Radiotherapy and Oncology 107 (2013) 147–152

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate morbidity

Prediction of rectum and bladder morbidity following radiotherapy of prostate cancer based on motion-inclusive dose distributions

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ARTICLE INFO

Article history:
Received 12 November 2012
Received in revised form 19 March 2013
Accepted 26 March 2013
Available online 14 May 2013

Keywords:
Radiotherapy
Morbidity
Toxicity
Organ motion
Rectum
Bladder
Prostate cancer

ABSTRACT

Background and purpose: In radiotherapy (RT) of prostate cancer the key organs at risk (ORs) – the rectum and the bladder – display considerable motion, which may influence the dose/volume parameters predicting for morbidity. In this study we compare motion-inclusive doses to planned doses for the rectum and bladder and explore their associations with prospectively recorded morbidity.

Materials and methods: The study included 38 prostate cancer patients treated with hypo-fractionated image-guided intensity-modulated RT that had an average of nine repeat CT scans acquired during treatment. These scans were registered to the respective treatment planning CT (pCT) followed by a new dose calculation from which motion-inclusive dose distributions were derived. The pCT volumes, the treatment course averaged volumes as well as the planned and motion-inclusive doses were associated with acute and late morbidity (morbidity cut-off: $\geqslant$Grade 2).

Results: Acute rectal morbidity (observed in 29% of cases) was significantly associated with both smaller treatment course averaged rectal volumes (population median: 75 vs. 94 cm^3) and the motion-inclusive volume receiving doses close to the prescription dose (2 Gy-equivalent dose of 76 Gy).

Conclusion: Variation in rectum and bladder volumes leads to deviations between planned and delivered dose/volume parameters that should be accounted for to improve the ability to predict morbidity following RT.

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The risk of developing normal tissue morbidity following radiotherapy (RT) is tightly connected to the doses received by the involved organs at risk (ORs) [1–3]. However, the dose/volume parameters determining the probability of morbidity for an OR is confounded by any geometrical uncertainties concerning the organ [1–11]. In RT of prostate cancer the key ORs, the rectum and the bladder, display extensive motion due to variations in organ filling [5–8]. Previous investigations have shown that the delivered rectum and bladder dose–volume histograms (DVHs) as obtained either by dose summation [4–8,12–14] or by deformable image registration (DIR)-based dose accumulation [14,15] might deviate considerably from the planned dose distributions for these organs [1,2,4,13–17]. However, few studies have associated the delivered doses with morbidity with the aim of establishing 'motion-inclusive' DVH constraints for rectal and urinary morbidity. We have previously shown that the associations with rectal morbidity are different if using motion-inclusive DVHs rather than planned DVHs, although in these studies the motion-inclusive DVHs were based on simulated motion patterns and not actual motion data [9–11].

In the present study we have therefore compared delivered rectum and bladder doses, assessed from dose re-calculations on repeat CT scans, to the corresponding planned doses in a series of prostate cancer patients. The associations between each of these dose distributions and prospectively recorded rectal and urinary morbidity were explored.

Material and methods

Image acquisition

The study included 38 patients treated with image-guided intensity-modulated RT (IMRT) for locally advanced prostate cancer, including the seminal vesicles and the pelvic lymph nodes, using a simultaneously integrated boost (SIB) technique at Haukeland University Hospital in Bergen, Norway during 2007 and 2008. The median (range) age was 63 years (53–79 years), median T-stage 3 (1–3), median pre-treatment prostate specific

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http://dx.doi.org/10.1016/j.radonc.2013.03.029

antigen (PSA) 27 ng/ml (5–123 ng/ml) and the median Gleason score 7 (6–9) [18,19]. The patients were given androgen blockade (luteinising hormone-releasing hormone analogue and at least four weeks of anti-androgens) starting three months prior to RT and continuing for two years. All patients were computed tomography (CT) scanned (Brilliance CT Big Bore, Philips Healthcare, Best, the Netherlands) from the lower pelvis to L4 in supine position, using 2–3 mm slice thickness. For each patient two subsequent CT scans were acquired every week resulting in totally 7–10 (median: 9) repeat CT scans/patient. Altogether 336 repeat scans were acquired.

Organ definitions and treatment planning

The responsible radiation oncologist delineated all tumour volumes and ORs on the treatment planning CT (pCT). Three clinical target volumes were defined; CTV67.5 (prostate gland and affected seminal vesicles), CTV60 (prostate and seminal vesicles) and CTV50 (CTV60 and pelvic lymph nodes) [20]. The respective CTV-planning target volume margins were 2 mm, 5 mm and 10 mm. The ORs relevant for this study – the rectum and the bladder – were delineated as hollow organs, for the rectum from the recto-sigmoid flexure to the anal verge and for the bladder, from the apex to dome. No preparation protocol was used. The same definitions and cranio-caudal extensions as for the pCT volumes were used when delineating the two ORs in all subsequent repeat scans. In addition, rectum and bladder walls were defined, as 3 mm inner margins applied to the original delineations in order to circumvent influence of the biologically likely irrelevant contents [21,22].

