Physica Medica 31 (2015) 1022–1028

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original Paper

Hypofractionation of partial breast irradiation using radiobiological models

Michele Avanzo [a,*], Marco Trovo [b], Joseph Stancanello [c], Rajesh Jena [d], Mario Roncadin [b], Giulia Toffoli [e], Chiara Zuiani [e], Elvira Capra [a]

[a] Medical Physics Department, CRO Aviano, 33081 Aviano, Italy
[b] Radiation Oncology Department, CRO Aviano, 33081 Aviano, Italy
[c] MRI Applications and Workflow, General Electric, 78533 Buc, France
[d] Department of Oncology, University of Cambridge, Cambridge CB2 0QQ, UK
[e] Institute of Diagnostic Radiology, Department of Medical and Biological Sciences, University of Udine, 33100 Udine, Italy

ARTICLE INFO

Article history:
Received 20 April 2015
Received in revised form 10 July 2015
Accepted 3 August 2015
Available online 23 October 2015

Keywords:
Hypofractionation
Partial breast irradiation
NTCP
TCP
Breast
Fibrosis

ABSTRACT

Purpose: To reduce the fraction number in Partial Breast Irradiation (PBI) with initial prescription of 40 Gy in 10 fractions using radiobiological models with specific focus on risk of moderate/severe radiation-induced fibrosis (RIF) and report clinical results.
Methods and materials: 68 patients (patient group A) were treated with 40 Gy in 10 fractions delivered by field-in-field, forward-planned IMRT. Isotoxic regimens with decreasing number of fractions were calculated using Biological Effective Dose (BED) to the breast. Risk for RIF in hypofractionated treatment was predicted by calculating NTCP from DVHs of group A rescaled to fractions and dose of novel regimens. Moderate/severe RIF was prospectively scored during follow-up. Various NTCP models, with and without incomplete repair correction, were assessed from difference to observed incidence of RIF. In order to verify the value for α/β of 3 Gy assumed for breast, we fitted α/β to observed incidences of moderate/severe RIF.
Results: Treatments with 35 Gy/7f and 28 Gy/4f were selected for the fraction reduction protocol. 75 patients (group B) were treated in 35 Gy/7f. Incidence of moderate/severe RIF was 5.9% in group A, 5.3% in group B. The NTCP model with correction for incomplete repair had lowest difference from observed RIF. The α/β obtained from fitting was 2.8 (95%CIs 1.1–10.7) Gy.
Conclusions: The hypofractionated regimen was well tolerated. The model for NTCP corrected for incomplete repair was the most accurate and an assumed α/β value of 3 Gy is consistent with our patient data. The hypofractionation protocol is continuing with patients treated with 28 Gy/4f.

Introduction

In recent years partial breast irradiation (PBI) performed with external photon beams has gained acceptance in the post-operative management of early stage breast cancer after breast conserving surgery [1–4]. In our hospital, PBI treatments were delivered following a novel protocol consisting of 40 Gy in 10 daily fractions of 4 Gy over two weeks which produced good cosmetic results [5].

In radiotherapy (RT) treatments it is desirable to reduce the overall treatment time to enhance convenience to the patient as well as reduce the treatment burden of breast radiotherapy in busy treatment centers. Strategies to shorten treatment time include reducing the number of fractions (hypofractionation) and increasing the number of fractions per day (accelerated treatment). Good results in terms of side effect profile and local control rate [1] have been generally reported with accelerated PBI (APBI), which is delivered in twice daily fractions but, in two APBI studies, significant short term toxicities have been observed [3,4]. On the other hand, trials of whole breast RT hypofractionation provided evidence that lower total doses of RT delivered in fewer fractions with larger doses per fraction are as safe and effective as conventional regimens (50 Gy in 25 fractions) for women after primary surgery for early breast cancer [6,7]. A strategy to reduce fraction number was therefore adopted in our hospital to reduce the duration of PBI from the consolidated regimen of 40 Gy/10 fractions.

