Radiotherapy and Oncology 140 (2019) 131–142

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

Stereotactic body radiation therapy with optional focal lesion ablative microboost in prostate cancer: Topical review and multicenter consensus

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ARTICLE INFO

Article history:
Received 27 February 2019
Received in revised form 13 June 2019
Accepted 14 June 2019
Available online 2 July 2019

Keywords:
Prostatic neoplasms
Radiotherapy
Stereotactic body radiotherapy
Focal boost

ABSTRACT

Stereotactic body radiotherapy (SBRT) for prostate cancer (PCa) is gaining interest by the recent publication of the first phase III trials on prostate SBRT and the promising results of many other phase II trials. Before long term results became available, the major concern for implementing SBRT in PCa in daily clinical practice was the potential risk of late genitourinary (GU) and gastrointestinal (GI) toxicity. A number of recently published trials, including late outcome and toxicity data, contributed to the growing evidence for implementation of SBRT for PCa in daily clinical practice. However, there exists substantial variability in delivering SBRT for PCa. The aim of this topical review is to present a number of prospective trials and retrospective analyses of SBRT in the treatment of PCa. We focus on the treatment strategies and techniques used in these trials. In addition, recent literature on a simultaneous integrated boost to the tumor lesion, which could create an additional value in the SBRT treatment of PCa, was described. Furthermore, we discuss the multicenter consensus of the FLAME consortium on SBRT for PCa with a focal boost to the macroscopic intraprostatic tumor nodule(s).

External beam radiotherapy (EBRT) is one of the standard treatment options for patients with prostate cancer (PCa), still the most common non-skin malignancy and an important cause of cancer-related mortality in men in industrialized countries worldwide [1]. Traditionally the prescribed radiation dose is being delivered by means of small daily fractions (1.8–2 Gray (Gy)). However, from a radiobiological point of view, PCa has a high fractionation sensitivity. While most cancers typically have a high α/β ratio ($\sim$10 Gy), PCa appears to have a very low α/β ratio (1–2.2 Gy), which is even lower than that of the surrounding organs at risk (OARs) such as the rectum [2]. Hypofractionated regimens, either moderate (2.4–3.4 Gy per fraction) or extreme/ultra- ($\geq$5 Gy per fraction) hypofractionation delivered by stereotactic body radiotherapy (SBRT), can thus be used to escalate the biologically effective dose, potentially improving disease control while maintaining current levels of toxicity [3]. Furthermore, several studies are investigating the safety of physical dose-escalation in SBRT for PCa. Whereas whole-gland dose-escalation up to 40 Gy in 5 fractions seemed to be well tolerated without severe urinary or rectal toxicities [4], whole-gland dose-escalation up to 50 Gy was associated with greater rectal and urinary toxicity [5].

In addition to dose escalation by hypofractionation, adding a focal boost to the tumor may improve disease control since local recurrences still occur and most often are situated at the location of the primary tumor prior to treatment [6]. Since in focal boosting trials the dose is being escalated only to the macroscopic intraprostatic tumor nodule(s) instead of the whole prostate gland, the toxicity profile might be more favorable as compared to whole-gland dose-escalation. Using hypofractionated SBRT in conjunction with focal tumor boosting one could combine the potential advantages of both strategies.

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https://doi.org/10.1016/j.radonc.2019.06.023
0167-8140/

Besides the theoretical radiobiological benefit of SBRT for PCa, the use of prostate SBRT significantly reduces the number of treatment fractions and consequently hospital visits, thereby having a major impact on patients' quality of life (QoL) during treatment. Additionally, fewer treatment sessions in general will be more resource-effective.

Based on recent trial results, there is a rising interest to implement SBRT for early stage PCa as standard of care in the majority of radiotherapy centers in Europe during the next years, in particular for low and intermediate risk disease. Furthermore, depending on the trial results of SBRT for high risk PCa at five year follow-up, it could be expected that SBRT with or without focal boosting for PCa will be introduced. Despite this trend toward more SBRT for PCa in daily clinical practice, there exists significant variability in the equipment used, the methodology of planning, the treatment delivery and the patient follow-up schedules. This high variability can be explained by the continuous progress in new radiotherapy techniques and the rapid implementation of these new techniques.

The aim of this report is to provide relevant information for implementing SBRT with optional focal boosting for patients with PCa. For this purpose we have summarized current literature in a topical review, supplemented with a multicenter consensus from the FLAME-consortium concerning focal boost dose escalated prostate SBRT.

Methods

To synthesize the results, used treatment strategies and equipment of clinical trials on prostate SBRT with and without focal dose escalation on the dominant intraprostatic lesion(s), we performed a topical literature search in MEDLINE (Pubmed). Following search terms were used: "Prostatic Neoplasms [MESH Terms]" and "Stereotactic Radiation Therapy [MESH Terms]". The last literature search was performed on October 25, 2018. The search included meeting abstracts and was restricted to reports available in English. After abstract screening, relevant articles, abstracts, and review articles on prostate SBRT were selected. Furthermore, new relevant articles found in the references of the retracted articles were also retained for the development of this topical review. To summarize the current evidence on SBRT trials for PCa, 40 or more patients needed to be included into the clinical trial. We used a cut-off of at least 40 included patients for trial selection, based on the first published clinical trial results of extreme or ultra-hypofractionation for PCa in which 40 patients were included [7]. Furthermore, the treatment must have been delivered in $\geq$5 Gy per fraction, according to the ASTRO-ASCO-AUA evidence-based guideline [8]. The flowchart of literature search is shown in Fig. 1. Furthermore, a synthesis of multiple articles on current and emerging treatment strategies and techniques for prostate radiotherapy is included in this topical review. To synthesize, share and summarize the multiple institutions' consensus of the FLAME consortium, we convened a group of experts in PCa, SBRT and focal boosting existing out of radiation oncologists (KH, FP, RJS and LK) and medical physicists (UVH, HDB, TD and MKB).

