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High dose rate brachytherapy for prostate cancer: rationale, current applications andclinical outcome

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Abstract

High-dose rate brachytherapy (HDR BRT) has been enjoying rapid acceptance as a treatment modality offered to selected prostate cancer patients devoid of risk group, employed either alone or in combination with external beam radiation therapy (EBRT) and is currently one of the most active clinical research areas. This review explores the rationale of HDR BRT as a highly conformal dose delivery method enabling safe dose-escalation to the prostate, its current clinical indication spectrum backed up by valid long-term data in regard to the encouraging oncologic outcomes and favourable toxicity profile, as well as emerging applications and how it will feature alongside stereotactic radiosurgery.

Introduction

In patients diagnosed with clinically prostate-confined cancer, radical prostatectomy (1, 2), external beam radiation therapy (EBRT) (3–5), permanent low-dose rate (LDR) brachytherapy (BRT) (6–8) and temporary high-dose rate (HDR) BRT (9–19) are considered established therapeutic options. However, in the absence of randomized clinical trials, the optimal therapeutic management remains trivial, with treatment assignment being mainly influenced by physician's bias and patient's preference. In this regard, choice and consecutively impact of treatment on quality of life, has gained increasing importance, with BRT gaining ground due to its high effectiveness and at the same time its relatively low morbidity. Currently, validated long term data support the efficacy of BRT in the treatment of localized prostate cancer with technological advancements fuelling active research in the field of HDR BRT owed mainly to refinement of the technique (20), employment of modern biomolecular imaging (21–23), and investigation of focal and focused approaches (24), all of which ensure high standards of implant quality and precision. The dosimetric superiority of HDR BRT translates into excellent clinical results (25–27), thus backing up the notion that HDR BRT is an innovative alternative to permanent LDR BRT (28). This review presents a comprehensive analysis of the rationale, current clinical indications and oncologic outcomes, including a representative data report.

Background

Rationale for HDR Brachytherapy

Dose escalation data suggest that the utilisation of comparatively higher dose for definitive radiation therapy (RT) in organ-confined prostate adenocarcinoma improves biochemical control (BC) (4, 5, 29) but at the same time results in improved metastasis-free survival (MFS) (5, 30–34).

Dose escalation data suggest that the utilisation of comparatively higher dose for definitive radiation therapy (RT) in organ-confined prostate adenocarcinoma improves biochemical control (BC) (4, 5, 29) but at the same time results in improved metastasis-free survival (MFS) (5, 30–34). In this light, it is only reasonable to assume that further amelioration of the therapeutic ratio could be achieved by escalating the treatment dose, while simultaneously enhancing dose conformity, especially in patients devoid of regionally advanced and/or metastatic tumour load. HDR BRT fully exploits its radiobiological advantage to perfectly meet this objective, through the utilisation of extreme hypofractionation (35–37) and at the same time its incomparably superior three-dimensional (3D) dosimetry (38). HDR treatment planning allows for anatomy-based dose optimization through modulation of multiple parameters such as catheter geometry, radiation source positions and source dwell times (39, 40). This enables for optimal dose modulation, delivering higher doses to target volume or selectively reducing the dose to organs at risk (OARs) (25).

In relation, HDR BRT employs "high density" dosimetry, owed to the roughly twofold dwell positions number when compared to seeds in a typical LDR implant. Again in comparison to LDR, anatomic and thus dosimetric changes are kept to a minimum, since seed/source migration and tissue deformation which are often issues associated with permanent LDR BRT implants do not occur (41–43). On the other hand, intra-fractional anatomic alteration caused by organ motion during EBRT delivery (44–46), as well as setup inaccuracies are overcomed with HDR due to rectification of theses error during the implantation procedure with interactive online dosimetry or modified prior to dose delivery with realtime anatomy-based treatment planning (25). This minimisation of errors allows for a decrease in the therapeutic margins required beyond the intended target, thus exposing less healthy tissue in unnecessary radiation, transforming HDR BRT to the optimal intraprostatic dose- escalation technique, where needed, especially in combination with EBRT. This is of particular clinical importance in patients where treatment area includes the regional lymphatic drainage which is treated to a moderate dose, while offering an intraprostatic escalated dose.

