Radiotherapy and Oncology 117 (2015) 509–514

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate cancer radiotherapy

Feasibility of dominant intraprostatic lesion boosting using advanced photon-, proton- or brachytherapy

Piotr Andrzejewski [a,c,*], Peter Kuess [a,c], Barbara Knäusl [a,c], Katja Pinker [b,c], Petra Georg [c,d], Johannes Knoth [a], Daniel Berger [a], Christian Kirisits [a,c], Gregor Goldner [a,c], Thomas Helbich [b,c], Richard Pötter [a,c], Dietmar Georg [a,c]

[a] Dept. of Radiation Oncology, Comprehensive Cancer Center; [b] Dept. of Biomedical Imaging and Image-guided Therapy; [c] Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Vienna, Austria; and [d] EBG MedAustron GmbH, Wiener Neustadt, Austria

ARTICLE INFO

Article history:
Received 29 October 2014
Received in revised form 22 May 2015
Accepted 21 July 2015
Available online 6 September 2015

Keywords:
VMAT
IMPT
HDR-BT
DIL
Prostate cancer
SIB

ABSTRACT

Background and purpose: Advancements in imaging and dose delivery enable boosting of the dominant intraprostatic lesions (DIL), while maintaining organs-at-risk (OAR) tolerances. This study aimed to assess the feasibility of DIL boosting for volumetric modulated arc therapy (VMAT), intensity modulated proton therapy (IMPT) and high dose rate brachytherapy (HDR-BT).

Material and methods: DILs were defined on multiparametric magnetic resonance imaging and fused with planning CT for twelve patients. VMAT, IMPT and HDR-BT plans were created for each patient with an $EQD2_{\alpha/\beta}$ DIL aimed at 111.6 Gy, $PTV_{initial}$ D_{pres} was 80.9 Gy (EBRT) with CTV $D_{90\%}$ = 81.9 Gy (HDR-BT). Hard dose constraints were applied for OARs.

Results: Higher boost doses were achieved with IMPT compared to VMAT, keeping major OAR doses at similar levels. Patient averaged $EQD2_{\alpha/\beta}$ $D_{50\%}$ to DIL were 110.7, 114.2 and 150.1 Gy(IsoE) for VMAT, IMPT and HDR-BT, respectively. Respective rectal wall D_{mean} were 30.5 ± 5.0, 16.7 ± 3.6, 9.5 ± 2.5 Gy(IsoE) and bladder wall D_{mean} were 21.0 ± 5.5, 15.6 ± 4.3 and 6.3 ± 2.2 Gy(IsoE).

Conclusions: DIL boosting was found to be feasible with all investigated techniques. Although OAR doses were higher than for standard treatment approach, the risk levels were reasonably low. HDR-BT was superior to VMAT and IMPT, both in terms of OAR sparing and DIL boosting.

Various techniques are used for treating prostate cancer (PCa) with radiation. Different external beam therapy (EBRT) and brachytherapy (BT) methods can be utilized depending on stage, experience and other clinical aspects. For low-risk patients comparable results are achieved with both EBRT and BT techniques in terms of tumor control and toxicity [1–3].

Recent developments in radiation oncology are stimulated by the advancements in medical imaging. Positron emission tomography (PET), perfusion computed tomography (CT) or magnetic resonance imaging (MRI) methods like dynamic contrast enhanced (DCE) imaging, magnetic resonance spectroscopy (MRS) and diffusion weighted imaging (DWI) are explored for improved target definition and response assessment [4]. In PCa, multiparametric MRI (mp-MRI) is used for lesion characterization [5].

Over the last ten years several dose escalation trials have been conducted for PCa. Based on these results, prescribed doses (D_{pres}) around 78 Gy are now common practice in EBRT and higher doses are known to be related to unacceptable toxicity risks [6–9]. On the other hand local recurrences tend to occur at the site of primary tumor [10,11]. Consequently, different boosting techniques and dose ranges have been investigated [12–20], most of them with EBRT photon techniques.

