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Original paper

The influence of inter-fractional anatomy variation on secondary cancer risk estimates following radiotherapy

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ABSTRACT

Purpose: In silico studies comparing estimated risks of radiation-induced secondary cancer (SC) are frequently performed in assessment of radiotherapy techniques. Since inter-patient anatomy variations can result in considerable differences in estimated risk we aimed to explore the influence of inter-fractional organ motion patterns on SC risk.

Methods: Volumetric modulated arc therapy (VMAT) and intensity-modulated proton therapy (IMPT) plans were generated on the planning CT (pCT) scans of eight prostate cancer patients. In addition, the treatment plans were re-calculated on 8–9 repeat CTs (rCTs) of each patient acquired throughout the treatment course. Relative risk (RR) of SC (VMAT/IMPT) was calculated for the planned and the re-calculated dose distributions using the organ equivalent dose concept adapted to a linear and a bell-shaped competition dose–response model.

Results: Day-to-day variations in anatomy lead to fluctuations in SC risk estimates of the same order of magnitude as those caused by inter-patient variations. Using the competition model, the RR range for bladder cancer based on the pCTs was 0.4–3.4, while a considerably wider range was found when including all rCTs (0.2–6.7). There was nevertheless a correlation in RR based on repeat CTs for individual patients, indicating that patient-specific SC risks could be estimated.

Conclusions: The estimated relative risks varied considerably across rCTs and could change the risk in favour of VMAT/IMPT depending on the anatomy of the day. The results demonstrate the importance of performing in silico studies of SC risk on a cohort of patients or multiple CTs when structures subject to organ motion are involved.

1. Introduction

Radiation-induced secondary cancer (SC) is a serious late effect following radiotherapy of a primary malignancy [1] that may occur decades after treatment [2,3]. With the rapid technology development, follow-up data from late complications such as SC remains unavailable until contemporary techniques are outdated. Methods to assess risk associated with the long-term outcomes of emerging techniques are therefore needed. Model estimates based on dose distributions as planned on computer tomography (CT) scans of patients are frequently applied in the literature to rank treatment techniques, also widely employed in prostate cohorts [4]. Such estimates are associated with considerable uncertainty and are often based on multiple dose-response scenarios [5].

Follow-up data from prostate patients have shown an association between radiotherapy and increased risk of secondary bladder and rectal cancers [6], reaching as high as 1 of 70 patients in long term survivors (> 10 years) [3]. The 10-year relative survival rate for men diagnosed with prostate cancer has greatly improved the past decades and the choice of treatment is an important determinant of long-term risk of morbidity [7]. Prostate cancer has been a primary site for introduction of new treatment techniques in radiotherapy, most recently with the widespread adoption of volumetric modulated arc therapy (VMAT). VMAT achieves dose reductions in high-dose volumes at the expense of increased volumes receiving lower doses compared to previous conformal radiotherapy techniques. Intensity-modulated proton therapy (IMPT) achieves similar high-dose conformity in treatment of localised prostate cancer as VMAT [8], and has been explored due to its potential to also reduce the integral normal tissue doses [9]. Several planning studies have estimated lower SC risk for the bladder and

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rectum with proton techniques compared to 3D-CRT and IMRT [4]. With respect to VMAT, risk estimates are lower or comparable for protons depending on model used [10].

Besides model-dependent differences in risk, considerable inter-patient variations in SC risk estimates for the bladder and rectum have been shown [10,11]. The planning CT (pCT) is considered the primary model of the patient for treatment planning, although it is well known that anatomy variations occur throughout the course of therapy [12,13]. The bladder and rectum are both highly mobile structures much due to variations in organ filling which in turn can shift the relative position of the prostate [14], and thereby considerable deteriorations with respect to dose distributions are known to occur [15]. Estimation of SC risk has so far been based on using a single CT scan of each patient. However, the substantial effects of patient-specific anatomy variations on the dose-distribution indicate that also the influence of inter-fractional organ motion patterns of individual patients should be examined. This includes how distinctive the SC risk estimate based on a pCT is for the specific patient and how to interpret a spread in risk estimates due to differences in dose distributions as calculated on repeat CTs of the same patient. Such quantifications are required to obtain a risk profile for the patient, and certainly if optimisation of risk is explored. The aim of this study was therefore to investigate the influence of organ motion (positional and volumetric changes) of the bladder and rectum in estimation of SC risk after radiotherapy for prostate cancer with photons vs. protons.

2. Methods

The study was based on a cohort of eight prostate cancer patients that received radiotherapy at Haukeland University Hospital (Bergen, Norway) during 2007–2008. These patients were a sub-set of a series of patients presented in a previous paper [10], selected based on availability of multiple rCTs. In the following paragraphs the key aspects of target volume and normal tissue delineations, dose fractionation schedules and treatment planning specifics are described; however, further details can be found elsewhere [10].

