Physica Medica xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Review Paper

SBRT for prostate cancer: Challenges and features from a physicist prospective

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ARTICLE INFO

Article history:
Received 1 December 2015
Revised 29 February 2016
Accepted 12 March 2016
Available online xxxx

Keywords:
SBRT
SABR
Prostate
Medical physics

ABSTRACT

Emerging data are showing the safety and the efficacy of Stereotactic Body Radiation Therapy (SBRT) in prostate cancer management. In this context, the medical physicists are regularly involved to review the appropriateness of the adopted technology and to proactively study new solutions. From the physics point of view there are two major challenges in prostate SBRT: (1) mitigation of geometrical uncertainty and (2) generation of highly conformal dose distributions that maximally spare the OARs. Geometrical uncertainties have to be limited as much as possible in order to avoid the use of large PTV margins. Furthermore, advanced planning and delivery techniques are needed to generate maximally conformal dose distributions. In this non-systematic review the technology and the physics aspects of SBRT for prostate cancer were analyzed. In details, the aims were: (i) to describe the rationale of reducing the number of fractions (i.e. increasing the dose per fraction), (ii) to analyze the features to be accounted for performing an extreme hypo-fractionation scheme (>6–7 Gy), and (iii) to describe technological solutions for treating in a safe way. The analysis of outcomes, toxicities, and other clinical aspects are not object of the present evaluation.

Contents

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http://dx.doi.org/10.1016/j.ejmp.2016.03.011
1120-1797/

Introduction

Stereotactic Body Radiation Therapy (SBRT), or Stereotactic Ablative Radiotherapy (SABR) as nowadays is commonly known, is a radiation therapy approach able to provide high radiation doses in few fractions focused on small extracranial tumors with rapid dose fall off between target and surrounding healthy tissues. SBRT showed its efficacy in several patient populations with primary and metastatic limited tumors [1]. To date, compared to other tumor sites, the adoption of SBRT in the management of genitourinary malignancies remains still limited to selected cases, especially inside clinical trials. Nevertheless, emerging data are showing the safety and efficacy of this treatment modality in prostate cancer [2] and the new National Comprehensive Cancer Network (NCCN) guidelines on prostate version 2.2014 considers SBRT on prostate "as a cautious alternative to conventionally fractionated regiments at clinics with appropriate technology, physics and clinical expertise". Furthermore, ASTRO model policy update of 2013 acknowledged that SBRT could be considered an appropriate alternative for selected patients with low to intermediate risk disease as well as NCCN guidelines, where SBRT for prostate is recommended in the same setting cautiously, as an alternative of conventional approach, outlining the importance of the available technology and the experience of clinical and physics staff.

The implementation and maintenance of a SBRT program for prostate cancer is challenging for each profession involved. In this context, the medical physicists (MPs) are involved into the process standardization (simulation with multi-imaging, treatment plan optimization, quality assurance, and delivery). Furthermore, the continuous evolution of SBRT-related technology requires the MPs to regularly review the appropriateness of the technology and to proactively study new solutions.

From the physics point of view there are two major challenges in prostate SBRT: (1) mitigation of geometrical uncertainty and (2) generation of highly conformal dose distributions that maximally spare the OARs. Geometrical uncertainties have to be limited as much as possible in order to avoid the use of large PTV margins. Furthermore, advanced planning and delivery techniques are needed to generate maximally conformal dose distributions.

In this non-systematic review, the technology and physics aspects of SBRT in prostate cancer were analyzed. In detail the scope of this review was: (i) to describe the rationale of reducing the number of fractions (i.e. increasing the dose per fraction), (ii) to analyze the features to be accounted for when applying an extreme hypo-fractionation scheme (>6–7 Gy), and (iii) to report the technological solutions for managing and treating it in a safe way. The evaluation of the clinical outcomes was not investigated.

The search engines of the PubMed were utilized. In addition, relevant references based on personal experience were utilized.

The radiobiological rationale

The background of severe hypo-fractionation in prostate SBRT is based on the hypothesis of α/β lower for the tumor than the adjacent organs at risk (OAR). In 1999, Brenner and Hall estimated $\alpha/\beta = 1.5$ Gy, with 0.8–2.2 Gy as 95% confidence interval [3]. Alpha was calculated from low-dose-rate brachytherapy data and β from external-beam-radiotherapy (EBRT). After fifteen years of debates (including the evaluation of repopulation and tumor hypoxia effects), quite definitive consensus on $\alpha/\beta = 1.5$ Gy for the prostate is now reached [4]. Near OARs seems to have higher α/β than for prostate cancer, even if less robust data are available (rectum $\alpha/\beta = 3$–6 Gy), or need to be determined (urethra).

