EXTREME HYPOFRACTIONATED IMAGE-GUIDED RADIOTHERAPY FOR PROSTATE CANCER

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ABSTRACT

An emerging body of data suggests that hypofractionated radiation schedules, where a higher dose per fraction is delivered in a smaller number of sessions, may be superior to conventional fractionation schemes in terms of both tumour control and toxicity profile in the management of adenocarcinoma of the prostate. However, the optimal hypofractionation scheme is still the subject of scientific debate. Modern computer-driven technology enables the safe implementation of extreme hypofractionation (often referred to as stereotactic body radiation therapy [SBRT]). Several studies are currently being conducted to clarify the yet unresolved issues regarding treatment techniques and fractionation regimens. Recently, the American Society for Radiation Oncology (ASTRO) issued a model policy indicating that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low-to-intermediate risk disease. The present article reviews some of the currently available data and examines the impact of tracking technology to mitigate intra-fraction target motion, thus, potentially further improving the clinical outcomes of extreme hypofractionated radiation therapy in appropriately selected prostate cancer patients. The Champalimaud Centre for the Unknown (CCU)'s currently ongoing Phase I feasibility study is described; it delivers 45 Gy in five fractions using prostate fixation via a rectal balloon, and urethral sparing via catheter placement with on-line intra-fractional motion tracking through beacon transponder technology.

Keywords: Prostate cancer, radiation therapy, hypofractionated, hypofractionation, IGRT, beacon transponders.

INTRODUCTION

External beam radiation therapy given with conventional fractionated schedules (1.8-2 Gy daily) to a total dose of 78-86 Gy is an effective definitive treatment modality for all risk groups of prostatic adenocarcinoma. Patients are classically stratified according to their biopsy Gleason score, serum prostate-specific antigen (PSA) level, and clinical stage, and defined as: low-risk, clinical stage T1c and T2a, PSA level ≤10 ng/mL, and biopsy Gleason score ≤6; intermediate-risk, clinical stage T2b or biopsy Gleason score of 7 or PSA level >10 and ≤20 ng/mL; high-risk, clinical stage ≥T2c or PSA level >20 ng/mL or biopsy Gleason score ≥8. A great deal of scientific debate revolves around the optimal choice of treatment strategy for all risk categories, and, more specifically, about the choice of radiation modality and the role of androgen ablation therapy in selected patient groups.[1]

Multiple randomised Phase III studies have confirmed the utility of dose escalation in prostate cancer by improving local control, freedom from biochemical failure, and freedom from distant metastases. However, conventional fractionation schedules do not permit further escalation beyond doses currently used because of unacceptably high rates of acute and late toxicities using 3D-conformal techniques. Recently, radiotherapy has witnessed the introduction of major technological advances, which have permitted the implementation of intensity modulated radiotherapy (IMRT). IMRT is a further advancement in 3D-conformal radiotherapy. Its

primary advantage, compared to conventional 3D-conformal treatment techniques, is the ability to produce very sharp dose gradients and to deliver highly conformal target doses with better sparing of normal structures. The benefits of IMRT delivery are particularly pronounced in the context of concave-shaped target-critical structure geometries and, in the treatment of localised prostate cancer, its implementation has resulted in improved toxicity profiles using conventional fractionation regimens.[2]

Current research efforts are aimed at the incorporation of high-quality imaging in the radiotherapy process, both at the level of target volume delineation, with the use of state-of-the-art imaging modalities (e.g. magnetic resonance imaging [MRI]) for accurate morphological identification of the target volume and, at treatment delivery, with the specific aim to minimise uncertainties and reduce exposure to normal tissues. This process is commonly referred to as image-guided radiation therapy (IGRT). The ultimate goal of IGRT, of course, is that radiation dose can be delivered to an accurately defined target volume exactly as planned. Indeed, 3D volumetric imaging tools for near real-time verification of target position (on-board imaging devices) are now available, and appropriate correction strategies are rapidly being developed.