A clinically acceptable hypofractionation regimen should yield equivalent effect to the tumor and risk of normal tissue toxicity. These goals can be achieved using the concept of Biologically Effective Dose (BED), which accounts for the effect of fractionation on clinical outcome, and analytical models of Normal Tissue Complication Probability (NTCP), which correlate outcome of RT with

* Corresponding author. Medical Physics Unit, CRO Aviano National Cancer Institute, 33081 Aviano, Italy. Tel.: +39 0434659175; fax: +39 0434659524.
E-mail address: mavanzo@cro.it (M. Avanzo).

http://dx.doi.org/10.1016/j.ejmp.2015.08.016
1120-1797/

Table 1
Models for NTCP and BED, and radiobiological parameters used in the present study.

Model, description, reference	Parameter values
(1) Model for moderate/severe RIF prediction model accounting for incomplete repair and latency of effect, derived from published average clinical and dosimetrical data of PBI and WBI [9]	n = 0.15, m = 0.22, $BEUD_{50}$ = 105.8 Gy, α/β = 3 Gy, μ = 0.46 years, σ = 1.27 years
(1a) Model 1, calculated from average DVH and average follow-up time of the patient groups	
(1b) Model 1, with α/β = 2.8 Gy derived from fitting clinical results in the present study	
(2) Model for moderate/severe RIF accounting for latency of effect, derived from published average clinical and dosimetrical data of PBI and WBI [9]	n = 0.06, m = 0.22, $BEUD_{50}$ = 107.2 Gy, α/β = 3 Gy, μ = 0.46 years, σ = 1.27 years
(3) Moderate/severe RIF prediction model, derived from analysis of pooled individual patient clinical data of EORTC and START trials, with two-compartment DVH model [10]	n = 0.012, m = 0.35, $BEUD_{50}$ = 132 Gy, α/β = 3 Gy
(4) Moderate/severe RIF prediction model, derived from published clinical data of PBI and WBI and DVHs from in-phantom generated treatments [8]	n = 0.78, m = 0.27, $BEUD_{50}$ = 104 Gy, α/β = 3 Gy
(5) Biologically effective dose (BED) for breast cancer based on linear quadratic model and Poisson statistics [15]	α = 0.27 Gy^{-1}, α/β = 4 Gy, T_{pot} = 15 days, T_k = 0

dose-volume data and fractionation scheme [8–11]. These predictive models have now been implemented in clinical practice, specifically as a tool for comparison of treatment schedules [12,13].

To model toxicity, we use models of NTCP for subcutaneous radiation induced fibrosis (RIF). RIF is characterized by progressive induration, edema formation, and thickening of the dermis and subcutaneous tissue. It is considered one of key side effects of PBI influencing cosmetic outcome [14]. We recently derived NTCP models for the risk of severe (grade 2 or more) RIF from published incidences of RIF on PBI [9]. The best fit parameters for the model were estimated using average dosimetric parameters (prescription dose, fraction dose, mean follow up time) from published Whole Breast Irradiation (WBI) studies and external beam PBI studies.

The purpose of this study was to derive consistent fraction reduction protocol for PBI using radiobiological models and report clinical results on patients treated with the newly designed regimen. In our previous work, verification of NTCP models for RIF used to design the hypofractionation protocol could be made in a very limited dataset with limited follow-up time (35 patients with 12 months average follow up) [9]. As follow up data for incidence of side effects were prospectively collected in the present work, the accuracy of NTCP models can be tested against a more diverse and mature dataset. Moreover, since in NTCP modeling of RIF the value of α/β of RIF was assumed as 3 Gy, we want to test the validity of this assumption by fitting α/β to incidences of severe RIF in the hypofractionation study already available at our institution.

