Hypofractionation for Localized Prostate Cancer

Subjects: Urology & Nephrology

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Prostate cancer is the most commonly diagnosed cancer among men around the world. Radiotherapy is a standard of care treatment option for men with localized prostate cancer. Over the years, radiation delivery modalities have contributed to increased precision of treatment, employing radiobiological insights to shorten the overall treatment time, improving the control of the disease without increasing toxicities.

extreme hypofractionation | hypofractionation | prostate cancer | stereotactic body radiation therapy (SBRT)

1. Introduction

External beam radiation therapy (EBRT) is considered one of the standard treatments for organ-confined prostate cancer (PCa), with cure rates similar to those of radical prostatectomy. Hypofractionation uses a higher dose-per-fraction of radiation, which reduces the number of fractions and the total duration of treatment, allowing greater comfort for the patient and lower costs, in addition to providing a therapeutic advantage in terms of tumor control and toxicity, as the α/β of PCa is lower than that of adjacent healthy tissues [1]. In 2018, a group of experts from the American Societies of Radiation Oncology, Medical Oncology, and Urology (ASTRO/ASCO/AUA) concluded that there is sufficiently robust evidence to justify using moderate hypofractionation in PCa as common clinical practice [2], and a recent Cochrane review indicated that moderate PCa hypofractionation (with fractions up to 3.4 Gy) provides oncological outcomes in terms of overall survival (OS), disease-free survival (DFS), and metastasis-free survival (MFS) similar to conventional fractionation, without a significant increase in acute or late toxicity [3].

In addition, technical advances in the field of radiotherapy in recent years, such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic radiotherapy (SBRT), have enabled the progressive implementation of extreme hypofractionation (defined by fractions of at least six Gy) in various scenarios of localized PCa treatment. The use of SBRT in PCa has provided sufficient evidence in terms of tumor control results, quality of life reported by the patient, and low toxicity [4][5][6] to back its implementation in daily clinical practice. Moreover, the PCa working group of the German Society of Oncology (DEGRO) endorses the use of SBRT in the treatment of localized low- and intermediate-risk PCa, recommending its use in clinical trials in patients with the localized high-risk disease [7].

The recent publication of two randomized trials comparing the use of extreme hypofractionation versus conventional fractionation (HYPO-RT-PC [5], PACE-B trial [6]) has been crucial in supporting its use, although only the Scandinavian study (HYPO-RT-PC) reported results of long-term tumor and toxicity control. In 2020, a randomized systematic review and meta-analysis of phase III trials were published comparing SBRT with normofractionated and hypofractioned regimens. It concluded that the ultra-hypofractionated regimens obtained similar 5-year disease-free survival results, with late gastrointestinal and genitourinary toxicity of <15% and <21%, respectively, when compared to hypofractionated regimens and conventional radiotherapy [8].

At a time when there is growing interest in adopting extreme fractionation schedules in treating PCa in our usual practice, this review aims to capture the current evidence and recommendations for using it in different scenarios of PCa treatment.

2. SBRT in Low- and Intermediate-Risk Prostate Cancer

There are multiple published prospective trials in which thousands of patients with extreme hypofractionation have been treated, with different doses, fractions, and techniques. The most relevant have been analyzed in four reviews or meta-analysis studies.

In 2019, Roy and Morgan published a review of the hypofractionated and ultra-hypofractionated studies in localized prostate cancer. They concluded that SBRT is an option in treating patients with low and intermediate-risk, even though the evidence remains less solid than that supporting the use of moderate hypofractionation in these groups of risk [9].

A review of studies conducted between 2001 and 2018 evaluating genitourinary, gastrointestinal, and sexual effects in patients treated with SBRT has recently been published [10], describing a relationship between dose received and genitourinary and gastrointestinal toxicity. However, there are few studies that examine the possible relationship between erectile dysfunction and dose to organs at risk (OAR) [11].