Radiobiological Considerations

Radiobiological data suggest that there is variability between normal and malignant tissue and the probability of acute and late radiation sequelae development, variation which is also being noted in-between different fractionation schedules. Based on the linear-quadratic model (47), the α/β ratio acts as a mean of expressing the sensitivity of a particular tissue to altered fraction size, allowing comparison between various treatment schedules and at the same time, estimates the impact of each given fractionation schedule on tumour control and toxicity.

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Recent radiobiological reports suggest a low α / β ratio for prostate cancer, ranging between 1.2–3.0 Gy, which is relatively lower than the α/β ratio of acutely and late-reacting normal tissues (36, 48, 49). Having this in mind, hypofractionated dose schemes are favoured and seem to result in superior tumour control with remarkable reduction in late side effects. In this background HDR BRT represents the ideal method for conformal dose escalation (50).

Patient Selection for HDR Brachytherapy

Based on the hypothesis that failure of local control in organ-confined prostate cancer may lead to regional and distant metastasis development, the fundamental indication for HDR BRT is histologically proven localized disease in patients considered suitable candidates for radical treatment (51, 52). In line with the National Comprehensive Cancer Network (NCCN) guidelines (53), which see the patients with low- and intermediate-risk as optimal candidates for local radical treatment, considering they bear the highest probability for organconfined prostatic disease. Concomitantly, reports from mature retrospective series encourage the use of HDR BRT monotherapy in a selection of high-risk patients, based on the notion that the therapeutic margin provided is superior to RP, with OARs' dose (urinary bladder and rectum) remaining significantly lower in comparison with definitive dose-escalated EBRT plans. On the other hand, in patients stratified as intermediate- and high risk (53); (1, 54), the utilisation of combined HDR BRT as a boost modality with EBRT is a wellestablished treatment supported by valid data (55–58). Again, HDR BRT may find implementation in the clinical setting of regional lymphadenopathy, with or without presence of distant metastatic spread, as a combination with EBRT in an individualized treatment concept, aims at minimising toxicity where RT is employed, with the goal of increased local disease control. In the local recurrence setting after definitive RT, as proposed by international guidelines (51, 52, 59), any patient presenting histological and/or radiological (also biomolecular imaging) proved, prostate-confined disease is a potential candidate for local radical treatment, therefore prostate salvage HDR BRT (sHDR BRT) should be considered. Prior to HDR BRT, complete clinical staging should be attempted following the European Association of Urology (60), European Society for Radiotherapy and Oncology (ESTRO) (52), and American Brachytherapy Society (ABS) (51) guidelines. Precise stratification based on thorough clinical work up, consisting of histological confirmation of malignancy, in this case prostate cancer, and clinical investigations for evaluation of disease burden including digital rectal examination, transrectal ultrasound (TRUS), computed tomography (CT) and/or magnetic resonance imaging (MRI) and bone scintigraphy. In equivocal cases of regional lymphadenopathy, laparoscopic pelvic lymphadenectomy or positron emission tomography may be considered. Although functional outcome following HDR BRT is predicted by the baseline urinary function (61), neither larger gland size nor previous transurethral resection of the prostate (TURP), given a sufficient amount of time has surpassed (>3 months) and residual gland volume remains for image-based 3D treatment planning (62– 64) should be considered as absolute contraindications. When comparing HDR to LDR or EBRT, the exacerbation of lower urinary tract symptoms appears to be less prolonged, based on the fact that even patients with high International Prostate Symptom Score (IPSS) (≥20) tend to have a relatively rapid return to pre-treatment baseline urinary function (65). Selection criteria for HDR BRT as monotherapy, combined with EBRT and in the salvage setting are presented in Table 1. In contrary to permanent LDR implants, HDR BRT afterloading catheters can be implanted in order to cover extracapsular lesions or the seminal vesicles or even the bladder pouch, permitting the extension of its indication to cover even T4 tumors as part of individualised curative treatment schemes (14, 66, 67). Previous pelvic EBRT, prior pelvic surgery and inflammatory bowel disease are not considered absolute contraindications for HDR prostate BRT, but always a very thorough evaluation of the potential risks and benefits should take place, based on anatomy-based dosimetry including carefully defined OARs dose constraints (25).