A 7-field SIB IMRT technique was used to treat all patients, delivering over 25 fractions 67.5 Gy (2.7 Gy/fx) to CTV67.5, 60 Gy (2.4 Gy/fx) to CTV60 and 50 Gy (2 Gy/fx) to CTV50. The optimisation criteria being used for 51, 50, 40 and 30 Gy were 0, 2, 52 and 65% of the relative rectum volume and 0, 4, 66 and 71% of the relative bladder volume [20]. The relative volume of the rectal circumference receiving doses $\geqslant$50 Gy was in addition kept below 50%.

Calculation of planned and motion-inclusive dose distributions

Each repeat CT scan was rigidly registered (translations only) to the corresponding pCT by means of intra-prostatic fiducial gold markers (2–3/patient), according to the clinical image-guidance protocol. The clinical treatment plan for each patient was then 'transferred' to each of the repeat CT scans utilising the rigid registrations followed by a new dose calculation with the preset number of monitor units applied [14,23,24]. The analytic anisotropic algorithm (Eclipse v.10.0, Varian Medical Systems, Palo Alto, Inc., CA, US) was utilised for the dose calculations using 15 MV photons and the Millenium MLC-120 multileaf collimator.

For each patient the planned rectum and bladder DVHs and dose–wall histograms (DWHs) were extracted and for each of these structures one motion-inclusive DVH/DWH [14,24,25] sampled in 1 Gy-intervals was assessed. This DVH/DWH was calculated as an average of the re-calculated DVHs/DWHs for each patient (n = 7–10) based on the parameters Dv [14,24–26].

Follow-up

Rectal and urinary morbidity were scored as gastro-intestinal (GI) and genitourinary (GU) morbidity, respectively [27]. Acute morbidity was based on follow-up assessments during the last week of the RT course whereas late morbidity was assessed from three months up to four years (every third month the two first years and then twice a year) after end of RT. The morbidity cut-off in this study was Grade $\geqslant$ 2 RTOG toxicity, assessed as the maximum recorded grade. The clinical parameters (age, T stage, PSA and Gleason score) were associated with each morbidity end-point on univariate logistic regression analysis.

Dose-volume comparisons and statistics

Initially, the planned (VpCT) and treatment course averaged (VrepCT) rectum and bladder volumes were compared between the patients with and without each of the respective morbidity end-points. A Wilcoxon rank-sum test was applied with the hypothesis of no difference in population median volume between patients with and without morbidity.

For the planned and the motion-inclusive rectal DVHs and DWHs the patients with vs. without $\geqslant$Grade 2 morbidity were compared according to the rectum constraints of the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) project: V50 Gy < 50%, V60 Gy < 35% and V70 Gy < 20% [2]. For the bladder there is currently no established dose/volume relationship and consequently no reliable constraints [16,17]. We therefore investigated three bladder dose/volume parameters spread out over the *likely* relevant dose interval: V40 Gy, V60 Gy and V70 Gy [4]. For these comparisons, the rectum dose levels [2] and the bladder dose levels were translated over to the hypo-fractionated regime using the equivalent dose in 2-Gy fractions (EQD_2) expression (Eq. (1)),

$$EQD_2 = D \cdot \left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right), \tag{1}$$

where the dose/fraction, d, was 2.7 Gy, the total physical dose, D was 67.5 Gy and the α/β ratio was 3 Gy focusing on late complications for both ORs [28], e.g. the prescription dose level corresponded to an EQD_2 of 77.0 Gy. Hence the investigated dose levels for the current fractionation were 44, 53 and 61 Gy for the rectum and 35, 53 and 61 for the bladder. A Wilcoxon rank-sum test was applied to test for the hypothesis of no difference in median of the relative volume irradiated to these dose levels between patients with and without morbidity.

The planned and the motion-inclusive DVHs and DWHs were finally associated with morbidity using logistic regression and also permutation tests to validate the results for this fairly small population [9]. Dose levels at which significant differences ($p \leqslant 0.05$) were found were converted to EQD_2 (Eq. (1)) [28]. For the dosimetric comparisons of patients with vs. without Grade $\geqslant$ 2 morbidity the generalised equivalent uniform dose (gEUD) was calculated [29] (Eq. (2)).

$$gEUD = \left(\frac{1}{N}\sum_i D_i^k\right)^{\frac{1}{k}}, \tag{2}$$

where N is the number of voxels of each organ, D_i the dose for each voxel and k the volume dependence parameter (rectum: k = 11 [2]; bladder: k = 8 [12,15]). The motion-inclusive gEUD was found for each patient and organ by averaging the gEUDs obtained from the re-calculations. The gEUDs were compared between patients with and. without morbidity using a Wilcoxon rank-sum test with the hypothesis of no difference in the median population gEUD.

All statistical analyses were performed in STATA (STATA v.11, StataCorp LP, College Station, TX, US). P-values, odds ratios and the 95% confidence interval (CI) of the odds ratio are given for the appropriate statistical test.

Results

Acute GI morbidity was identified in 11 (29%) of the patients whereas 13 (34%) experienced acute GU morbidity. With a median follow-up time of 42 months, late GI and GU morbidity was seen in 3 (8%) and 7 (18%) patients, respectively, with only one case of Grade 3 GU morbidity (obstruction, requiring permanent use of