Pending the results of biochemical control and late toxicity of PACE-B, Widmark et al. establish the bases of what could be the standard of care in patients with localized PCa, considering certain features.

3. SBRT in High-Risk Prostate Cancer

The administration of combined ERT treatments, which additionally applied a boost with SBRT, has been analyzed in a lower percentage of patients. The follow-ups in published studies have been short [12][13].

Despite the high level of available evidence of increased overall survival with ADT addition to normal and hypofractionated radiotherapy in high-risk patients, its appearance in SBRT studies with this subgroup of patients is very heterogeneous, with its use in some series being omitted [14][15], and widespread omission of ADT in published studies of intermediate-risk patients [16][17].

At this time, we cannot establish the true role of ADT or its optimal duration in high-risk patients treated with SBRT, given the lack of sufficient levels of evidence for this subgroup of patients. Regarding the optimal sequencing to administer treatment with ADT in combination with SBRT in localized prostate cancer, there are no data in published studies in which ADT is used that indicate the optimal period to start ADT treatment [18][19], using as reference the timing established in studies employing normo- or moderate hypofractionated regimens [20][21][22].

Prophylactic nodal irradiation with normofractionated radiotherapy in patients with high-risk PCa has shown an increase in bRFS and DFS rates without showing benefits in OS [23]. Three studies have analyzed prophylactic lymph node irradiation with SBRT to date, one of them prematurely halted because of high rates of genitourinary and gastrointestinal toxicity [24].

4. SBRT on Prostate Bed

Radical prostatectomy remains a standard treatment for prostate adenocarcinoma. However, up to 33% of patients will experience a biochemical relapse at follow-up [25][26].

Postprostatectomy radiotherapy includes both early adjuvant radiotherapy after surgery (ART) and salvage radiotherapy in patients with a recurrence of abnormal PSA levels after surgery (biochemical relapse). To demonstrate the viability and safety of the use of SBRT in this clinical scenario, Repka et al. [27] conducted a theoretical feasibility study of SBRT after prostatectomy based on the NTCP (Normal Tissue Complication Probability) model, using patients who had previously been treated by conventional EBRT for biochemical recurrence after prostatectomy. Using the presimulation CT, RTOG recommendations were applied to define postprostatectomy volumes, and a dose of 30 Gy was prescribed to the PTV in five fractions, corresponding to an equivalent dose in 2 Gy fractions (EQD2) of 64.3 Gy, assuming an α/β value of 1.5. The NTCP model was applied to estimate the risk of late rectal and/or bladder toxicity. According to the NTCP model, the mean of grade ≥ 2 late rectal toxicity was estimated at 0.28% (±0.03%) and of late grade 2 toxicity on the bladder neck at 0.00013% (±0.000084%), while the calculated average for the exacerbation of late urinary symptoms was 4.81% (±0.52%). The conclusion by the authors, considering the limitations of the NTCP model, is that using SBRT after surgery seems feasible and may offer a safe, convenient treatment option for patients in both the adjuvant and salvage after biochemical failure. **Table 1** shows a comparative analysis of equivalent doses in terms of EQD2 and biological effective dose (BED) with three different treatment schedules (normofractionation, moderate hypofractionation, and ultra-hypofractionation or SBRT).

Table 1. Comparison of EQD2Gy and BED figures with different radiotherapy schedules in treatment after tumor prostatectomy (α/β= 1.5 Gy) and normal late response tissues (α/β= 3 Gy).

Radiotherapy Schedules	Total Dose (Gy)	Dose/Fraction (Gy)	Number of Fractions	EQD2 ($Gy_{1,5}$)	BED ($Gy_{1,5}$)	EQD2 (Gy_3)	BED (Gy_3)
Conventional fractionation	70	2	35	70	163.3	70	116.7

Radiotherapy Schedules	Total Dose (Gy)	Dose/Fraction (Gy)	Number of Fractions	EQD2 ($Gy_{1,5}$)	BED ($Gy_{1,5}$)	EQD2 (Gy_3)	BED (Gy_3)
Moderate hypofractionation	62.5	2.5	25	71.4	166.7	68.8	114.6
Ultra-hypofractionation–SBRT	37.25	7.25	5	90.6	211.5	74.3	123.9

EQD2, equivalent dose in 2 Gy fractions; BED, biologically effective dose.