Topical review

SBRT trials

Schedules, toxicity and outcome

Prospective studies of extreme or ultra-hypofractionation have been published, with follow-up ranging from 11 months to 63 months. So far, excellent control rates for low and intermediate risk PCa were achieved by multiple phase II and some phase I trials [7,9–32]. Doses ranging from 32 to 50 Gy with varying doses per fraction from 6.7 to 10 Gy have been employed. The most common used dose schemes in clinical trials were 35 Gy and 36.25 Gy in 5 fractions. The dose was prescribed to 95% of the planning target volume (PTV) in 16 of the 21 trials that reported on prescription. The equivalent doses at fraction of 2 Gy (EQD2), calculated using the linear quadratic model with an α/β ratio of 1.5 Gy for PCa, are 85 Gy and 90 Gy when 35 Gy and 36.25 Gy respectively, are delivered in 5 fractions [33]. Biochemical relapse free survival rates for low and intermediate risk PCa patients vary from 90% to 100%, depending on their risk group, used treatment schedule and duration of follow-up. Acute grade $\geq$ 2 genitourinary (GU) or gastrointestinal (GI) toxicity rates range between 0% and 33.3%. Late grade $\geq$ 2 GU or GI toxicity rates vary between 0% and 33.4%. Recently, Widmark et al. presented the results of the first randomized phase III trial investigating SBRT for PCa, called HYPO-RT-PC trial. They demonstrated that extreme hypofractionated radiotherapy, delivering 42.7 Gy in 7 fractions (EQD2 = 93 Gy; α/β = 1.5) is non-inferior to conventional fractionated radiotherapy for men with intermediate risk PCa in terms of 5-year biochemical and

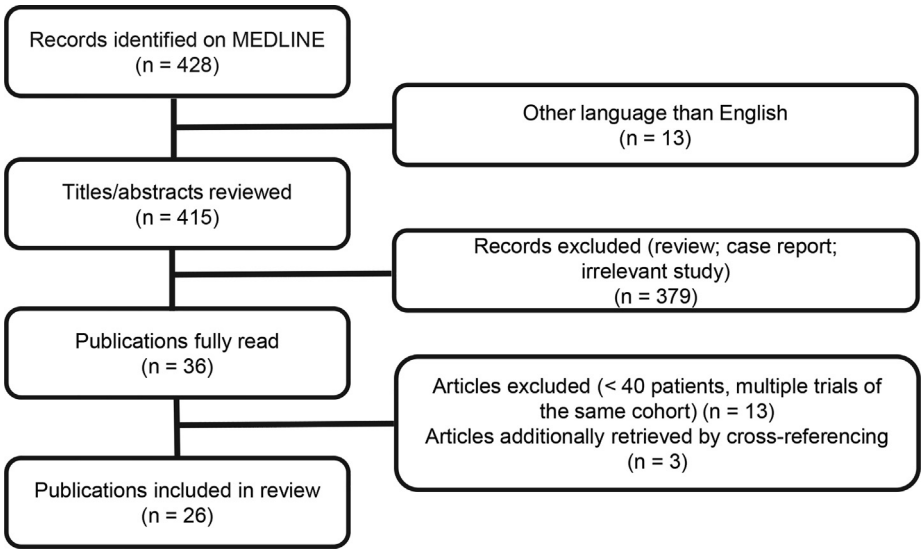

Fig. 1. Flowchart of study selection.

clinical disease free survival. The incidence of GU and GI adverse events grade 2 or worse was also comparable between both groups at 2, 4 and 6 years of follow-up [34,35]. More details about multiple phase I and II trials investigating SBRT for PCa and one phase III trial are depicted in Table 1.

Other phase III trials on SBRT for PCa, the HEAT trial (NCT01794403) and NRG GU005 trial (NCT03367702), are ongoing and will offer further insight into the efficacy of SBRT. Furthermore, the phase III PACE-A trial (NCT01584258) is currently assessing whether SBRT offers therapeutic benefit in comparison to prostatectomy or standard radiotherapy for early stage PCa [36]. Results of the PACE-B trial (NCT01584258), focussing on localized PCa patients and radiotherapy only, were reported as an abstract by Van As et al. [37]. Similar rates of acute GI and GU toxicity were shown for SBRT compared to conventionally fractionated or moderately hypofractionated external beam radiotherapy. The role of SBRT for high risk PCa is less well studied. However, several trials are currently investigating SBRT in cohorts of patients with high risk disease (NCT02296229; NCT01976962; NCT01584258 (PACE-C trial); NCT02145494 (SPARC trial); NCT02853110 (hypo-FLAME trial)). According to the ASTRO-ASCO-AUA evidence-based guideline, extreme hypofractionated or ultrahypofractionated prostate SBRT may be offered to low risk PCa patients as an alternative to conventional fractionated regimens and to intermediate risk PCa patients as part of a clinical trial or multi-institutional registry [8]. Further implementation of prostate SBRT into the international guidelines can be expected in the coming years based on the HYPO-RT-PC trial, especially when these promising results will be confirmed by other ongoing clinical phase III trials [38,39]. The question raises how far the number of fractions with SBRT can be reduced. To our knowledge, the ONE SHOT trial (NCT03294889) is the first phase I/II trial assessing the efficacy and safety of a single-dose SBRT treatment, aiming to include more than 40 patients [40].

Table 1
Overview of published phase III and phase I/II trials for prostate SBRT.