Implantation Techniques

Interstitial catheter implantation is carried out under anaesthesia, spinal or general. In respect to TRUS-guided implantation (13, 68, 69) extensive experience exists, while MRI-based techniques also being practiced (52, 53). Table 2 describes key features of the technique. In case of the TRUS-based technique, implantation is carried out transperineally with the patient in high lithotomy position, using a template to aid catheter placement and a continuous probe movement technique. The clinical workflow includes image acquisition of the prostate, urethra, and anterior rectal wall and the creation of virtual volumes prior to implantation for inverse treatment preplanning (40). Threedimensional (3D) volume reconstruction follows based on a 0.1 cm image distance. Contouring commences based on the GEC/ESTRO guidelines (52). Based on the acquired 3D anatomy, appropriate virtual catheter positions are generated, catheter source dwell positions located within the PTV are activated, and radioactive source dwell times are calculated using an intraoperative treatment planning system (Fig. 1). The final evaluation of the anatomy-oriented dose optimization (39) is based on the dose-volume histogram (DVH) of the PTV and the OARs (i.e., intraprostatic urethra, anterior rectal wall, and urinary bladder). If the dosimetric protocol parameters are met, TRUS-guided implantation is performed at the pre-defined catheter positions (Fig. 1). In the MRI-based implantation procedure, transperineal catheter placement ensues with the patient in left lateral decubitus position employing a template device. Paralleling the workflow of TRUS-guided implantation, the MRI-guided procedure involves a preplanning step, based on 3D image reconstruction from the acquired pre-interventional MRI sequences (of at least 0.3 cm slice thickness). The number, distribution and distance between the catheters are determined by the preplanning which calculates the peripheral catheter arrangement with arbitrary optimization for target coverage. Catheter implantation with control of maximum insertion depth and positional verification of the implanted catheters is performed by interactive MRI scanning. An attempt to obtain the optimum from both worlds has already been made. In our department, a T2-MRI sequence, with a placed urinary catheter, is obtained just before the TRUS-guided transperineal implantation procedure begins. Based on clearly visible landmarks, such as the urinary catheter balloon, the vesicourethral anastomosis both on MRI and US images can be easily identified, aiding in optimal fusion of the two modalities and thereby precise prostate capsule definition, especially of the prostatic apex and base (Fig, 2).

Clinical Data HDR Brachytherapy in Combination with EBRT Dose-escalation trials, in reference to the management of intermediate- and high-risk prostate cancer, demonstrated an improvement both in BC as well as MFS (4, 5, 29, 30, 32–34, 70–73). In this context, the combination of EBRT with hypofractionated HDR BRT as a boost allows for safe delivery of high biologically equivalent doses to the prostate, which in the present circumstances is not even achievable by image-guided EBRT (29, 74–76). Of particular importance, is the dosimetric superiority of HDR BRT which derives from its high-precision in terms of conformality, especially when compared to stereotactic approaches (77, 78). Randomised studies in conjunction with mature retrospective data from major institutions justify the superiority of combined modalities over EBRT alone in the primary treatment of localised highrisk prostate adenocarcinoma. Hoskin et al. (55) randomized 220 patients to receive either combined with HDR BRT with hypofractionated EBRT alone or EBRT alone. The EBRT-only treatment (n = 111) consisted of 55 Gy administered over 20 fractions where as in the combined group (n = 109) of 35.75