In recent years, various studies have explored the possibility of administering SBRT for treating the prostate bed (**Table 2**). Sampath et al. performed a postprostatectomy SBRT dose-escalation study up to 45 Gy in five fractions. Although 45 Gy in five fractions was safe for prostate bed SBRT, it did not improve clinical outcomes, so the authors recommend a total dose of 40 Gy in five fractions as a prescription dose [28][29]. Ballas et al. performed a phase I trial in 24 patients with three dose levels: Fifteen fractions of 3.6 Gy, 10 × 4.7 Gy, and 5 × 7.1 Gy. With a median follow-up of 1.2 years, dose-escalation showed promising results, with no patients experiencing relevant severe toxicities (grade ≥ 3) [30]. A recent phase II multicenter trial in which 30–34 Gy was administered in five fractions to the prostate bed reported its dosimetric results after applying a specific bladder and rectum filling protocol. In this study, cone-beam CT intrafraction showed that CTV volume remained stable, with minimal volumetric and dosimetric changes, although patients with 95% CTV < 93% had a higher risk of CTV intrafraction volume changes [31]. In view of the recent data from the SAKK 09/10 study [32], the dose going forward in the next few years should probably be 30 Gy in five fractions as suggested by Repka et al. [27], pending validation in future clinical trials.

Table 2. Extreme hypofractionation studies after prostatectomy.

Extreme Hypofractionation Studies after Prostatectomy	Sampath 2020		Ballas 2019	Detti 2015
N patients	3	8	15	12	16 (50% after surgery and radiation therapy; 50% after only surgery)
SBRT dose	7 Gy × 5, alternate days	8 Gy × 5, alternate days	9 Gy × 5, alternate days	7.1 Gy × 5, consecutive days	6 Gy × 5 after previous surgery and radiation therapy on alternate days 7 Gy × 5 after only surgery on alternate days
ART/SRT (%)	0/100	0/100	0/100	NE	NE

Extreme Hypofractionation Studies after Prostatectomy	Sampath 2020		Ballas 2019	Detti 2015	
Basal PSA (medium)	0.4 ng/mL	0.4 ng/mL	0.4 ng/mL	0.05 ng/mL	Surgery + EBRT: 4.9 ng/mL Surgery: 3.3 ng/mL
Concurrent Hormonotherapy (%)	0	50	40	33	Surgery + EBRT: 12.5% Surgery: 50%
TOXICITY					
GU-A	G1: 33%	G1: 37.5%	G1: 40%	G1-2: 25%	G1-2: 12.5%
GI-A	G2: 33%	G1: 37.5% G2: 37.5%	G1: 33% G2: 7%	G1-2: 8%	G1-2: 12.5%
GU-T	G3: 33%	G1: 25% G2: 25% G3: 12.5%	G1: 33% G2: 27% G3: 13%	G1-2: 12.5%	0
GI-T	G2: 66%	G1: 25% G2: 12.5%	G1: 47%	0	0

EBRT, external beam radiation therapy; ART/SRT, adjuvant radiotherapy/salvage radiotherapy; PNI, perineural invasion; CK, cyberknife; CBCT, cone-beam CT; GU-A, acute genitourinary; GI-A, acute gastrointestinal; GU-L, late genitourinary; GI-L, late gastrointestinal; NS, not specified.

Detti et al. described their experience with SBRT for isolated recurrence in the PCa bed, in which 16 patients received 30 Gy in five fractions for re-irradiation or 35 Gy in five fractions for patients without prior radiotherapy treatment. With a median follow-up of 10 months, treatment tolerance was good, and only one patient experienced grade 2 acute genitourinary and gastrointestinal toxicity [33].