The primary clinical target volume (CTV) was contoured on the pCT and included the prostate gland and the seminal vesicles. An additional boost dose CTV was generated including the prostate only. When adding margins from the CTVs to the planning target volumes (PTVs), we assumed image-guided patient positioning with fiducial markers: The primary PTV was generated by isotropically expanding the prostate and seminal vesicles by 5 mm, while the boost PTV was defined by a 2 mm margin to the prostate. The rectum was outlined from the rectosigmoid flexure to the anal verge while the bladder was contoured from apex to dome.

A moderately hypo-fractionated dose scheme was used (also in actual treatment of these patients) with a simultaneously integrated boost approach, prescribing 67.5 Gy to the prostate and 60 Gy to the seminal vesicles divided over 25 fractions. The unit Gy(RBE) was used for protons as recommended by the ICRU [16].

VMAT and intensity-modulated proton therapy (IMPT) plans were generated in the Eclipse treatment planning system (TPS) [Varian Medical Systems, Palo Alto, CA, USA] (Figure A1 Supplementary Material). The VMAT plans were generated using a partial 6 MV single arc with a 12° posterior avoidance sector. The proton plans had two opposing lateral fields generated from generic beam data based on the first generation Varian ProBeam machine using the Proton Convolution Superposition algorithm (PCS_11.0.31-90 MeV).

Each patient had 8–9 repeat CT (rCT) scans acquired throughout the course of treatment on which the bladder and rectum were contoured (Fig. 1). Median volume of the bladder contours in the planning CTs were 106 cm^3 and for the rectum 54 cm^3, while the corresponding values for the rCTs were 113 cm^3 and 68 cm^3 (Supplementary Table S1). Both the VMAT and IMPT plans were then re-calculated on all rCTs, assuming fiducial marker based image-guidance. The pCT and original plans were co-registered with the rCTs by matching to the prostate gold markers with subsequent re-calculation of the original plan and dose distribution (verification plans) on each rCT.

Risks of radiation-induced SC were subsequently estimated for the rectum and bladder based on the planned as well as all re-calculated dose/volume distributions, for each individual patient and treatment technique. We considered a linear-no-threshold (LNT) dose-response and a bell-shaped competition model incorporating effects of fractionation and cell sterilisation [17]. The model parameters used were taken as suggested in the original model publication from Dasu et al. [17]. The two dose-response relationships considered were adapted according to the Organ Equivalent Dose (OED) concept suggested by Schneider [18] and thereby represent the same radiation-induced hazard as the equivalent amount of uniform organ dose. The dose was integrated and normalised to the number of calculation points, representing the relative organ volume (details in supplementary material of [10]). Relative risks (RR) were calculated and OEDs were compared directly to avoid the uncertainty contribution involved in absolute risk measures [19].

Two-factor ANOVA [20] without replication (p-values) was used to assess the variation between the individual patient-specific RR calculated from the rCTs. Intraclass correlation (ICC) was calculated for RR based on patient-specific rCTs against all rCTs and pCTs. ICC values of 0 and 1 corresponded to *no* and *perfect* correlation between the RR based on the CTs for each patient.

3. Results

There were considerable variations in the bladder and rectum OEDs calculated using all CTs (both planning and repeat CTs) for the patients (Fig. 2), although the applied plan acceptance criteria for the rectum (V50 Gy < 50%) and bladder (V60 Gy < 50%) were fulfilled also when calculated on the repeat CTs. While the CTV dose coverage (D98%) were 99–100% of prescription dose for both CTVs on the planning CTs, medians of D98% were 91–97% for CTV67.5 and 93–101% for CTV60s (Supplementary Table S2). For most patients the OED ranges were wider for the VMAT distributions compared to IMPT.

Using the competition model, the RRs of bladder cancer based on the pCTs ranged from 0.4 to 3.4, while a considerably wider range was found when including all rCTs (from 0.2 to 6.7). The corresponding ranges for rectal cancer were narrower than observed for bladder cancer (Fig. 3). Similar trends were also seen for both organs with the linear model although generally the ranges were narrower with this model compared to the competition model. In four of the eight patients for the bladder and one of the eight for the rectum, the estimated risks were consistently lower for IMPT compared to VMAT according to the competition model. Using the linear model the corresponding numbers were six and seven of the eight patients. The remaining patients had repeat CTs resulting in RR variations favouring either VMAT or IMPT, except one of the patients with all repeat CTs in favour of VMAT with respect to rectal cancer according to the competition model. For the competition model, the RRs according to the pCT were for some of the patients found at the upper or lower RR range across the rCTs. Two cases for secondary bladder cancer (E and G) and three cases for secondary rectal cancer (D, G and H) had RR < 1 when evaluated with the planning CT but a median RR > 1 across the repeat CTs (Fig. 3).

Although the range of individual RRs based on rCTs were wide, there was a significant difference in RR estimates between the patients ($p < 0.05$ for both models). The ICC was lowest for RR of rectal cancer calculated with the linear model and highest for rectal cancer with the competition model. The intermediate values of ICC (0.44–0.78) showed that there was a fair degree of consistency between the repeat CTs from the same patient compared to RRs across different patients. Dose volume histograms for the pCT and rCTs for patient D illustrate the inter-fraction variations in dose for the bladder and rectum (Fig. 4).