Gy EBRT applied over 13 fractions followed by a 17-Gy HDR boost given in two fractions with a single implant. The mean biochemical failurefree survival in the EBRT-only group was 4.3 years versus 5.1 years in the combined arm (p=0.03), without any statistically significant differences being noted in higher-grade GU- and GI toxicity. In an earlier study, Sathya et al. (56) randomised 104 patients to conventional EBRT with a total physical dose of 66 Gy in 33 fractions or to 35 Gy pulse-dose-rate BRT delivered in 48 hours plus supplemental EBRT of 40 Gy in 20 fractions 2 weeks later. In a recent update of this study (79), attaining a median follow-up of 14 years, the authors reported an overall survival of 67% in the EBRT arm compared to 77% in the combined modality arm without statistically significant differences in late GU and GI toxicity. Although BC remained improved in favour of the combined modality, it did not achieve statistical significance, mainly owning to the fact that the trial was underpowered. The recent ASCENDE RT Trial (80) compared two dose escalation methods, with patients being randomized between a standard arm (n=200) consisting of ADT for 12 months and pelvic EBRT to 46 Gy plus a EBRT boost to 78 Gy, and an experimental arm (n=198) employing a LDR BRT boost with minimal peripheral prostatic dose of 115 Gy. At a median follow-up of 6.5 years, the 7-year biochemical failure-free survival in the BRT arm was 86% compared to 75% in the EBRT arm. Despite the favourable oncologic outcomes of the study, the LDR boost was associated with increased rates of acute and late GU but not GI toxicity, with a 5-year cumulative incidence of grade 3 GU of 18.4% for LDR BRT versus 5.2% for the EBRT boost (p< .001 for both). In one of the largest retrospective series, our group (19) treated 303 high-risk patients with an HDR BRT boost consisting of two fractions of 10.5- Gy preceded by EBRT delivering 45.0 Gy. The 7-year biochemical relapse-free survival and metastasis-free survival rates were 88% and 93% respectively. The reported incidence of late Grade 3 GU adverse events was 2.2%, with no GI grade 3 being reported. Acknowledging the methodological advantages of HDR BRT in comparison with LDR, in regard to the very steep falloff in dose beyond the PTV together with the versality of intratarget dose modulation, the avoidance of systematic errors and imprecision in dose application due to anatomic deformities and source migration, it is only reasonable to state that all LDR outcomes can be reproducible, if not superior (82), with the employment of HDR BRT. Overall, despite the heterogeneity of clinically implemented treatment schemes, which makes it challenging to propose uniform recommendations for a standardized protocol, the published oncological results on combined RT are consistent and reproducible (Table 3). Most institutions use BRT fractions ranging from 6 to 10.5 Gy yielding total physical HDR doses of 12–21 Gy applied in two to four fractions. The supplemental EBRT doses range from 45 to 54 Gy (normofractionation), generating total BED 1.5 and EQD2 doses in the range of 171– 366 Gy and 74–137 Gy, respectively (9, 10, 14–16, 56, 59, 68, 69, 79, 83–104). The reported severe late GU and GI adverse events rates compare favourably with late toxicity rates in dose-escalated EBRT series (71, 98, 99, 105). It must be noted, that hypofractionated EBRT protocols are gaining momentum (101, 102), appearing equieffective in regard to clinical outcome, whilst demonstrating favourable toxicity profile. HDR Monotherapy As already mentioned, HDR BRT was originally used in combination with EBRT, as a boost modality mainly due to concerns regarding normal tissue toxicity with the application of hypofractionated treatment regimes. Dose escalation studies established the safety and efficacy range for HDR in the context of combined EBRT and BRT (106–108). At the same time, the employment of other locally directed treatments such as RP, radical EBRT and LDR BRT, together with the fact that image-guided HDR with its anatomybased dose optimization allows for high precision in prostate dose coverage while simultaneously for total dose control to adjacent OARs (25), laid the way for broad practice of HDR BRT in the monotherapy setting. By now, a dynamically growing body of literature considers HDR as safe and effective radical treatment with consistent