The objective of the present study was to assess the feasibility of boosting the dominant intraprostatic lesions (DIL) with volumetric modulated arc therapy (VMAT), intensity modulated proton therapy (IMPT) and high-dose-rate BT (HDR-BT) with focus on the dosimetric differences to organs-at-risk (OAR).

Methods and materials

Patient data and volume definition

The study involved twelve patients with biopsy-confirmed localized PCa (average Gleason score 7.8; $PSA_{average}$ of 12.1 ng/mL, 5 patients intermediate risk, 7 high risk). All patients underwent planning CT and received VMAT treatments. CT scans (Somatom Volume Zoom, Siemens, Germany) were performed in

* Corresponding author.
E-mail address: piotr.andrzejewski@meduniwien.ac.at (P. Andrzejewski).

http://dx.doi.org/10.1016/j.radonc.2015.07.028
0167-8140/

supine position (2 mm slice thickness) with an air-filled endorectal balloon (40 cm^3, Rüsch-AG, Germany). For each patient a pre-treatment mp-MRI (T2-weighted, DCE, DWI, MRS) was performed on a 3T scanner (Magnetom TrioTim, Siemens, Germany) (cf. Fig. S1).

The clinical target volume (CTV) was defined as the prostate capsule expanded to cover extra-capsular and seminal vesicle disease (in 4 cases). For DIL delineation the planning CT was registered with T2-weighted images using iPlan (BrainLab, Germany). CT-MR registration was performed with a focus on the prostate: automated registration was followed by manual adjustments by an experienced radiation oncologist and MRI-specialized radiologist. The DIL was identified using mp-MRI and defined as a visible lesion with score $\geqslant$4 according to PI-RADS classification, which is widely used by radiologists to evaluate prostate MRI [5]. Altogether 14 lesions were defined, 4 in the central and 10 in the peripheral zone.

For EBRT the following two planning target volumes (PTV) were created: PTV_{boost} was defined as the DIL plus a 5 mm safety margin in anterior–posterior direction and 4 mm in all other directions. $PTV_{initial}$ was created from the CTV with the same margins but by subtracting PTV_{boost} [21,22].

Additionally, the following OARs were delineated: rectal wall (RW), bladder wall (BW) (derived by extracting 3 mm from the external wall of the respective structure), femoral heads (FH), urethra, penile bulb (PB), internal anal sphincter (IAS), external anal sphincter (EAS), puborectalis (PRM), levator ani (LAM) muscles and normal tissue (NT) as body structure excluding the CTV.

Treatment techniques

For each patient VMAT, IMPT and HDR-BT treatment plans were generated using constraints similar to the ones applied in the FLAME trial [23] (Supplementary Table S1b). For EBRT techniques ICRU-83 plan normalization criteria were followed, with prescription to the median dose. 95% of D_{pres} was to cover 95% of the target volume.

Volumetric modulated arc therapy

77 Gy (in 35 fractions) was prescribed to $PTV_{initial}$. The dose to PTV_{boost} was escalated with a simultaneously integrated boost (SIB), if possible up to 95 Gy. Dose constraints for bladder and rectum were considered as hard constraints (see Supplementary Table S1b). The electron density (ED) of the bladder was changed to water to account for contrast agent differences. VMAT plans were based on two 315° arcs with 10 MV flattening filter free beams and shaped with an Agility™ multileaf collimator, with the isocenter in the center of PTV_{boost}. Dose calculation was performed with the Monte Carlo algorithm on a 3 mm grid using Monaco (V3.30; Elekta).

Intensity-modulated proton therapy

Dose prescription and OAR constraints for IMPT were the same as for VMAT. IMPT plans were calculated for two opposed lateral beams with the isocenter in the center of PTV_{boost} (3 mm grid) [24]. For IMPT planning the TPS XiO (V4.41; Elekta) was used. The lateral spot spacing of the pencil beams was 5 mm, the initial σ in air was 3 mm; the scanning layer distance was 0.8 times the Bragg-Peak width at the respective depth [25]. The spot selection algorithm accounts for possible proton range uncertainties, which is rather low for opposed lateral beams [24,26]. The number of beam spots was on average 3419 (2655–4525) with energies varying from 133 to 205 MeV. A relative biological effectiveness (RBE) of 1.1 was assumed. In addition to the ED change of bladder, also the rectum ED was set to be water equivalent as the rectal balloon in proton treatment is usually filled with water.