	Patient cohort	Risk group			Dose per fraction	n	Schedule	Follow-up (Median) (months)	bRFS	Acute G2+ toxicity		Late G2+ toxicity	
		L	I	H						GU	GI	GU	GI
Randomized Phase III trials prostate SBRT without boost													
Widmark et al. [35]	1200		x		2 Gy	39	Daily	59.7	83.8%	22.8%	5.3%	3.5%	2.3%
					6.1 Gy	7	2.5 weeks		83.7%	27.6%	9.4%	2.5%	1.2%
Van As et al. [37]	874	x	x		2 Gy/ 3.1 Gy	39/ 20	Daily/ 4 weeks	3.0	NA	27.2%	12.1%	NA	NA
					7.25 Gy	5	1–2 weeks	3.0	NA	23.2%	10.1%	NA	NA
Phase I/II trials prostate SBRT without boost													
Madsen et al [7]	40	x			6.7 Gy	5	Daily	41.0	90%	23.0%	13.0%	20.0%	7.0%
Friedland et al* [9]	112	x	x		7 Gy	5	Daily	24.0	97%	0.0%**	0.0%**	0.0%**	0.8%**
King et al [10]	67	x			7.25 Gy	5	Daily/EOD	32.4	94%	NA	NA	8.5%	2.0%
Boike et al [11]	15	x	x		9 Gy	5	Daily	30.0	100%	27.0%	0.0%	13.0 %	7.0%
	15				9.5 Gy	5		18.0	100%	7.0%	27.0%	20.0%	7.0%
	15				10 Gy	5		12.0	100%	33.0%	7.0%	7.0%	7.0%
McBride et al [12]	45	x			7.25 Gy/7.5 Gy	5	OTT = 10 days	44.5	100%	19.0%	7.0%	19.5%	12.0%
Loblaw et al [13]	84	x			7 Gy	5	Weekly	55.0	98%	20.0%	10.0%	5.0 %	8.0%
Katz et al*,† [14]	304	x	x	x	7 Gy/7.25 Gy	5	Daily	60.0	97% (L); 90.7% (I); 74.1% (H)	4.6%	3.6%	9.9%	4.5%
Bolzicco et al [15]	100	x	x	x	7 Gy	5	Daily	36.0	94.4%	12.0%	18.0%	4.0%	1.0%
Fuller et al [16]	79	x	x		9.5 Gy	4	NA	60.0	100% (L); 92% (I)	10.0%	0.0%	15.0%	1.0%
Hannan et al [17]	91	x	x		9 Gy	5	NA	54.0	98.6%	33.3%	6.7%	20.0%	0.0%
					9.5 Gy	5				6.7%	26.7%	33.4%	6.7%
					10 Gy	5				23.0%	24.6%	24.6%	27.9%
Lee et al [18]	45	x	x	x	7.2 Gy	5	Daily/EOD	63.0	89.7%	4.4%	4.4%	8.8%	4.4%
Chen et al* [19]	100	x	x	x	7 Gy/7.25 Gy	5	EOD	27.6	99%	25.0%	1.0%	18.0%	0.0%
Kang et al* [20]	44	x	x	x	8 Gy/8.5 Gy/9 Gy	4	Daily	40.0	100% (L); 100% (I); 90.8% (H)	13.6%	9.1%	6.8%	11.4%
Oliai et al* [21]	70	x	x	x	7 Gy/7.25 Gy/ 7.5 Gy	5	Daily	31.0	94.4%	23.0%	4.0%	32.0%	9.0%
Tree et al* [22]	51	x	x	x	7.25 Gy	5	EOD	14.5	NA	26.0%	14.0%	NA	NA
D'Agostino et al [23]	90	x	x		7 Gy	5	EOD	28.0	97.8%	32.2%	5.5%	2.2%	0.0%
Rucinska et al [24]	68	x	x		6.7 Gy	5	Median OTT = 15 days	24.0	NA	36.8%	10.3%	11.8%	4.4%
Boyer et al [25]	60	x	x		7.4 Gy	5	EOD	27.6	NA	25.0 %	5.0%	6.7%	10.0%
Koskela et al* [26]	240	x	x	x	7 Gy/ 7.25 Gy	5	EOD	23.0	95.4%	1.4%	0.4%	10.5%	4.1%
Miszczyk et al* [27]	400	x	x		7.25 Gy	5	EOD	15.0	97.8%	6.5%	2.0%	2.5%	1.2%
Katz et al*,† [28]	230	x			7 Gy/7.25 Gy	5	Daily	108.0	93%	0.0%**	0.0%**	12.0%	4.0%
Jackson et al [29]	66	x	x		7.4 Gy	5	Median OTT = 17 days	36.0	100%	23.0%	4.0%	9.0%	5.0%
Alongi et al [30]	52	x	x		7 Gy/ 7.5 Gy	5	EOD	34.0	98%	10.0%	2.0%	4.0%	4.0%
Meier et al [31]	309	x	x		8 Gy	5	Median OTT = 8 days	61.0	97.2%	26.0%	8.1%	13.3%	2.0%
Phase I trial prostate SBRT with simultaneous integrated boost													
Aluwini et al [32]	50	x	x		9.5 Gy + 11 Gy (SIB)	4	EOD	23.0	100%	23.0%	14.0%	16.0%	3.0%

Abbreviations: SBRT: stereotactic body radiation therapy; L: low risk; I: intermediate risk; H: high risk; d: dose per fraction; n: number of fractions; bRFS: biochemical relapse free survival; G2+: ≥grade 2 toxicity; GU: genitourinary; GI: gastrointestinal; Gy: Gray; EOD: every other day; NA: not available; OTT: overall treatment time; SIB: simultaneous integrated boost.

* Retrospective analysis of prospectively collected data.