Although contradictory results in terms of (biochemical) local control were reported when comparing 'soft' forms of hypofractionation (i.e. 2.5–3.5 Gy per fraction) vs. conventional fractionation [5,6], for prostate SBRT, however, the picture from phase II studies on large population of selected patients [7,8] is encouraging in terms of both tumor control and toxicity outcomes. A pooled analysis of phase II clinical trials over 1100 patients reported 5-year biochemical relapse free survival rate of 95% for low-risk patients, and 93% for all patients reinforcing the small α/β value for prostate [7]. Furthermore, low late urinary and rectal toxicities after median follow-up of 3 years were reported, supporting the α/β value greater for the OARs than the prostate tumor [8]. Such a low $\alpha/\beta = 1.5$ Gy further implies for SBRT a reduced attractiveness [9] from simultaneous dose boosting to dominant intra-prostatic lesions (DILs), an approach which was conceived to improve local control in standard fractionation.

Geometrical uncertainties

Inter-fractions prostate deformation and motion

Using multiple CT scans, Deurloo, did not find any significant changes in prostate volume during 7–8 weeks treatment course [10]. In particular, small shape variations along anterior–posterior direction ($\sigma \leqslant 0.9$ mm) and negligible variations along lateral and longitudinal directions ($\sigma \leqslant 0.5$ mm) were observed. Larger shape variations for the seminal vesicles (SV) ($\sigma \leqslant 1.6$ mm) were detected. Multiple cine-MRI scans along sagittal planes were used by Ghilezan to observe that intra-fraction prostate motion mostly depends on rectal filling variations [11]. Quantitatively, vertical shift <3 mm at mid-posterior gland was observed in 90% of patients after 10 and 2 min for, respectively, empty and full rectum. Both studies supported the use of CBCT with rigid registration only with empty rectum [10,11].

In 36 daily fractions treatment of 56 patients with 3 internal markers (IM) (radiopaque seeds), Kupelian observed an average absolute variation of IM distances with respect to their first alignment equal to 1 (±1) mm [12]. From 25 patients with 3 IMs and empty rectum, Nichol estimated 0.05 mm/fraction marker migration [13]. Therefore, for extreme hypo-fractionated prostate SBRT, the use of IMs for prostate localization is adequate.

Using MRI, Kerkhof et al. analyzed the potential impact of prostate deformation/shift on 8 volunteers and 6 different rectal filling conditions [14]. An isotropic PTV margin of 4 mm from the prostate gland without SV was considered. The reference IMRT plan was performed on the minimum rectal volume series, and the plan was recalculated on the remaining MRIs with larger rectum filling (up to 3 times greater). A significant increase in rectum D_{2cc} (mean: 8.3%; range: 2–15%) was observed, while no significant reduction in target dose coverage ($D_{95\%}$) was detected. Therefore, for patients with empty rectum, if pre-treatment control with CBCT is performed and adequate margins to the prostate ($\geqslant$4 mm) are adopted, the prostate deformation is negligible.

In contrast, the rigid prostate model is inadequate when the target includes the SV as observed by Deurloo et al. [10]. Furthermore, de Boer at al. analyzed 780 daily CBCT from 20 patients with 2–3 IMs and observed a negative correlation ($R = -0.5$) between the prostate and SVs lateral rotations (*pitch*) [15]. This is likely determined by a full bladder condition, which pushes the SV posteriorly and the prostate anteriorly. Therefore, when the SV is included into the target of prostate SBRT, extended PTV margins in the cranial direction might be necessary. As an alternative, a hybrid CBCT registration technique was suggested, which finally adapts the pitch on the SVs after a previous IM-based 6D-registration is performed [15].

Intra-fraction prostate motion

Bittner et al. observed prostate centroid shift using RF-transponders for patients in prone position, and found an

Please cite this article in press as: Mancosu P et al. SBRT for prostate cancer: Challenges and features from a physicist prospective. Phys. Med. (2016), http://dx.doi.org/10.1016/j.ejmp.2016.03.011