Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Statistical motion modelling for robust evaluation of clinically delivered accumulated dose distributions after curative radiotherapy of locally advanced prostate cancer

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ARTICLE INFO

Article history:
Received 7 August 2017
Received in revised form 16 May 2018
Accepted 4 June 2018
Available online xxxx

Keywords:
Dose accumulation
Organ motion
Prostate
Robustness
Image-guided
Intensity modulated radiotherapy (IMRT)

ABSTRACT

Purpose: Planned doses are used as surrogate for the actually delivered dose in radiotherapy. We have estimated the delivered dose in a dose-escalation trial of locally advanced prostate cancer by statistical dose-accumulation and by DVH-summation, and compared to planned dose.

Materials and method: Prescribed dose-escalation to the prostate was 67.5 Gy/25fr., corresponding to 81GyEQD2 assuming $\alpha/\beta = 1.5$. The 21 patients had three targets (i.e. CTV67.5 + 2 mm, CTV60 + 5 mm, CTV50 + 10 mm) irradiated by a simultaneous-integrated-boost technique. Analysis was based on 213 CT scans and 5-years of follow-up. For statistical dose-accumulation, we modelled 10 000 possible treatment courses based on planned dose and deformation-vector-fields from contour-based registration. For DVH-summation we recalculated dose on repeat-CTs and estimated median D98%/EUD. Groups with/without disease recurrence were compared.

Results: Discrepancies between planned and accumulated dose were mostly seen for CTV67.5, where under-dosage was found at different locations in the prostate in 12/21 patients. Delivered dose-escalation (D98%) was on average 73.9GyEQD2 (range: 68.3–78.7GyEQD2). No significant difference in accumulated-D98% was found in patients with ($n = 8$) and without ($n = 13$) recurrence ($p > 0.05$). Average D98%/EUD with statistical dose-accumulation vs DVH-summation was significantly different in CTV60, CTV50, rectum and bladder but not in CTV67.5.

Conclusion: The planned dose escalation was not received by more than half-of-the patients. Robustness of the prostate target (CTV67.5) should therefore be better prioritized in these patients given the low toxicity profile. Estimates of delivered dose were less conservative for dose-accumulation due to interaction of random organ motion with the dose matrix.

Optimal treatment design with radiotherapy (RT) depends on reliable estimates of dose to the individual patient and knowledge of the related treatment effects. RT has become more individualized and increasingly complex with the introduction of image-guidance and modern delivery techniques, now allowing for dose escalation with tighter margins and simultaneous treatment of several targets with different motion characteristics and dose prescription levels [1,2]. With state-of-the-art RT, the impact of geometrical uncertainties on dose and decisions made at planning are therefore not easily anticipated without explicit evaluation of robustness [3–7]. Inter-fractional organ motion is the dominating cause of geometrical uncertainties in pelvic radiotherapy [2,8–10]. Although inter-fractional organ motion has been carefully investigated on a population level, only few studies consider the impact on the planned dose distribution [2,9,11–14]. In some patients large amplitude motion with substantial impact on dose have been observed, while for others the motion-effects are only limited [12,15]. The aim of the current study was to investigate how we could best exploit repeat CT information of individual high-risk prostate cancer patients to estimate actually delivered doses, and furthermore to learn how the decisions and compromises made at planning actually affected treatment.

The availability and use of methods to identify patients in need for treatment adjustments by quantifying and visualizing the effect

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https://doi.org/10.1016/j.radonc.2018.06.004
0167-8140/

of patient-specific pelvic organ motion on dose are currently limited in clinical practice of RT. In a recent review of pelvic adaptive radiotherapy only few studies used patient-selection in their ART workflow and none of the clinical studies with external beam therapy used feedback from delivered dose to trigger adaptations [16]. Also for dose–effect analysis, dose-volume parameters are commonly based on the planned dose distribution, which when biased can potentially jeopardize correlation results [8,17–19]. Some authors have explored the use of surrogate "motion-inclusive" dose volume histograms (DVHs) in normal tissue complication probability estimation. In dose-volume-response relations for rectal morbidity after prostate RT, Thor and colleagues have investigated the use of planning organ at risk volumes as well as simulation of rigid organ translations to generate so-called "motion-inclusive" DVHs [20–22]. In collaboration with Thor we used repeat CTs to extract average dose-volume-parameters for prediction of rectal and bladder morbidity after prostate RT [23]. However, these studies suffer from the use of simplistic motion-models, either ignoring patent-specific organ deformations completely or by averaging dose parameters from repeat CTs instead of accumulating dose to tissue. Better estimation of expected delivered dose accumulated in the patient over a fractionated treatment is therefore desirable as it will potentially improve decision-making and patient selection for ART as well as precision in dose–effect analysis.

In the current study we have therefore implemented and examined a method for robust evaluation published by Söhn and colleagues, which enables complete dosimetric assessment of the effects of patient-specific inter-fractional deformable organ motion on the planned dose distribution [7]. We used this method to evaluate expected clinical delivered accumulated dose in high-risk locally advanced prostate cancer patients treated with image-guided moderately hypo-fractionated intensity-modulated RT (IMRT) simultaneously to three defined targets with separate margins and dose prescriptions. We have furthermore compared these estimates of delivered dose with the treatment plan dose and the more straight-forward approach of summing dose parameters from the repeat CTs. Our dosimetric analyses were subsequently associated to clinical follow-up of recurrence and late gastro-intestinal and genitourinary side-effects.

