25 fractions	(normofractionation)	–	–	5
41.6 Gy/13 fractions	START A_1	51.6 Gy	58.2 Gy	5
39 Gy/13 fractions	START A_2	46.8 Gy	52.0 Gy	5
40 Gy/15 fractions	START B	45.3 Gy	48.9 Gy	3
42.5 Gy/16 fractions	Whelan *et al.* [2] (Canadian)	48.1 Gy	51.8 Gy	3.2

EQD_2, equivalent uniform dose in 2 Gy fractions. Reported EQD_2 values are for the prescribed dose.