** Grade 3 toxicity instead of ≥grade 2 toxicity, grade 2 toxicity is not reported.

† Low risk subpopulation 10 year ([28]) <cohort [14]).

Apart from the most optimal dose schedule, the impact of shortening the overall treatment time (OTT) in extreme hypofractionated regimens on disease free survival is currently under investigation as well. King et al. showed there was less rectal toxicity in patients treated each other day compared to consecutive daily treatment [41]. Recently, Quon et al. published their results on the impact of the OTT on toxicity and QoL, based on a randomized phase II study (PATRIOT-trial) [42]. They compared SBRT (5 fractions; 40 Gy) once per week vs. every other day with the OTT varying between 9 and 12 days in the every other day group. Acute urinary and bowel QoL were worse in the group treated every other day. Zilli et al. showed similar tolerance and toxicity profiles, using an urethra-sparing planning technique for both 9 and 28 day OTT schedules with a minimum follow-up of 18 months [43]. Further investigation of the optimal OTT regarding treatment outcome, toxicity and patient comfort remains necessary.

Simultaneous with the gaining interest in prostate SBRT, the introduction of (multiparametric) magnetic resonance imaging ((mp)MRI) primarily aimed to achieve a more accurate local tumor staging, has provided the opportunity to delineate intraprostatic tumor nodules for focal boosting. In the conventional fractionated treatment setting, both the phase III FLAME [44] and HEIGHT (NCT0141132) trial investigate the benefit of focal boosting, delivering a gross tumor volume (GTV) boost of 95 Gy with whole prostate gland doses of 77 Gy and 76 Gy, respectively. Toxicity results are already available for the FLAME trial and show no increase in GU and GI toxicity up to 2 years after treatment in the boosted group relative to the standard treatment group [45]. Today, this focal boosting strategy is also under investigation in multiple phase II trials with extreme hypofractionated treatment schedules. Aluwini et al. boosted 17 patients to the MRI-defined tumor in four 11 Gy-fractions [32]. Herrera et al. [46] performed a phase Ia/Ib trial of 36.25 Gy in 5 fractions to the whole prostate gland while simultaneously boosting the visible dominant intraprostatic lesion up to 45 Gy, 47.5 Gy, and 50 Gy in five fractions. Dose escalation to 50 Gy on the dominant intraprostatic nodule was tolerable and determined as the recommended phase Ib dose. Furthermore, the phase II multicenter hypo-FLAME study (NCT02853110) investigates whether SBRT of 35 Gy in 5 weekly fractions with an additional integrated focal boost up to 50 Gy to the MRI-visible tumor volume is feasible and safe. In addition to this Dutch/Belgian phase II trial, two Canadian trials investigate the feasibility and safety of MRI-based boosting in two different treatment settings. On the one hand, the 2SMART-trial (NCT03588819) by Loblaw et al. tests MRI-based boosting when delivering SBRT in 2 fractions, delivering 26 Gy to the whole prostate gland and 32 Gy to the intraprostatic tumor nodule(s). On the other hand, MRI-based focal boosting combined with a pelvic irradiation is performed in a 5-fraction schedule delivering up to 50 Gy to the intraprostatic tumor, 35 Gy to the whole prostate gland and 25 Gy to the pelvic lymph node regions. This trial is currently being extended as a multicenter trial named the 5STAR-PC-trial (NCT02911636).

In addition to the outcome data, which suggest at least equivalent efficacy and toxicity of SBRT to conventional fractionated EBRT for selected patient groups [47], different studies found SBRT a more cost-effective treatment strategy compared to standard EBRT [48,49].

Patient selection

All patients included in the aforementioned trials were newly diagnosed, biopsy proven, mainly low and intermediate risk PCa patients without evidence of lymph node or distant metastases. The cut-off of the International Prostate Symptom score (IPSS) for patient exclusion varied between the different mentioned trials, ranging from non-defined to 15. Furthermore some trials excluded patients who had prior transurethral resection of the prostate (TURP), prior radiotherapy, severe comorbidities, hip prostheses, or a bleeding risk which hampers safe fiducial marker insertion. Patients who were not eligible for MRI scans due to several reasons (e.g. gadolinium allergy, MRI-incompatible devices, claustrophobia) were excluded for all trials investigating focal boosting strategies for prostate SBRT [32,46].

Treatment techniques

To date, most of the clinical trials related to prostate SBRT used the CyberKnife (CK) (Accuray Inc, Sunnyvale, California) non-coplanar robotic SBRT platform (16 out of the 26 retained trials). However, over the last few years, there is a gradual shift toward conventional C-arm linacs with many trials opting for intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) (10 out of the 26 retained trials). Indeed, the results of comparative treatment planning studies between CK, IMRT [50,51] and VMAT [52,53] showed that all treatment techniques were capable to create highly conformal dose distributions. In addition, both IMRT and particularly VMAT have reduced treatment times compared to CK and are more widely available. The use of high dose rate flattening filter free (FFF) beams could further reduce this treatment time (2 out of the 26 retained trials) [54].