Materials and method

Patient data

The present study included twenty-one patients age 47–76 years with locally advanced T2-T4 prostate cancer (Nx-1, M0, PSA > 10 or Gleason score > 3 + 4). Patient characteristics as well as outcome data after five years are summarized in Table S1, in Supplementary material. All patients gave their consent before being enrolled in a phase II dose-escalation trial delivered with moderately hypo-fractionated pelvic IMRT at Haukeland University Hospital, Bergen, Norway. The trial had been approved by the local ethical committee before enrolment starting in 2007. All patients received luteinizing hormone-releasing hormone (LHRH) analogues 3 months before initiation of RT. The patients had follow-up visits every third month (up to 2 years), and thereafter every six months up to 5 years after treatment. At each follow up visit, late gastro-intestinal (GI) and genitourinary (GU) morbidity were scored according to RTOG scoring system [24,25]. Biochemical failure was defined according to Phoenix criteria (PSA nadir + 2). Local recurrence was confirmed by biopsy or radiological findings on MRI or PET/CT. During the course of RT, twenty-one patients had repeat image information (CT) acquired twice a week during the treatment period of five weeks, giving detailed individual data on organ motion.

Treatment planning and delivery

The patients had three gold markers implanted into the prostate before start of RT. RT was prescribed in 25 fractions simultaneously delivering fraction doses of 2.7 Gy to the clinical target volume (CTV67.5) with margin, 2.4 Gy to CTV60 with margin and 2.0 Gy to CTV50 with margin. Narrow margins of 2 mm were used around CTV67.5 to create the planning target volume (PTV67.5) and in an overlap with rectum the latter was prioritized to reduce the risk of adverse GI effects. The CTV60 was isotropically expanded by 5 mm and CTV50 by 10 mm to create PTV60 and PTV50, respectively. Using an α/β of 1.5 or 3 (with or without a time-factor) [26,27], this corresponded for the three targets to prescription equivalent doses given in 2 Gy fractions (EQD2) of 81/67/50 Gy or 77/64.8/50 Gy, respectively. All patients were treated with 7-field image-guided IMRT and beam quality of 15 MV in supine position with knee and ankle fixation. Rectum sparing was prioritized during optimization and rectum doses were constrained to less than 10 ml receiving $\geq$60 Gy. Additionally, planning experts aimed for further reduction in rectum doses such that less than half the circumference of rectum should receive $\geq$50 Gy. PTV coverage (95–107% of prescribed dose) was prioritized over bladder and bowel sparing, and doses to these organs at risk (OARs) were reduced 'as much as possible' without compromising PTV homogeneity and hot-spots in the healthy tissue outside PTV. All patients were positioned based on daily image-guidance with orthogonal 2D kV-kV images of the implanted markers. Treatment was planned using Eclipse treatment planning system (Varian medical systems, Palo Alto, USA) and administered on identically tuned Varian Clinacs (also from Varian medical systems) equipped with Millennium MLCs and applying the sliding window technique for IMRT.

CT-scanning

Each patient had a planning CT scan with bladder contrast (pCT) and on average 9 (7–10) repeat CT scans without contrast (rCTs) acquired with knee and ankle fixation in supine position covering L3/L4 to the anus. The density of the bladder with contrast on the pCT was replaced by HU = 0 in order to minimize the effect of the high density contrast agent on dose calculation. In total 213 CT scans were included in the analyses of this study. All pCT and rCT scans were acquired on at Phillips Big Bore CT scanner (Philips Healthcare, Cleveland, OH, USA) with slice thickness of 2–3 mm. The rCTs were acquired as close to the treatment session as practically possible; 166 rCTs on average 20 min after treatment setup, 26 rCTs on average 30 min before treatment setup. No laxatives were given to the patients.

Contouring

In total 1128 volumes of interests were manually contoured for the purpose of this study, i.e. three targets as well as rectum and bladder in all CTs for all patients. For each patient, the three overlapping CTVs with different dose prescriptions were defined on the pCT scan prior to treatment planning: CTV67.5 included the prostate gland inclusive the capsule as well as tumour extension outside the prostate gland, CTV60 overlapped with CTV67.5 and also included the seminal vesicles and CTV50 was defined as CTV60 and the pelvic lymph nodes contoured according to the RTOG guidelines but omitting the pre-sacral nodes. The CTVs of the pCT for all patients were also re-contoured to enable estimation of the magnitude of delineation uncertainties in relation to uncertainties from motion. All CTV contouring was performed retrospectively by the trial initiating oncologist (SIH) using the protocol as for the original treatment. The rectum was defined with content from the recto-sigmoid flexure to the anal verge, and the bladder

Please cite this article in press as: Hysing LB et al. Statistical motion modelling for robust evaluation of clinically delivered accumulated dose distributions after curative radiotherapy of locally advanced prostate cancer. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.06.004