intermediate- and long-term BC rates over a range of risk groups (13, 17, 18, 69, 109–123, 123). The longest followup for clinical results exists for moderate hypofractionation (four to nine fractions), nevertheless consistent data are also reported for extreme hypofractionated protocols (one to three fractions). At this point, there was an attempt with the emergence of ultrahypofractionation (112, 124, 125) (one fraction) to make HDR logistically comparable with LDR BRT. Unfortunately, up to this point single shot scheme has been proven inferior in respect to clinical outcomes and requires further validation (112, 126–129). Again, due to the variation of clinically implemented dose fractionation regimens, direct comparisons are proving difficult. Despite that, the oncological outcomes yielded with single- or multiple implant schemes for extreme or moderated hypofractionated treatment protocols are uniform (Table 4). Hauswald et al. (110) published on 448 patients with low-/intermediate-risk disease treated with 6 fractions in 2 implants (spaced 1 week apart) to a median of 43.5 Gy,. Temporary ADT was administered in 42 patients (9%). With a median follow-up of 6.5 years, the actuarial 6-and 10-year overall BC rate was 98.6% and 97.8%, respectively, with no significant difference in respect to biochemical progression free survival at 10 years being noted between low- and intermediate-risk group (98.9% versus 95.2%). No late grade 3-4 GI was reported, while late grade 3-4 GU toxicity was 4.9%. One patient (0.2%) experienced grade 4 late GU sequelae. These results are in line with experience from other major institutions proving that HDR BRT monotherapy is applicable for intermediate- and selected cases of highrisk disease (13, 110, 111, 118, 120–122). The Offenbach group (17) in Germany reported on 718 consecutive patients and is considered one of the largest patient collective to time, utilizing three different protocols (four fractions of 9.5 Gy in single implant, four fractions of 9.5 Gy in two implants, and three fractions of 11.5 in three implants). It included 44.9% of intermediate- and high-risk patients, with approximately 60 % of high- and 27 % of intermediate-risk cases receiving temporary ADT. The 5-year BC rate for intermediate- and high-risk patients was 93 % and 93 %, respectively. Late grade 3 GU and GI were reported at 3.5% and 1.6%, respectively. Data on erectile dysfunction after BRT monotherapy have been rarely reported, using various multidimensional or ordinal scales for assessment. However, potency preservation rates of 60–90 % have been documented in recent literature (17, 26, 110, 112, 116–120, 130). In the series by Hauswald et al. (110), 315 (70%) patients were able to attain an erection sufficient for intercourse before treatment. Data from 225 patients in regard to sexual function data were evaluated with a median of 6 years following treatment. An ability to engage in intercourse, with or without the use of erectile aids, was reported by 60% of patients with median age of 69 years at time of assessment. To date, only nonrandomized evaluations have put LDR and HDR monotherapy in comparison in regard to their toxicity profile and confirmed that both acute and late high-grade toxicities are in favour of HDR monotherapy (117, 120). Martinez et al. (117) compared HDR monotherapy (n=248) and LDR seed patients (n=206), showing that temporary HDR is being associated with significantly less Grade 1– 2 chronic dysuria (LDR 22 % vs. HDR 15 %) and urinary frequency/urgency (LDR 54 % vs. HDR 43 %). The rate of urethral stricture was equal for both modalities (LDR 2.5 % vs. HDR 3 %) and late Grade 3 GU sequelae was low in both groups. The 5-year potency preservation rate was 80 % for HDR versus 70 % for permanent LDR BRT. Overall, the clinical outcome data of HDR monotherapy reflect the current radiobiological considerations for optimal tumour control through hypofractionation. The biologically effective dose (BED) values in Table 5 range from 208–299 Gy with a median value of 256 Gy (α/β-ratio of 1.5 Gy), further calculated into EQD2 values ranging from 89 to 128 Gy tendering such dose coverage impossible to be achieved with current EBRT techniques. In contrast to clinical data arising from definitive EBRT, the potential advantage of temporary ADT for patients treated with HDR monotherapy remains an issue of ongoing