Proton therapy, as compared to conventional photon therapy, holds great potential in terms of normal tissue toxicity due to its more favorable dose-depth characteristics. Indeed, the sharp localized high dose delivery at the Bragg peak could allow for further focal dose escalation with proton therapy compared to photon therapy. However, this potential is not yet fully exploited due to the lack of advanced online image-guidance [55] and suboptimal choice of beam orientations [56]. Most proton treatments use two lateral opposing beams where the protons travel through a large amount of tissue and the femoral heads. This causes an increase in range uncertainty and a considerable degradation of the lateral penumbra limiting the sparing of surrounding organs. Anterior-oriented beams could in theory limit the high-dose exposure to the rectum but are highly susceptible to interfractional anatomy variations [57,58]. Hence, there is still room for technological improvements before the full potential of proton therapy will be reached [59]. Furthermore, there remains uncertainty about the relative biological effectiveness (RBE) of protons for prostate cancer [60]. Currently, a constant value of 1.1 is used in proton treatment planning. However, there is increasing evidence that the RBE of protons varies with the proton energy (through the linear energy transfer (LET)), the dose per fraction and the radiosensitivity of the tissue (i.e., the α/β ratio) [61]. More specifically, experimental data indicate that the RBE decreases with increasing dose per fraction [62]. The magnitude of this effect depends on the α/β ratio of the tissue, with prostate tumors showing a larger effect [63]. The impact of a variable RBE on prostate fractionation was addressed using theoretical models and was shown to be of less importance for the hypofractionated schedules compared to a conventional fractionation schedule [64]. Nevertheless, given the remaining uncertainty on the proton RBE, care must be taken when comparing the results of proton therapy to photon therapy [65].

Delineation

Accurate delineation of the prostate gland and nearby OARs is crucial, as a treatment plan is created based on these contours. Due to the use of narrow margins and a sharp dose fall-off in SBRT treatments, the precision of the delineation for extreme hypofractionated treatments is of utmost importance. The contouring definitions for SBRT prostate are similar to the definitions which are used in conventional radiotherapy treatments. For target

delineation of the prostate gland, seminal vesicles and rectum, ESTRO ACROP formulated recently a consensus guideline on computed tomography (CT)- and/or MRI-based target volume delineation for primary radiation therapy of localized PCa [66]. Furthermore, the Radiation Therapy Oncology Group provides an additional guideline for pelvic normal tissue contouring [67].

Specific guidelines on contouring of intraprostatic tumor lesions based on mpMRI or prostate specific membrane antigen (PSMA) positron emission tomography (PET) for radiation treatment are not yet available. However, an acceptable correlation between the delineation of intraprostatic lesions on mpMRI and histopathologic proven tumor on histopathology was found [68,69]. In a study by Steenbergen et al., it was shown that 6 teams, each consisting of a radiation oncologist and a radiologist, all detected 18 out of 20 histopathology-proven dominant intraprostatic lesions on mpMRI [68]. Currently, the PI-RADS v2 provides the best available clinical guideline for the interpretation of mpMRI images and the detection and delineation of dominant intraprostatic lesions [70]. According to this guideline, the detection of prostate lesions is based on T2 weighted (T2w), diffusion weighted (DWI) and, with a decreased relevance since the updated version 2 (2015), dynamic contrast enhanced (DCE) images. Furthermore, verification of the boost delineation by a tumor prediction model could create an added value for quality assurance of the intraprostatic tumor delineation [71–73]. Regarding PSMA PET/MRI, Zamboglou et al. recently reported a sensitivity and specificity of 75% and 87% to detect intraprostatic tumors on PSMA PET. For mpMRI a sensitivity and specificity of respectively 70% and 82% was reported [74]. Although there is high accuracy in the detection of PCa on PSMA PET and mpMRI, the lack of available guidelines leads to inter-institutional differences in the interpretation of mpMRI for delineation [68,73].

Motion management

Prostate motion

The mobility of the prostate is known as a potential source of error during radiotherapy. Its complex and unpredictable nature has been described extensively [75]. Inter-fraction prostate motion occurs predominantly in the sagittal plane and has a substantial rotational component with a systematic and random lateral rotation of 5.3° and 4.9° respectively [76]. Lateral rotations up to 30.7° were described for certain extreme cases. These rotations are driven by variations in rectal filling which cause mainly prostate motion in the anterior–posterior (AP) direction, causing a rotation due to the tethering of the prostate to the pelvic floor muscles at the apex [77,78]. The significance of these rotations increases within the context of focal boosting due to the localized high boost dose delivered inside the prostate [79]. In addition, prostate rotations may limit margin reduction as margins up to 3 mm may be required to account for rotations of up to 5° [80].

Of similar concern is the unpredictable intra-fraction motion of the prostate. Using an electromagnetic tracking system, Kupelian et al. observed displacements $\geq$3 mm or $\geq$5 mm for cumulative durations of at least 30 s during 41% and 15%, respectively, of the monitored sessions [81]. In individual patients, up to 56% of fractions had displacements $\geq$5 mm. Substantial intra-fraction rotation occurs as well. Huang et al. reported a lateral rotation >5° for 35% of the time during a double-arc VMAT treatment of approximately 2.5 min [82]. Lateral rotations up to 30° were observed for certain extreme cases.

There are two general types of intra-fraction motion [83,84]. The first is a slow continuous drift, mainly posteriorly and inferiorly with a lateral rotation around the apex, which does not resolve spontaneously within the timescale of a treatment fraction. This motion is likely to be caused by pelvic muscular relaxation, rectal content that gradually moves away from the prostate area and changes in the bladder volume. The second type of intra-fraction motion is a sudden transient change in the anterior rectal wall position causing an anterior superior displacement and deformation at the midposterior level of the prostate. This unpredictable motion often resolves spontaneously and is the result of peristaltic motion. It occurs mostly in patients with a filled rectum [83].

As each fraction of an SBRT treatment represents approximately 20% of the total dose, the consequences of a "geographic" miss are more dramatic. Additionally, intra-fraction motion increases with time, predominantly during the first few minutes of treatment [85]. The probability of prostate movements >3 mm is approximately 10% after 5 min but increases to above 20% after 10 min of treatment [84,86]. The increased treatment time, necessary to deliver the high dose per fraction characteristic of SBRT, thus increases the probability that significant motion occurs during treatment delivery.