5. Contribution of Endorectal Devices in Prostate SBRT

In SBRT treatments of PCa, it is important to reduce the variations and the movement of the organs at risk, to obtain greater precision. By using endorectal devices, it is possible to control the movement of the prostate and rectum, either by fixing the rectum or by separating it from the prostate, decreasing the exposure of the anterior-lateral rectal wall to high radiation dosage. Currently, there are different types of endorectal devices, and the most widely used are: Endorectal balloon (**Figure 1**), hydrogel spacer (**Figure 2**), and rectal retractor.

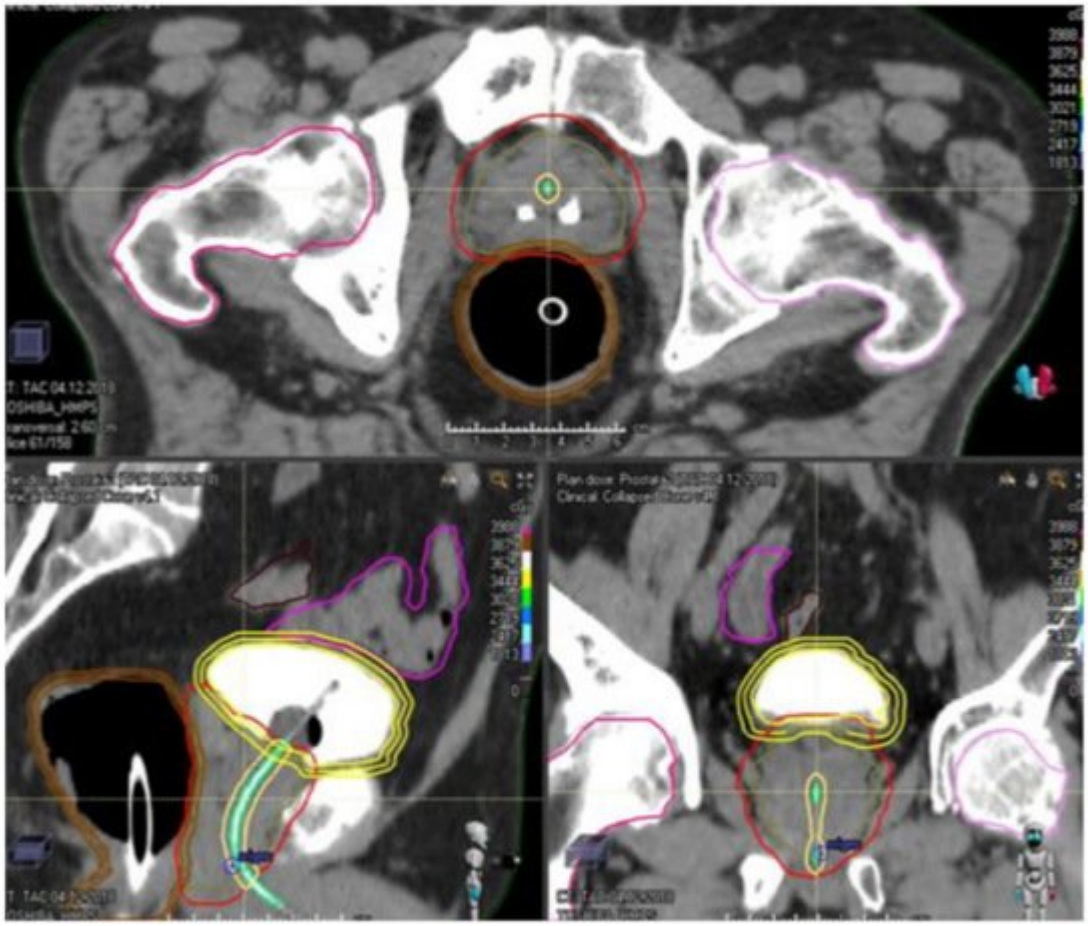

Figure 1. Endorectal balloon in the treatment of localized prostate cancer with SBRT.