Dose-limiting toxicities observed with conventional fractionation as well as the extremely protracted length of the treatment (up to 8-9 weeks) have been recently challenged through the advent of improved technology. This has led to the investigation of new approaches with hypofractionated regimens that would deliver the same or higher biologically-equivalent tumour dose in fewer sessions while maintaining or decreasing toxicity rates. An emerging body of data suggests that mildly hypofractionated radiation schedules (with dose per fraction up to 4 Gy), where treatment is delivered more quickly and conveniently, do not compromise biochemical control or toxicity, so long as careful treatment planning and delivery techniques are adopted.[3-5] Schemes adopting between 20 and 28 sessions have become established in the clinical practice and are currently routinely employed, largely through the adoption of IMRT plans with tighter safety margins to account for organ motion, based on patient set-up techniques which enhance inter-fraction reproducibility. Three ongoing multi-institutional non-inferiority trials in patients with low and intermediate-risk treated with contemporary dose prescription, planning, and delivery techniques will soon shed light on the potential advantages of moderate hypofractionation over conventional fractionation. A preliminary report on late toxicity with over 4 years median follow-up in one of these studies indicates similar side-effects regardless of treatment regimen with less than 5% Radiation Therapy Oncology Group (RTOG) rectal toxicity and less than 3% RTOG bladder toxicity.[4]

THE CASE FOR EXTREME HYPOFRACTIONATION

Extreme hypofractionated image-guided radiotherapy, sometimes referred to as stereotactic body radiotherapy (SBRT), or stereotactic ablative radiotherapy (SABR), aims to deliver even fewer high doses of radiation to the target volume with extreme accuracy and conformity. Growing radiobiological evidence indicates that prostate cancer may have a greater sensitivity to large dose per fraction compared to the surrounding normal tissues due to its generally very low alpha/beta ratio, generally believed to be as low as 1.5. Therefore, a potential increase in the therapeutic ratio may be achieved through extreme hypofractionation where the biologically effective dose (BED) to the target tissues is enhanced, while a reduction in the risk of radiation-induced complications may be expected.[6,7] Furthermore, ultra-high dose per fraction may differ from moderate hypofractionation in terms of cell kill with laboratory as well as clinical evidence suggesting a direct effect on the endothelial cell and tumour vasculature.[8]

In recent years, clinical outcomes supporting the safety and increasingly longer-term efficacy of extreme hypofractionation have been published. Initially, extreme hypofractionation was performed by means of high-dose rate (HDR) brachytherapy. In the 1990's this approach was shown to yield excellent tumour control with reasonably low morbidity. In one study, 5-year freedom from biochemical failure rates of 91% and 88% were reported in low-risk patients treated using a total dose of 38 Gy delivered in four fractions, or 42 Gy delivered in six fractions, respectively.[9] However, HDR brachytherapy entails hospitalisation and anaesthesia and is uncomfortable for the patient particularly for multi-day delivery regimens

where needles remain inserted into the patient for an extended time period.

The advent of image-guided delivery technologies in the early 2000's with their improved accuracy rapidly opened the doors for high-dose external beam delivery. To date, only a few publications have reported on the clinical outcomes of external-beam extreme hypofractionated delivery and no data from randomised studies are yet available.[10-13] The first prospective experience using ultra-high dose external-beam SBRT was reported by the Stanford University group. In this Phase II clinical trial, 41 low-risk, hormone naïve patients received a dose of 36.25 Gy delivered in five fractions.[11] CT scans were only used for treatment planning. The planning target volume (PTV) was identified with the prostate only with a 5 mm margin all around, except posteriorly where a 3 mm margin was used. The prescribed dose was normalised to the 90% isodose line. At a median follow-up of 33 months, no failures were noted. At median 5-years follow-up the actuarial freedom from biochemical failure was 94%. However, Grade 2 and Grade 3 late GU toxicity was observed in 7% and 2.5% of cases, respectively.[14] In a recent dose escalation study, three groups of 15 patients each received either 45 Gy, 47.5 Gy, or 50 Gy (the regimen with the highest dose reported to date) delivered in five fractions every other day.[10] If prostate cancer has, indeed, an alpha/beta ratio of 1.5, and if the extrapolation with the linear-quadratic formalism holds for such high-dose per fraction, the biologically equivalent doses to the tumour with 2 Gy per fraction would be 135, 149, and 164 for the three dose levels, respectively.[15] Undoubtedly, this trial has tested the limits of hypofractionated dose escalation for prostate cancer. A great deal of care was used to minimise treatment uncertainties. A rectal balloon was used to push the posterior and lateral rectal walls away from the PTV and to stabilise the prostate. Fiducial markers and cone-beam CT were used for daily set-up, but intra-fraction guidance was not used. A 3 mm expansion of the clinical target volume (CTV) was used to create the PTV. Median follow-up was 30, 18, and 12 months for the 45, 47.5, and 50 Gy groups, respectively. Overall, genito-urinary (GU) Grade 2 and Grade 3 toxicity occurred in 31% and 4% of patients, respectively, and one case of Grade 4 GU toxicity was reported at the highest dose level. Rectal Grade 2 and Grade 3 toxicity was found in 18% and 2% of patients, respectively. Biochemical control was 100% with a mean PSA of 0.2 ng/mL at 30 months.