Besides time, rectal filling also predicts the occurrence of prostate motion. Patients whose rectum is filled with gas show more prostate displacements than patients with an empty rectum [87]. For instance, Ghilezan et al. found in a cine-MRI study that the midposterior level of the prostate has a standard deviation (SD) of 1.72 mm compared to 0.79 mm in case of a full and empty rectum, respectively [83]. Moreover, the probability for this point of interest to move >3 mm reaches 10% within a time frame of 1 minute for a full rectum as opposed to 20 min for an empty rectum.

Furthermore, seminal vesicles experience substantial intra-fraction motion as well. Displacements in the superior–inferior (SI) direction are significantly larger for seminal vesicles than for the prostate. In addition, the prostate and seminal vesicle centroids do not move in unison in real time in the majority of patients [85]. This should be taken into account when simultaneously treating the seminal vesicles using motion mitigation techniques that focus solely on the prostate displacement as this is not a reliable surrogate for seminal vesicles displacement.

Treatment margins

The quantification of inter- and intra-fraction prostate motion allows to determine treatment margins based on expansion recipes [88]. The majority of clinical SBRT trials uses a 3 mm margin in the posterior direction and 5 mm in other directions (15 of the 24 retained trials that reported on margins). Note that almost all of these trials used CK and its automated marker tracking system to mitigate intra-fraction prostate motion (12 out of 15). A study investigating prostatic displacement using pre- and post-treatment orthogonal images during VMAT delivery found that margins of 2.6 mm lateral (LR), 3.2 mm SI and 3.9 mm AP were necessary to account for intra-fraction motion [89]. The average time of treatment delivery for a given fraction was 195 ± 59 s. Larger margins for the seminal vesicles might be necessary when being treated simultaneously due to its more mobile nature, especially when treatment localization is limited to the prostate only [85,90].

Bowel and bladder preparation

As previously mentioned, rectal filling is, next to time, the most important variable causing prostate motion in the AP direction [91]. Recommendations for bowel preparation were given in 13 of the 26 retained SBRT trials (Table 1), whereas bladder preparation was mentioned in 6 studies. The other trials did not report a specific preparation protocol. In general patients were treated with an empty rectum and moderate, comfortably filled bladder. The used strategies for bowel preparation included dietary advices to minimize the presence of rectal gas and the use of fleet enemas. Currently, there is no evidence to recommend one rectal emptying

strategy over another based on the available literature in conventional fractionated radiotherapy [92].

Prostate immobilization and rectal sparing techniques

Given the close anatomical relationship between the prostate and the anterior rectal wall it can be hypothesized that indirect immobilization of the prostate can be achieved by stabilizing the rectum. Both endorectal balloons (ERBs) and rectal displacement devices utilize this anatomical relationship to improve intra-fraction prostate and OAR stability. In addition, both applications distend part of the rectum away from the high dose region, potentially reducing GI toxicity.

ERBs are silicon or latex devices that are filled with either air or water and are inserted into the rectum prior to each treatment fraction [93]. Using an electromagnetic tracking system, Smeenk et al. found that the cumulative percentage of 3D displacements >3 mm after ten minutes reduced from 18.1% to 7.0% when an ERB was applied [94]. Especially, in the AP direction, the ERB reduces large displacements. Furthermore, studies have suggested the potential ability of ERB to spare the rectum by distending the posterior rectal wall away from the high dose region [95]. Wortel et al. reported on the local protocol variations for IGRT in the Dutch HYPRO trial and found that patients treated with an ERB, which was applied during all radiation sessions in one of the participating centers (85 of the 572 patients), showed favorable anorectal dose distributions and a significant reduction in patient-reported GI toxicity compared to patients treated at the reference center that did not apply an ERB (242 of the 572 patients) [96]. Note, that the observed differences might be related to the changes in prostate volume and shape due to insertion of the ERB as significantly smaller prostate volumes were contoured at the center that applied an ERB compared to the reference center (−26%) [96,97]. However, the use of an ERB may introduce large inter-fraction prostate rotation and deformation due to errors in the ERB position, predominantly the depth of insertion [98]. Jones et al. reported that 69% of the fractions required insertion adjustments of the ERB to reduce the prostate rotation and deformation observed on cone beam CT (CBCT) [99]. Hence, ERB insertion should be verified prior to each treatment fraction in order to minimize ERB-induced errors.

Rectal displacement devices (RDD) aim to stabilize the prostate by fixating the rectum to the treatment couch. For this purpose, the RDD is inserted into the rectum and downward pressure is applied to displace the rectum posteriorly away from the prostate. As a consequence both the anterior and posterior rectal walls are distended away from the high dose region. Using kV X-ray intra-fraction monitoring, Legge et al. found that the AP position of the prostate was within 1 mm of its initial position for 79.1% of the treatment time (average beam-on time of 364 ± 67 s) in the presence of a RDD [100]. In addition, AP displacements $\geq$3 mm occurred only 0.8% of the treatment time. Similar results were obtained by de Leon et al. who used cine-MRI at simulation and observed a significant reduction in AP displacements for both the prostate and rectum when using a RDD compared to no RDD [101]. To compare RDD with ERB, Nicolae et al. measured the 3D prostate displacement using pre-treatment CBCT and post-treatment CBCT for patients participating in two similar mono-institutional trials. They found smaller intra-fraction displacements for patients with RDD (1.83 ± 0.75 mm) compared to patients with ERB (2.61 ± 1.50 mm) for >6-min treatment times [102].