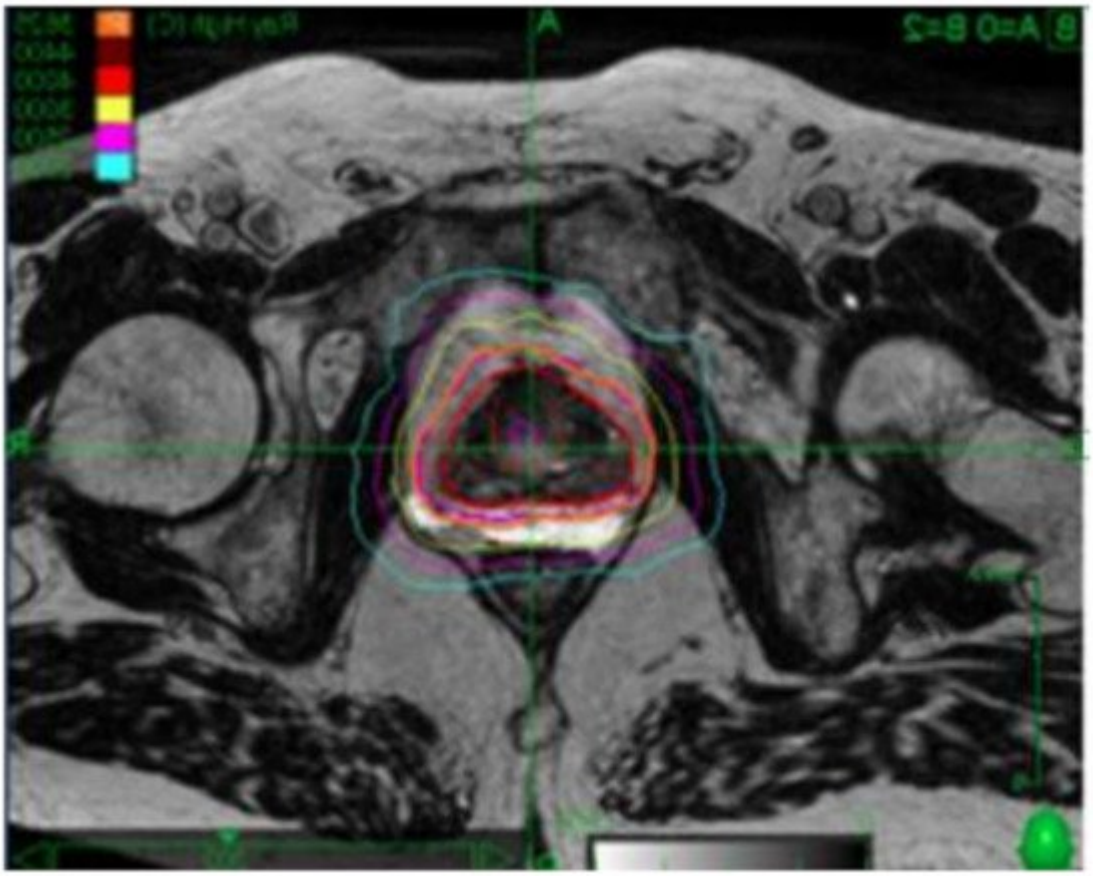

Figure 2. Hydrogel spacer in the treatment of localized prostate cancer with SBRT.