The largest prospective study of extreme hypofractionation comes from Winthrop University Hospital and includes 304 patients; mostly comprising low and intermediate-risk disease.[16] The study has reached a 5-year median follow-up for patients who received a prescription dose of 36.25 Gy in five daily sessions of 7.25 Gy. No patients experienced Grade 3 complications and fewer than 5% had Grade 2 rectal or urinary morbidity. Bowel and urinary quality of life (QoL) scores initially decreased, but later returned to baseline values. An overall decrease of 20% in the sexual QoL score was observed. For patients that were potent prior to treatment, 75% remained sexually active. Actuarial 5-year biochemical recurrence-free survival was 97% for low-risk, 90.7% for intermediate-risk.

Recently a multi-institutional pooled analysis with 1,100 cases from prospective Phase II studies has been published.[17] The 5-year biochemical relapse free survival (bRFS) rate was 93% for all patients and 95%, 84%, and 81% for low, intermediate and high-risk patients, respectively ($p<0.001$). For 135 patients possessing a minimum of 5-years follow-up, the 5-year bRFS rate for low and intermediate-risk patients was 99% and 93%, respectively.

Table 1 summarises the published studies on extreme hypofractionation. Toxicity appears acceptable, largely consisting of Grade 2 side-effects. Freedom from biochemical failure looks extremely promising and compares favourably with other definitive treatments for low and intermediate-risk patients. Currently available evidence supports consideration of extreme hypofractionation among the therapeutic options for low and intermediate-risk patients. Randomised trials involving extreme hypofractionation are currently ongoing. For instance, RTOG 0938 is actively recruiting low-risk patients and randomises between 36.25 Gy in five fractions versus 51.6 Gy in 12 sessions of 4.3 Gy in 2.5 weeks in both arms.

TREATMENT SAFETY, REPRODUCIBILITY AND ORGAN MOTION MANAGEMENT

Safe delivery of extreme hypofractionated treatments mandates the fulfillment of strict

Table 1. Extreme hypofractionation studies.

Author (ref)	Year	Patient number	Risk category	Median FU (months)	Fractionation Regimen	Grade ≥2 Toxicity	bRFS %
Friedland et al.[12]	2009	112	Low Intermediate – High	24	35 Gy (7 Gy x 5)	GU=6 GI=1%	97%
Boike et al.[10]	2011	45	Low (40%) Intermediate (60%)	30	45 Gy (9 Gy x 5) 47.5 Gy (9.5 Gy x5) 50 Gy (10 Gy x 5)	GU=31% GI=18%	100%
King et al.[14]	2012	67	Low Intermediate	32	36.25 Gy (7.25 Gy x 5)	GU=8.5 GI = 2	94%
McBride et al.[13]	2012	45	Low	44.5	37.5Gy (7.5 Gy x 5) or 36.25 Gy (7.25 Gy x 5)	Gu=19% GI=12%	97.7%
Katz et al.[16]	2013	304	Low (69%) Intermediate (27%) High (4%)	60	37.5Gy (7.5 Gy x 5) or 36.25 Gy (7.25 Gy x 5)	GU<5% GI<5%	97% (low-risk) 90.7% (intermediate) 74.1% (high)
King et al.[17]	2013	1100	Low (58%) Intermediate (30%) High (11%)	36	36.25 Gy (7.25 Gy x 5)		93% (overall) 95% (low-risk) 84% (intermediate) 81% (high)

bRFS: biochemical relapse-free survival; GU: genitourinary; GI: gastrointestinal.