Rectal spacers, on the other hand, aim solely to physically increase the distance from the prostate to the rectum by inserting bioabsorbable materials, such as hyaluronic acid or human collagen directly posterior to the prostate into the rectoprostatic fascia. Strom et al. found that the prostate-rectal separation increased to 12 ± 4 mm when using a hydrogel spacer compared to 4 ± 2 mm without spacer [103]. In a single-blind phase III trial using conventional fractionation, Hamstra et al. found that a hydrogel spacer was safe to apply and well tolerated and resulted in a significant rectal dose reduction [104]. This dose reduction resulted in less bowel toxicity at 15 months and a maintained or increased bowel QoL after a median follow-up period of 3 years [104]. Tissue spacers might be even more beneficial for focal boost dose escalation on lesions located in the posterior peripheral region and when high fractional doses of SBRT are used for treating PCa.

Online image guidance

All of the retained SBRT trials (26/26) used online image guidance to minimize the risk of a "geographic" miss. The majority uses intraprostatic radiopaque fiducial markers, typically gold seeds, with in-room kV X-ray imaging as this technique is low cost, easy to use, allows for fast image acquisition and has a high accuracy with limited inter-observer variability. Goff et al. reported earlier that fiducial marker-based daily image guided pre-treatment alignments are more precise in terms of the physician's ability to reproducibly align images than soft-tissue CBCT-based alignment [105]. In addition, fiducial markers allow for continuous monitoring of the prostate position using kV X-ray imaging. For example, the Cyberknife automated marker tracking system acquires stereoscopic kV images at a user-defined time interval (typically every 30–60 s) using a room-mounted X-ray system and automatically adjusts the position and orientation of the robotic manipulator during treatment fractions [80,106]. The on-board X-ray imaging system of standard-equipped linacs can also be used for marker-based monitoring of prostate motion [107,108]. However, most monoscopic images only provide the projected target position in the two dimensions of the imager plane and neglect the unresolved component parallel to the imager axis. This 2D monitoring allows for gross motion to be detected and can be used as input for beam gating, which pauses treatment delivery if the prostate motion exceeds a pre-set tolerance value followed by stereoscopic imaging and a treatment couch correction if necessary [108]. However, the treatment interruption, necessary for the acquisition of orthogonal images and the subsequent treatment couch correction, prolongs the treatment process, thus increasing the probability of prostate motion occurring during the remainder of the fraction. There are several techniques being implemented that aim to overcome the limitations of 2D kV X-ray monitoring on standard-equipped linacs and that offer real-time 3D information on the target position [109]. For example, Poulsen et al. uses a 3D Gaussian spatial probability density function to estimate the unresolved motion component and determines the 3D target position from the projected 2D positions of the markers via maximum likelihood estimation [110,111]. When three or more markers are available, rotations can be calculated using an iterative closest point algorithm to yield a 6-degree-of-freedom estimate of the prostate position [112,113]. A disadvantage of the implantation of fiducial markers is that it requires an invasive procedure that carries the risk of bleeding, infection and causes patient discomfort [114,115]. The use of liquid fiducial markers could potentially reduce patient discomfort as they can be injected using very thin needles. In addition, liquid markers showed favorable results both in terms of visibility and induced imaging artifacts for (CB)CT and mpMRI compared to solid gold markers [116].

Electromagnetic transponders (EMT) or beacons are an alternative to fiducial markers that allow both pre-treatment localization and real-time monitoring of the prostate position during treatment [117,118]. Their detection is based on electromagnetic resonance frequencies and needs no ionizing radiation in contrast to fiducial markers. A dedicated electromagnetic array that is positioned over the patient before and during treatment excites and localizes the beacon transponders using resonant radiofrequencies. This allows

to determine the real-time 3D centroid position of the prostate at a frequency of 10 Hz. Using EMT for prostate SBRT, Lovelock et al. reported that after initial setup, 1.7 interventions per fraction were required, with a concomitant increase in treatment time of approximately 65 s [119]. They observed that 10% of the patients would have a dose delivered that would not meet the clinical coverage requirement if no continuous monitoring was used despite using a 3 mm margin in the posterior direction and 5 mm in all other directions. The lack of ionizing radiation and its ability for real-time motion monitoring are advantages of this system. However, strict criteria for patient eligibility concerning metal implants and electromagnetic devices have to be followed. For patients with an excess in abdominal fatty tissue the transponders must be within a 27 cm distance from the array in order to be tracked adequately. In addition, the beacon transponders have a diameter of 1.85 mm, which requires insertion needles with a larger diameter than for regular fiducial markers.

Most standard-equipped C-arm linacs offer kV CBCT, which allow for daily visualization of the prostate and enables direct pre-treatment soft-tissue alignment with the planning CT. In addition, the volumetric images offer anatomical information concerning bladder filling and rectal distension, of which the latter can be indicative for the occurrence of prostate motion during treatment delivery [83]. However, CBCT acquisition is rather slow, with a full scan taking up to 1 minute, has limited resolution (typically 2 mm slice thickness) and is prone to inter-observer variability [120,121]. Nevertheless, the volumetric information of CBCT can be used for online adaptive radiotherapy [122]. Furthermore, the use of CBCT allows for a visual inspection of the seminal vesicle position, which is often overlooked when using fiducial markers or EMT for pre-treatment alignment.