Methods and materials

Hypofractionation modeling

The hypofractionated treatments were designed with the aim of being isotoxic, that is, of providing the same biological dose for the effect of moderate/severe RIF. A formula of BED based on the linear quadratic model was used to derive equivalent prescribed doses, with a value for α/β of 3 Gy for breast tissue (Eq. A1 in Appendix A.1). Hypofractionated treatments were required to have the same BED to the breast as the initial treatment of 40 Gy in 10 fractions. In order to evaluate the effect of change of regimen on the tumor, a formula corrected for repopulation of tumor cells was used to calculate tumor BED as described by Eq. (A2) in Appendix A.1. The radiobiological parameters of models are shown in Table 1. The total dose with the same BED as the initial treatment with 40 Gy in 10 fractions was plotted versus decreasing number of fractions in Fig. 1.

NTCP for severe RIF in the hypofractionated regimens was preliminarily estimated from data of patients already treated with 40 Gy/10f using a model originally derived from literature data on PBI [9] as described in Appendix A.2. Data from 68 patients (patient group A) treated with PBI between July 2008 and June 2012 were used to study the average NTCP as a function of dose and fraction number. These patients, previously treated by breast conserving surgery for an early stage ductal carcinoma, underwent non-accelerated external PBI with prescribed dose of 40 Gy in 10 daily fractions of 4 Gy over two weeks [5]. Patient characteristics are shown in Table 2. The clinical target volume (CTV) consisted of the lumpectomy cavity and the Planning Target Volume (PTV) consisted of the CTV plus 1 cm margin. Breast tissue visible on the computed tomography simulation scan was outlined. The RT technique consisted of "field-in-field" planning (forward-planned intensity modulated RT) [16] using

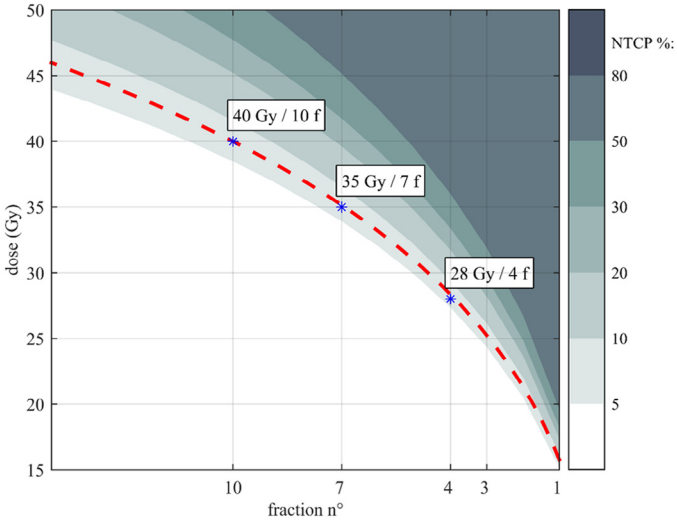

Figure 1. Design of hypofractionation protocol of PBI. The red dashed lines represent the prescribed dose giving the same tumor BED as the initial treatment of 40 Gy in 10 fractions for decreasing number of fractions. Levels of average $NTCP_{IR}$ of moderate/severe RIF (green areas) are calculated from DVHs of patients previously treated with the initial regimen of 40 Gy/10 fractions rescaled to different doses and fractions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Characteristics of patients treated at our institution with PBI in the initial (Group A) and hypofractionated regimens (Groups B and C). Incidence of fibrosis is not assessed in the third group due to short follow-up time.

Patient and treatment characteristics	Mean value (range)		
	Group A	Group B	Group C
Prescribed dose [Gy]	40 Gy	35 Gy	28
Fractions [number]	10	7	4
Patients [number]	68	75	15
Age [years]	71 (61–83)	70 (61–85)	70.5 (60–81)
Follow-up [months]	53 (17–23)	26 (9–38)	3 [0–6]
RIF grade ≥ 2 [yes/no]	4/64	4/71	/