dose/volume constraints to the adjacent normal tissues, namely the bladder and rectal walls, as well as the urethra, genito-urinary diaphragm, and penile bulb. Urethral sparing, in particular, may be difficult to achieve due to the inability to identify the organ on conventional CT planning without the aid of a catheter, and for the large variability in its anatomical position. Advanced imaging modalities including multiparametric MRI with CT fusion ought to be adopted to improve target volume and organ-at-risk contouring, and further exploit the potential benefits of the dose-painting capabilities of modern treatment-planning software. Moreover, due to the high-dose gradients of IMRT plans, measures to mitigate inter and intra-fraction movement of the prostate ought to be adopted. Inter-fraction motion has been extensively studied both with implanted radiopaque fiducials and electromagnetic beacon transponder technology.[18-20] Intra-fractional motion has been shown to be significant, especially in the dorso-ventral axis where >3 mm shifts may be observed within minutes of cone-beam CT (CBCT) matching with the planning CT. In a recent study, in which electromagnetic transponders were used for daily patient set-up followed by CBCT, with a prescription dose of 40 Gy delivered in five fractions, at a median follow-up of 36 months, no biochemical failures were found. At 18 months, the mean Expanded Prostate Cancer Index Composite (EPIC) scores for bowel, urinary, and sexual function showed no significant changes from baseline.[19] The electromagnetic transponder technology allows continuous detection of prostate translations, which, when coupled with manual intervention, permits correction of patient positioning. Through the aid of a six degrees of freedom couch capable to adjust for translational as well as rotational shifts in quasi real-time as they are detected by the device, these uncertainties may be further reduced. Additionally, measures to mitigate intra-fractional