debate, as no convincing evidence exists (25, 131). The excellent results of HDR BRT have prompted the implementation of stereotactic body radiotherapy (SBRT) for the percutaneous treatment of localized prostate cancer using extreme hypofractionation, utilizing continuous image guidance to automatically track, detect, and correct for intrafraction prostate movement (132–136). It seemingly combines "EBRT-like" noninvasiveness with "HDR BRT-like" biologic potency (78). However, Spratt et al. (137) analysed dosimetrically, virtual SBRT with actual HDR monotherapy plans from treated patients, demonstrating that HDR achieves significantly higher intraprostatic doses while achieving similar urethral doses and comparatively lower maximum rectal doses. Notwithstanding this, SBRT, HDR as well as LDR BRT have proven efficacy as safe for the treatment of localised prostate cancer. However, in order to confirm the theoretical advantages of one modality over the other, a randomised clinical trial is warranted, as it could especially resolve uncertainties concerning the clinical impact based on their well-known dosimetric differences. Adding to that, given the tight "surgical margin" associated with SBRT, it is not recommended for more advanced disease such as extracapsular extension or seminal vesicle involvement (133, 138). In conclusion, HDR BRT as monotherapy is an excellent modality for the management of low- and intermediate- and selected case of high-risk prostate cancer with long-term follow-up data justifying its safety and low side-effect rate. HDR Monotherapy as Salvage Treatment The optimal management of patients treated previously with definitive RT for clinically localized prostate cancer which are experiencing a biochemical recurrence (BCR) remains a challenging clinical issue (139), with salvage radical prostatectomy (sRP), salvage high-intensity focused US, and salvage EBRT (sEBRT) being clinically practiced (140–143). Clinical evidence suggests that approximately 70 % of patients with an increase in their PSA value will experience solely a local failure (144–146), devoid the variance in treatment-related BCR definition (147, 148). Salvage HDR BRT (sHDR BRT) with or without ADT for clinically, histologically and metabolically proven local recurrence after previous radical RT appears to be an effective, well-tolerated therapeutic option which can be favourably compared with other non-radiotherapeutic local treatment modalities, in regard to disease control and toxicity rates. (149–151). Considering that reports about local salvage modalities are in general scarce, only a few studies report the long-term oncological outcomes following sHDR BRT. Even though all data arise from retrospective reports and are unfortunately relatively restricted in regard to patient sample size, some of them have reached a 5-year follow-up with reported BC of the order of up to 77%. Table 6 lists the clinical outcomes of published studies reporting on sHDR BRT after definitive RT. In comparison to the primary setting an increase in adverse events is observed (25), although still acceptable when compared to sRP and sEBRT, with predominantly grade 2 GU and GI toxicity. When compared with series of sRP after previous definitive RT symptomatic anastomotic strictures in the range of 7–41% are reported, while rectal injury in 0–28%, complete erectile dysfunction in 80–100%, and complete urinary incontinence ranging from 21–90% of patients (141). Following sEBRT, late grade 3 GU adverse events of 7–18% have been reported (152, 153). With regard to LDR, no randomized trial has compared LDR and HDR in the primary or salvage treatment setting, however nonrandomized evaluations have confirmed that both acute and late high-grade toxicities are less frequent after primary HDR than LDR monotherapy (120). Similarly, late grade 3 GU and GI toxicity rates in the sLDR BRT literature range from 0–47% and 0–20%, respectively (154, 155). Once again, given the heterogeneity of clinically implemented protocols, uniform recommendations concerning the optimal dose-fractionation scheme for whole gland sHDR BRT are difficult to be defined. However, the oncological results deducted from single or multiple implant regimes exploiting extreme hypofractionated or moderately hypofractionated treatment are consistent and reproducible. At the same time, sHDR BRT has also been applied as a focal modality for the reirradiation of radiologically detectable recurrent disease (156, 157). Although significant dose reductions to OARs can be achieved using focal HDR BRT (158), the possible clinical impact on morbidity and tumor control remains to be further investigated. Currently, there is no consensus involving patient's eligibility for repeating a local therapy of organ-confined recurrent prostate cancer and the most suitable candidates have yet to be defined. Table 1 describes the selection criteria and contraindications. Nevertheless, the main rationale for HDR salvage treatment is the presence of local disease in non-metastatic patients considered otherwise suitable candidates for radical therapy. An ever growing literature body supports the safe utilisation of sHDR BRT solely or as part of individualized treatment approach also for high-risk patients (145, 159–161). Conclusion HDR BRT is an excellent radiooncological modality for the management of prostate cancer granting an extraordinary low side-effect rate. Valid long-term follow-up data support its safe and effective implementation in the treatment of prostate-confined cancer for any risk group. However, further prospective and randomized studies are warranted to fully establish its role in clinically challenging prostate cancer cases.

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