Radiotherapy and Oncology 120 (2016) 300–306

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Second cancer risks after RT

Modelling of organ-specific radiation-induced secondary cancer risks following particle therapy

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ARTICLE INFO

Article history:
Received 25 December 2015
Received in revised form 20 June 2016
Accepted 3 July 2016
Available online 13 July 2016

Keywords:
Particle therapy
Carbon ion
Proton
Secondary cancer
Prostate

ABSTRACT

Background and purpose: Radiation-induced cancer is a serious late effect that may follow radiotherapy. A considerable uncertainty is associated with carcinogenesis from photon-based treatment, and even less established when including relative biological effectiveness (RBE) for particle therapy. The aim of this work was therefore to estimate and in particular explore relative risks (RR) of secondary cancer (SC) following particle therapy as applied in treatment of prostate cancer.

Material and methods: RRs of radiation-induced SC in the bladder and rectum were estimated using a bell-shaped dose–response model incorporating RBE and fractionation effects. The risks from volumetric modulated arc therapy (VMAT) were compared to intensity-modulated proton therapy (IMPT) and scanning carbon ions for ten patients.

Results: The mean estimated RR (95% CI) of SC for VMAT/C-ion was 1.31 (0.65–2.18) for the bladder and 0.58 (0.41–0.80) for the rectum. Corresponding values for VMAT/IMPT were 1.72 (1.06–2.37) and 1.10 (0.78–1.43). The radio-sensitivity parameter α had the strongest influence on the results with decreasing RR for increasing values of α.

Conclusion: Based on the wide spread in RR between patients and variations across the included parameter values, the risk profiles of the rectum and bladder were not dramatically different for the investigated radiotherapy techniques.

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Radiation-induced malignancy is a serious late adverse effect that can result from exposure to ionising radiation [1]. Radiotherapy (RT) is an important component in the treatment of cancer, and due to the rapid advances in RT development, it is of interest to establish good predictive methods to assess both contemporary and emerging modalities [2]. For patients treated with RT for prostate cancer, an increased risk of secondary cancer (SC) is seen, yet with insufficient clinical data to draw firm conclusions about the impact of different treatment techniques [1]. Therefore, planning studies and theoretical risk estimations play an important role in the assessment of long-term consequences of new treatment techniques [3].

Several predictive models for SC risk are developed and frequently applied to photon-based RT [4–6] incorporating varying degrees of cell inactivation at high doses. The quite different underlying dose–response relationships result in divergent estimates depending on choice of model [7]. Particle therapy (commonly proton or carbon(C)-ion) is receiving increasing attention due to its potential for improved dose conformity and reduction in dose to healthy tissues [3,8]. The physical and biological properties of particle therapy more efficiently inactivate cancer cells, but also interact differently with healthy cells. While the functional relationship of carcinogenesis from photon-based RT remains uncertain, the additional dimension of relative biological effectiveness (RBE) of particle therapy is even less explored for cancer induction.

RBE depends on the linear energy transfer (LET) to the absorbing tissue on a microscopic scale and reflects the relative physical dose required to produce a given effect in tissue. High-LET radiation is usually more effective compared to low-LET photon irradiation with respect to cell inactivation as well as induction of mutations [9,10]. Furthermore, fractionation effects are more important for low-LET radiation than for high-LET radiation, and thus RBE also depends on the choice of fractionation. [11]. To assess the risk of radiation-induced secondary cancer from particle

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http://dx.doi.org/10.1016/j.radonc.2016.07.001
0167-8140/

therapy, models including these radiobiological concepts are required.

The aim of this work was therefore to estimate and in particular explore relative risks (RR) of secondary bladder and rectal cancer using dose distributions from photon, proton and C-ion therapy as applied in contemporary clinical practice of RT of prostate cancer. In our work we used a bell-shaped dose–response model suggested by Jones [12] combined with patient- and organ- specific dose distributions from clinically applied RT techniques. Due to the current lack of information to adequately establish model parameters, we also performed a model parameter scan to identify the influence of variations of these parameters.

Materials and methods

Patient material, target definitions and treatment planning

CT-scans from ten patients treated for localised prostate cancer at Haukeland University Hospital (HUH), Bergen, Norway in 2008 were used in this study. The primary clinical target volume (CTV) and organs at risk were based on the original contours used during treatment.

For each patient, three treatment plans with either VMAT, IMPT or C-ions were generated according to clinical protocols at the involved institutions and were approved by an experienced oncologist at each institution. The same primary CTV was used for all three techniques and included the prostate gland and the seminal vesicles. The treatments also included boost volumes, which for VMAT and IMPT covered the prostate only, while for the C-ion plans the boost target volume was reduced posteriorly.

For VMAT and IMPT, margins were defined by assuming image-guidance with fiducial markers, and the primary planning target volume (PTV) was therefore generated by isotropically expanding the prostate and seminal vesicles by 5 mm. Boost PTVs were defined by a 2 mm margin to the prostate. For the C-ions, patient positioning by bone matching was assumed. The primary PTV was thus created by adding anterior and lateral margins of 10 mm and a posterior margin of 5 mm to the CTV, while boost fractions were performed with the posterior edge cropped to the anterior wall of the rectum.