Figure 1.a

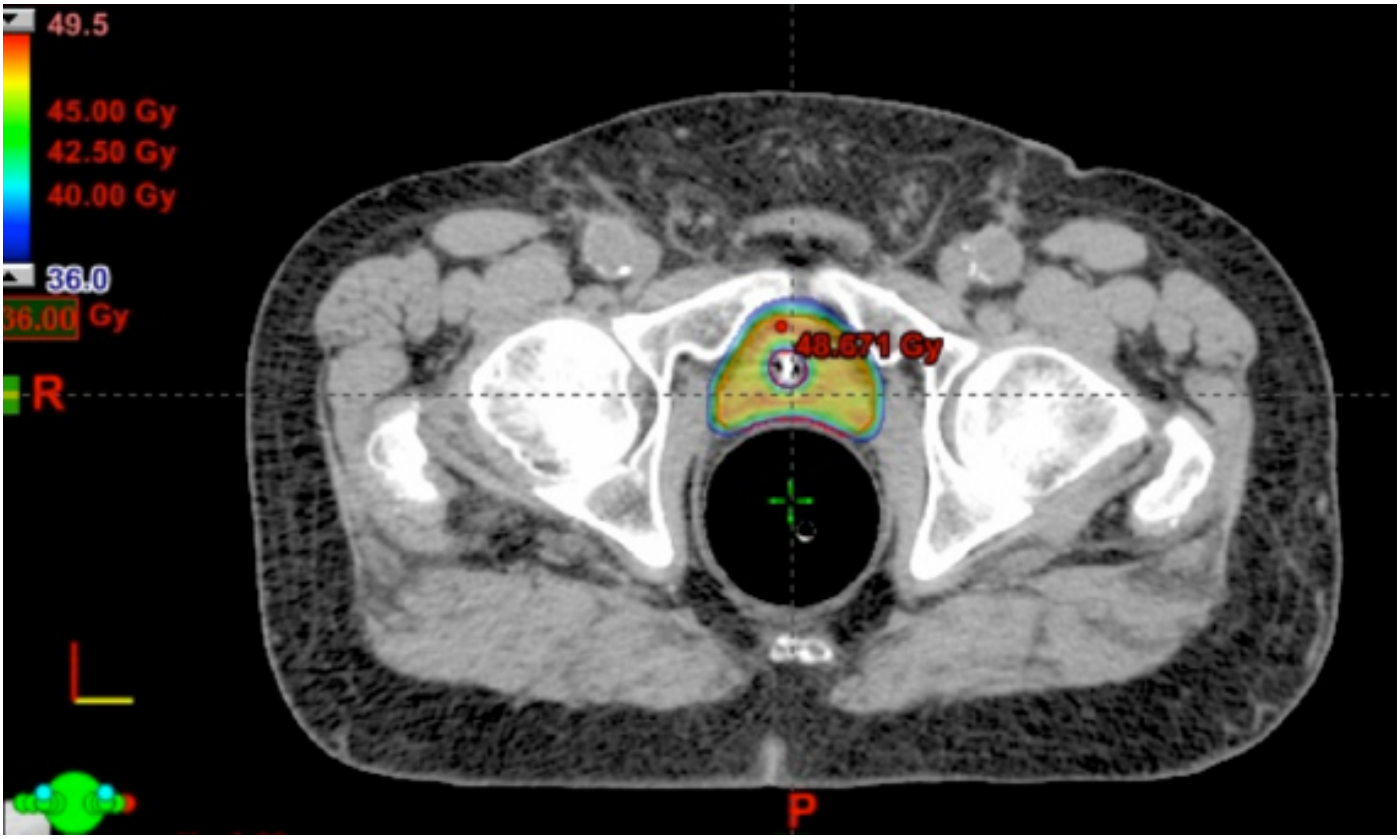

Figure 1.b

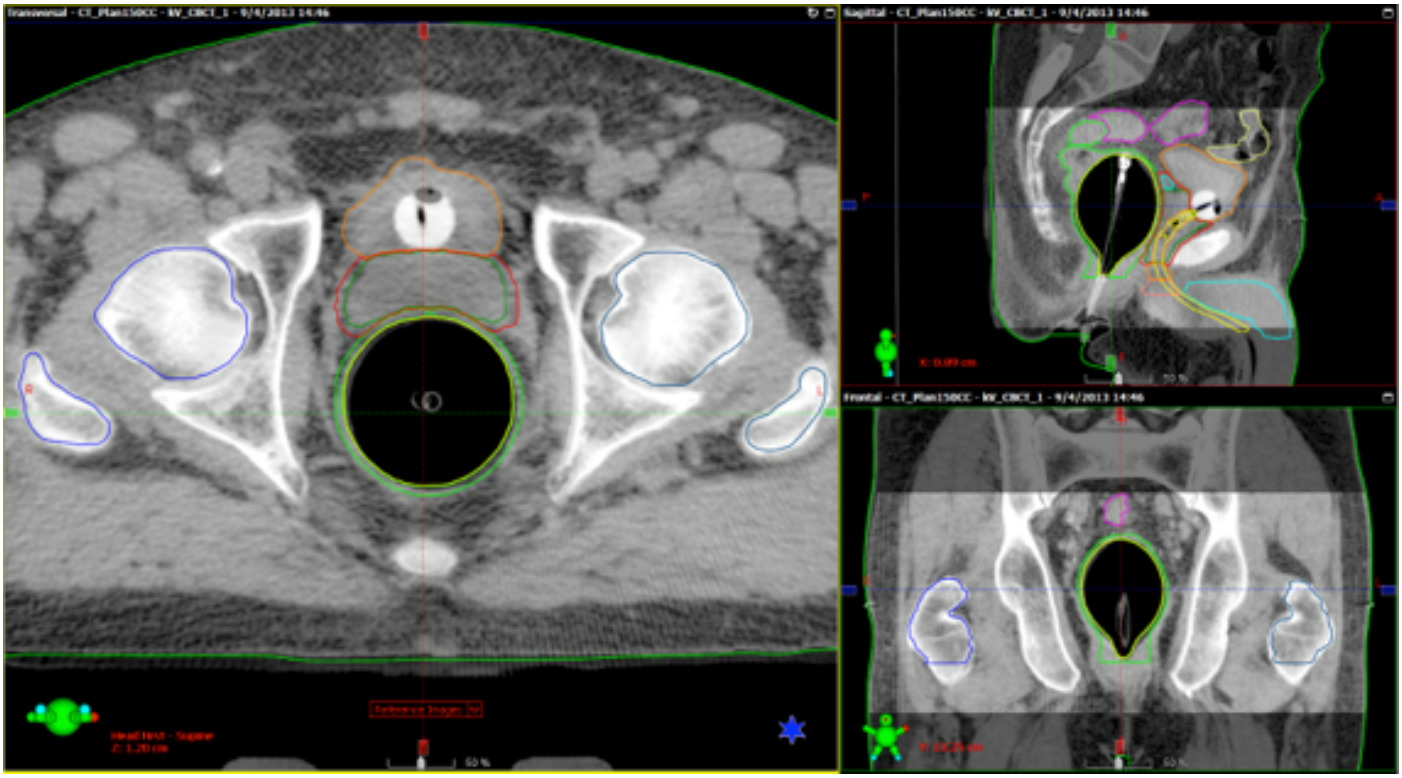

Figure 1. Dose distribution for the extreme hypofractionation protocol used at CCU.
The dose distribution to the target volume includes the whole prostate and seminal vesicles. The rectal balloon is filled with 150 cc of air to fix the anatomy, and the urethral catheter with transponders is used to identify and track the location of the urethra.
Figure 1a. Axial plane with dose distribution.
Figure 1b. Cone-beam CT (CBCT) and planning reference CT match show excellent anatomical correlation immediately prior to treatment delivery on the axial, sagittal and coronal planes.