In 2017, Hamstra et al. published the results of a single-blind, randomized phase 3 clinical trial that evaluated the use of hydrogel in patients treated with IMRT. Two hundred and twenty-two patients were randomized to either placement of a hydrogel spacer or not, administering a dose of 79.2 Gy in 44 fractions to the prostate with/without seminal vesicles. The study did not meet its primary objective, which was grade 1 or greater rectal or procedural adverse events in the first six months (34.2% vs. 31.5%, $p = 0.7$), although it did show a 75% reduction in grade 1 rectal toxicity in the hydrogel spacer group ($p < 0.03$), while no grade 2 toxicity was observed in this subgroup ($p < 0.015$). Likewise, an improvement was seen in grade 1 genitourinary toxicity, along with patient-reported bowel and urinary quality of life, all favoring using the hydrogel spacer, although without differences in the dosimetric analysis of the urinary structures that would explain this improvement in urinary toxicity. It was notable the absence of any evaluation as to the reliability of patient masking in the study [34].

In 2018, the results of the dosimetric analysis of 10 patients treated with SBRT in which endorectal devices were used were published, and it enabled a reduction in the dose on the rectal wall [35], with these results later confirmed in other series [36][37][38]. More and more studies are evaluating the results of SBRT toxicity in patients in whom hydrogel spacer is used. In 2018, King et al. [39] published a small comparative study of dosimetry in treatment plans before and after the placement of hydrogel, highlighting a reduction in rectal volume that would receive 36 Gy with using hydrogel (2.6 cc on average prespacer vs. 0.3 cc postspacer, $p = 0.031$). Hwang et al. [40] published the safety and efficacy results of 50 patients treated with SBRT and hydrogel spacer with 36.25 Gy in five fractions.

With a median follow-up of 1.6 years, there was no gastrointestinal toxicity or complications associated with hydrogel spacer insertion. In another prospective study of 42 patients treated for PCa with SBRT [41], a dosimetric analysis was performed comparing patients in whom hydrogel spacer was used, noting that the maximum dose received by the rectum is lower in patients in whom hydrogel spacer was used, as well as an improvement in most rectal dosimetric parameters, these results being corroborated by other studies [42][43]. A meta-analysis, published in 2020 [44], with 1011 patients, evaluated the role of hydrogel spacer in 486 patients who had hydrogel spacer inserted. The rectal separation in the hydrogel spacer group was wide, with a median distance of 11.2 mm between the rectum and prostate, while the complications related to the placement of hydrogel spacer were mild and transient, with incidence varying between 0% and 10%, and 66% less rectal irradiation described in the hydrogel spacer group at the isodosis of 70 Gy (rectum V70) compared to the controls, (p = 0.001). This dosimetric advantage contributed to a reduction of late grade 2 or higher rectal toxicity in patients with hydrogel spacer (1.5% vs. 5.7%; p = 0.05). [45]

Finally, the rectal retractor is a rigid device that reduces variations in the rectal filling, and rectal and prostate movements. Four studies show that the use of a rectal retractor can significantly reduce intrafractional movement and dose in the rectal wall. De Leon et al. [38] evaluated the intrafraction movement of the prostate and the dosimetric impact of using a rectal retractor in 10 patients who were due to have a boost of 19 Gy in two fractions after 46 Gy in 23 fractions to the pelvis, describing a reduced anterior displacement of the base and prostate apex in the sagittal plane in the rectal retractor group ($p < 0.05$), which resulted in significant improvement in rectal wall dosimetry. Rectal retractor significantly reduced rectal V16 and V14, the maximum dose, and the percentage of the posterior rectal wall that received 8.5 Gy. Nicolae et al. [46] analyzed 20 patients treated with SBRT with a dose of 26 Gy in two fractions, once a week, in which rectal retractor was used. No patient had a displacement of greater than 3 mm, and no statistically significant differences were seen between treatment plans with and without rectal retractor for the rectal and bladder contours; the authors concluded that rectal retractor allows the safe administration of extreme hypofractionation treatments, controlling the movement of the prostate, and ensuring the reproducibility of treatment.

We must consider that most of the studies published to date have not shown any clear clinical benefit to support the routine use of endorectal devices in these patients, and this adds to existing doubts about the cost-effectiveness of the use of the devices [47] or whether the oncological results might be affected in some patients by their use. We need more studies with longer to follow up [48], to define which patients could benefit particularly from using these devices.

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