The VMAT and IMPT plans were prescribed to deliver 67.5 Gy (RBE) to the prostate and 60 Gy (RBE) to the seminal vesicles over 25 fractions with an integrated boost. The C-ion plans were applied in total 12 fractions with 34.4 Gy (RBE) to the primary PTV and 51.6 Gy (RBE) to the boost volume (boost delivered during four final fractions). The rectum was contoured from the anal verge to the recto-sigmoid flexure and the bladder was contoured from apex to dome (both as organs including contents). Normal tissue dose criteria were applied according to standard procedure at each institution.

The VMAT plans were generated according to current clinical procedures at HUH using a partial 6 MV single arc with a 12° posterior avoidance sector. The IMPT plans were optimised using two opposing lateral scanning beams based on generic beam data from the first generation Varian ProBeam machine (using the Proton Convolution Superposition algorithm: PCS_11.0.31-90 MeV). Beam spot spacing was 5 mm in the scanning direction as well as between the twelve scanning layers delivering nominal energies just below 200 MeV. The C-ions were also optimised using lateral fields [13,14], however, by single field optimisation with 2 mm spot spacing and slice thickness. Eleven energy steps were available for the active scanning of C-ion beams, ranging from 140 to 430 MeV; depths lying in between the ranges of two adjacent energies were covered by applying range shifter plates. The clinical (biological) C-ion dose was optimised using the modified microdosimetric kinetic model (MKM), explained elsewhere [15]. The physical dose distributions converted from the optimised biological dose was then used as input for the secondary cancer risk modelling (Figs. B1 and B2, Appendix B). For the C-ion risk calculations, the total dose were divided into twelve equal fractions, hence assuming the boost fractions integrated and beam delivery from two angles every day.

The VMAT and IMPT plans were generated in the Eclipse treatment planning system [Varian Medical Systems, Palo Alto, CA, USA] while the scanning C-ions plans were generated in XiO-N [Mitsubishi Electric Corporation, Tokyo, Japan].

Estimation of secondary cancer risk

Physical dose distributions of the bladder and rectum were used to calculate RR for radiation-induced cancer, for VMAT/IMPT and VMAT/C-ion, using a multi-parameter model incorporating relative biological effects for protons and C-ions [12]. Briefly, the model formulates the RR of malignant induction between X-ray and particle therapy, expressed by means of low LET radio-sensitivity parameters α and β. For high-LET radiation, corrections were incorporated with the parameters RBE_{max} and RBE_{min}, which are the RBE defined at the low and high dose limit, respectively. Thus it is assumed that this adjustment provides validity for high-LET particles.

In this study, we used the above RBE adjusted dose–response function from Jones [12] but extended to whole organs (instead of per cell) by applying the organ equivalent dose (OED) concept suggested by Schneider [5]. The OED is the risk-weighted dose-distribution converted into a single dose in units of Gray representing the same radiation-induced hazard as the equivalent amount of uniform (organ) dose. The RR, based on a heterogeneous physical dose distribution to a specific organ volume, V, is given by:

$$RR = \frac{\int_V n_X(\alpha d_X + \beta d_X^2) e^{-n_X(\alpha d_X + \beta d_X^2)} dV}{\int_V n_p \left(\mathrm{RBE}_{\max} \alpha d_p + \mathrm{RBE}_{\min}^2 \beta d_p^2\right) e^{-n_p\left(\mathrm{RBE}_{\max} \alpha d_p + \mathrm{RBE}_{\min}^2 \beta d_p^2\right)} dV}$$

with fraction doses d and fractions n. Subscripts X and p refer to x-rays and particles, respectively. The model and calculation procedures are described in further detail in Appendix A.

A parameter scan was performed for the bladder and rectum dose distributions, where we calculated the mean RRs for all patients over different possible combinations of RBE_{max}, RBE_{min}, α and β. Further, we performed a one-dimensional scan over each

Table 1
Nominal model parameters and input distributions.

	Bladder	Rectum	Distribution	Ref. nominal value
α (Gy^{-1})	0.25 (σ = 0.075)*	0.25 (σ = 0.075)*	Gaussian	Dașu et al. [16] Table 2
β (Gy^{-2})	0.033 (σ = 0.0055)*	0.046 (σ = 0.0077)*	Gaussian	Dașu et al. [16] Table 2
RBE_{min} (C-ion)	1.25 (1.2, 1.3)	1.25 (1.2, 1.3)	Triangle	Jones [12]
RBE_{max} (C-ion)	6 (5, 7)	6 (5, 7)	Triangle	Jones [12]
RBE_{min} (proton)	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	Triangle	Jones [12]
RBE_{max} (proton)	1.25 (1.2, 1.3)	1.25 (1.2, 1.3)	Triangle	Jones [12]

* Percentage σ from Jones [12].