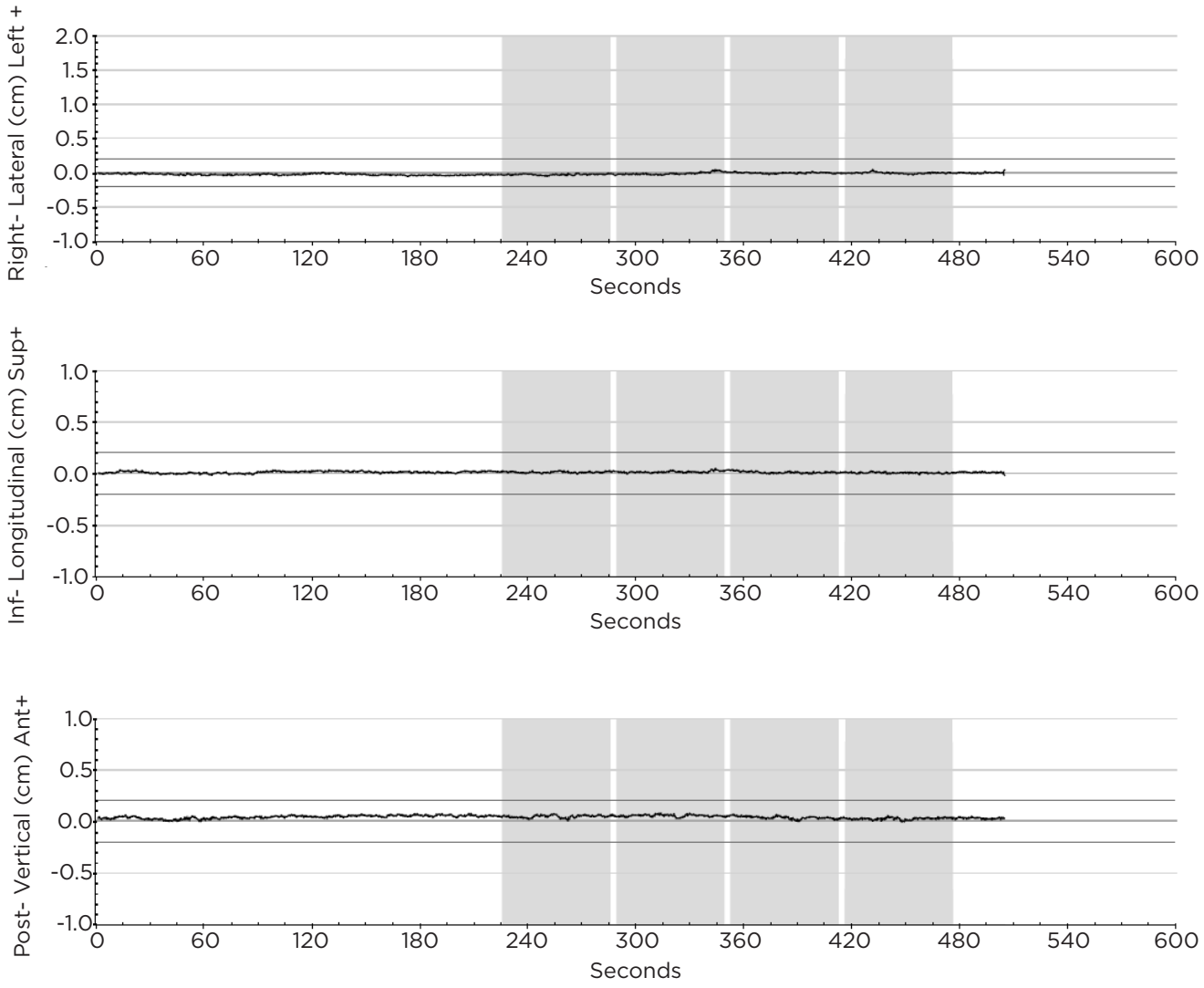

Figure 2. Treatment report for a treatment session of 9 Gy using beacon transponder technologies. Deviation from the reference location of the target is shown for the lateral, longitudinal and vertical axis, respectively (from top to bottom). Maximum displacement during the entire session is <1 mm. The four vertical grey bands correspond to actual beam-on for four consecutive arcs using VMAT with a 10 MV FFF beam.

motion of the prostate and create anatomical reproducibility of the rectum may be adopted by the use of endorectal balloons whose efficacy has been widely documented.[21-23] The accomplishment of urethral sparing via negative dose-painting to minimise GU toxicity is feasible through appropriate imaging procedures and via on-line tracking during treatment delivery. MRI image-fusion allows the identification of critical structures such as the neurovascular bundles and the penile bulb which may be electively spared from high-dose radiation with the intent to potentially reduce the incidence of radiation-induced erectile dysfunction.[24]

PHASE I FEASIBILITY STUDY AT CCU

At the Champalimaud Centre for the Unknown (CCU), Lisbon, Portugal, great emphasis has been placed in the accuracy of patient simulation, planning, and set-up procedures to maximise the potential benefits of extreme hypofractionation in selected cases. A Phase I feasibility study of a prescription dose of 45 Gy in 9 Gy sessions delivered every other day has just been concluded. MRI and CT simulations for planning have been performed with endorectal balloons. The optimal balloon volume as a function of the patient's specific anatomy is the subject of current investigation. Excellent anatomical reproducibility and target stabilisation at the time

of treatment have been confirmed for volumes ≥100 cc. Rectal wall, urethral, genito-urinary diaphragm, and penile bulb sparing are achieved via the fulfillment of strict dose-volume constraints. Set-up reproducibility prior to treatment delivery is monitored via intraprostatic electromagnetic beacon transponders and accurate anatomical matching is verified via CBCT immediately prior to a fast flattening filter-free (FFF) beam delivery. Electromagnetic transponder intra-fractional tracking has shown <1 mm variation in all directions during treatment delivery. 10 patients with low and intermediate-risk disease have completed treatment in this Phase I study and are currently being monitored for treatment-related toxicity using validated EPIC questionnaires for the GU, GI, and sexual domains. With a median follow-up of 3 months, no acute Grade 2 GU and GI toxicities have been observed so far. The feasibility of neurovascular bundle sparing is currently being investigated in selected cases. Figure 1 shows the dose distribution to the target volume to 45 Gy in five sessions. The target volume includes the whole prostate and seminal vesicles. The rectal balloon with 150 cc filling of air is used to fix the anatomy, and the urethral catheter with transponders is essential to identify and track the location of the urethra during treatment as performed in the CCU protocol. Figure 2 shows the treatment session report of measured motion using beacon transponder technology as used at CCU, indicating <1 mm deviation from the reference for the entire duration of the treatment.

CONCLUSION

Preliminary data convincingly indicate that extreme hypofractionation holds great promise of achieving excellent biochemical relapse-free outcomes in properly selected prostate cancer patients. Preliminary experiences with extreme hypofractionation are maturing, and randomised studies comparing moderate versus ultra-high dose regimens are currently being carried out. Recently, ASTRO has issued a model policy indicating that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an alternative for appropriately selected patients with low to intermediate-risk disease.[25] However, great emphasis on rigorous planning and delivery techniques must be placed when using extreme hypofractionated regimens to fully exploit their potential benefits in optimising the therapeutic ratio, thus yielding optimal uncomplicated clinical outcomes.

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