High-dose-rate brachytherapy

HDR-BT was designed as a single fraction monotherapy with $D_{90\%}$ of 17 Gy to the CTV and 20 Gy to the DIL. Target objectives were chosen to be biologically equivalent to EBRT, see Eq. {S1} and Supplementary Table S1a [27]. Treatment planning was performed with Oncentra-Prostate (V3.2.3; Elekta/Nucletron, Netherlands) assuming a ^{192}Ir-based afterloading technique with 18–20 needles. Automatically generated inverse plans were manually adjusted with regard to needles' positions and dwell times. Dose calculations were performed with the TG-43 algorithm on a 2 mm grid.

Treatment plan evaluation

To account for different fractionation schemes the physical (VMAT and HDR-BT) and RBE-weighted (IMPT) doses were converted with the linear-quadratic model [28]. In other words: all 3-dimensional dose distributions were recalculated to $EQD2_{\alpha/\beta}$ (cf. Supplementary Formula {S1}) applying a voxel by voxel conversion with an in-house-developed CERR-based (V4.1) script ([29] and http://www.cerr.info).

The assumed α/β ratios for all structures are summarized in Table 1. The following target parameters were determined: $D_{50\%}$, $D_{2\%}$, $D_{98\%}$, V_{70Gy}, $V_{95\%}$, $V_{100\%}$, $V_{110\%}$, $V_{120\%}$ and $V_{150\%}$. Additionally, $EQD2_{\alpha/\beta}$ D_{mean}, $D_{2\%}$, $D_{50\%}$ and $D_{98\%}$ to the CTV and DIL were extracted. Calculation of $EQD2_{\alpha/\beta}$ for PTVs was not performed due to overlapping structures. All investigated indices were averaged over all patients and standard deviations (SD) were calculated.

In addition, equivalent uniform doses (EUDs) were computed according to [30,31] (cf. Supplementary Formula {S1}). For EBRTs EUDs were also computed for the CTV and DIL structures. Since standard formula {S2} is sensitive to high doses in single voxels, what can cause dramatic elevations of the EUD values for BT, the corrected EUD (cf. Supplementary Formula {S3}) (EUD_{corr}) was introduced for HDR-BT [32]. This procedure has a negligible effect on the final OAR indices. Nevertheless it solves the issue of high sensitivity of the standard EUD formula for very high doses in the tail of the HDR-BT DVH. The parameters used for the EUD calculations are presented in Table 1.

Statistical evaluation

To assess the statistical significance ($p < 0.05$) repeated measures MANOVA with Bonferroni-corrected post hoc testing was performed utilizing SPSS (V17.0, SPSS Inc., USA) (cf. Supplementary material). All presented parameters were averaged over all 12 patients and reported with standard deviation.

Results

Target doses and coverage

All plans fulfilled the planning objectives for $PTV_{initial}$, CTV and OARs (cf. Supplementary Table S2). Statistically significant differences were observed between VMAT and IMPT for $V_{100\%}$ and $D_{50\%}$ for $PTV_{initial}$ and for $V_{100\%}$, $D_{50\%}$, $D_{2\%}$ and $D_{98\%}$ for PTV_{boost}. Except $D_{2\%}$ for PTV_{boost}, all other parameters were in favor of IMPT, with very good $PTV_{initial}$ coverage and median PTV_{boost} dose of almost 99% of D_{pres}. Furthermore, all SIB plans were close to fulfill ICRU-83 recommendations with respect to target ($PTV_{initial}$) $V_{95\%}$ and $D_{50\%}$. For VMAT, average $V_{95\%}$ reached 94.6 ± 2.6% and $D_{50\%}$ was within 5% of D_{pres} for 11 patients, but never lower than D_{pres}; for IMPT $V_{95\%}$ was on average 92.9 ± 4.3% and $D_{50\%}$ was within ±2.6% of D_{pres} [33]. This assures sufficient dose coverage and minimalizes the chance of disease progression or recurrence