MRI-guided radiotherapy is the latest innovation in online image guidance offering greatly improved soft-tissue contrast with respect to CBCT and allows for real-time visualization of anatomy deformations during treatment delivery, without the need for fiducial markers [123]. Two linac-based systems with on-board MRI are currently commercially available, the MRIdian (ViewRay Inc., Oakwood Village, OH, USA) and the Unity (Elekta Instrument AB, Stockholm, Sweden) [124], while two other systems are being implemented for clinical use [125,126]. In a comparison between a 0.35 T on-board MRI and kV CBCT, Noel et al. [127] found better anatomical visualization of the prostate, seminal vesicles, rectum, anal canal, bladder, colon and penile bulb on MRI. This improved anatomical information can be used for pre-treatment online adaptive workflows that mitigate the independent movement and deformation of multiple targets, such as the prostate and seminal vesicles, and anatomical changes in nearby OARs [128]. Tetar et al. reported on the clinical implementation of MRI-guided adaptive radiotherapy for 140 patients treated with prostate SBRT [129]. Re-optimization was performed in 97% (677 of 700 fractions) of all fractions. Gated IMRT delivery was performed using a 3 mm gating boundary around the CTV and the system automatically shut off radiation delivery if more than 7% of the CTV area in the sagittal cine-MRI plane was detected outside the gating boundary (which corresponds with the PTV). Treatment interruption and the application of 2D shifts were observed in more than 20% of all delivered fractions (149 of 700 fractions) and repeated 3D imaging was necessary in 6% of fractions (39 of 700 fractions). On average, 45 min was required for recontouring, re-optimization and quality assurance. In addition, the ability to perform on-board functional imaging, e.g. DWI, is of special interest for focal boosting as it allows to perform biology-driven dose painting of the macroscopic tumor or areas of more aggressive disease prior to each treatment fraction [130–132]. Multicenter MRI-guided prostate radiotherapy studies in a large research consortium are currently being performed with a 1.5 T MRI-linac system [128].

The ultimate goal of online motion management is to perform active motion mitigation during treatment delivery. In a multi-institutional study by Colvill et al., improved dose accuracy was reported, regardless of the technique (robotic, gimbaled, MLC or couch tracking), with real-time adaptation significantly outperforming non-adaptive delivery methods [133]. Most retained studies (16/26) used the Cyberknife automated marker tracking system to automatically compensate for small translations and rotations by adjusting the position and orientation of the robotic manipulator during treatment delivery. Tracking on conventional C-arm linacs can be performed by the MLC or by the treatment couch [134–136]. However, only MLC tracking has been clinically implemented, showing promising results in terms of geometric accuracy and target coverage [137,138]. Results of the TROG 15.1 SPARK trial, which investigates the targeting accuracy and treatment outcome of real-time adaptive prostate SBRT on a conventional linac using kV X-ray intra-fraction monitoring, were presented as an abstract by Keall et al. [139]. Real-time motion correction (beam gating or MLC tracking) improved the dose distribution to both the prostate and the rectum in 72% of the motion-corrected fractions (87 of 121 fractions) with the prostate dose (D95%) and rectum dose (V30Gy) being closer to the planned dose by an average of 4.6% (range −1.7% to 41%) and 1.5% (range −1.2% to 9.7%) respectively. In addition, real-time motion-including 4D dose reconstruction methods can be used for online treatment verification and to determine the actual delivered dose during adaptive RT [140,141]. It is important to note that robotic, MLC and treatment couch tracking only correct for the rigid motion of the prostate and thus neglect seminal vesicles displacement and prostate, rectum and bladder deformations. But, the real-time visualization of anatomy deformations offered by MRI-guided radiotherapy could enable intra-fraction plan adaptation based on incoming images of the current anatomy state [142,143].

Follow-up

Based on toxicity patterns of patients treated with moderate and extreme hypofractionated radiotherapy, acute toxicity reaches its maximum sooner in hypofractionated regimens compared to conventional fractionated treatment regimens [144–146]. Furthermore, benign PSA bounces are described after SBRT in a number of trials [14,19,41,147]. A benign PSA bounce is described as a PSA rise of 0.2 ng/mL or more above its previous nadir with a subsequent decline to that nadir or lower. The incidence of benign PSA bounces varied from 17% to 31% with a median PSA bounce of 0.5 ng/mL. The median time to PSA bounce was 17 months (9 months–30 months). Younger age was found as a predisposing factor for PSA bouncing [147].

Multicenter consensus within the FLAME consortium

Within the multicenter hypo-FLAME trial (NCT02853110; collaboration between the UMC Utrecht, NKI-AvL Amsterdam, UZ Leuven and Radboudumc Nijmegen), SBRT 35 Gy in 5 fractions with a simultaneous integrated boost up to 50 Gy to the visible intraprostatic tumor(s) is performed for intermediate and high risk PCa patients. We here summarize our consensus about this focal boosting SBRT strategy.

Since MRI is required for contouring of the target volume and boost GTV [66], SBRT with focal boosting for PCa is not possible for patients who are not eligible for MRI scans. Furthermore, patients with significant urinary obstruction symptoms (IPSS $\geq$ 15), or with a history of a TURP are not ideal candidates for a SBRT treatment, due to expected increased urinary severe toxicity. For those patients who are not eligible for prostate SBRT, we

recommend a conventional fractionated or moderately hypofractionated treatment schedule.

All FLAME-members perform transperineal or transrectal implantation of three or four gold seed fiducial markers under TRUS prior to radiotherapy simulation. For simulation and planning purposes, CT and MRI are registered based on the fiducial markers. Patients are asked to have a comfortably full bladder. At one out of the four participating centers a rectal balloon was used. Furthermore, at the other centers, in case of an extremely full rectum on CBCT, patients were advised to empty their bowel or use microklysms. All FLAME-members base the detection and delineation of prostate lesions on mpMRI (T2w, DWI and DCE images) [73]. Collaboration with an experienced uroradiologist is recommended. For target delineation of the whole prostate gland, the ESTRO ACROP guideline on CT- and MRI-based target volume delineation for primary radiotherapy of localized PCa is applied [66]. The prostate CTV includes the whole prostate gland and incorporates a 4 mm margin surrounding the delineated intraprostatic lesion(s) (GTV), excluding OARs. Contouring and inclusion of the seminal vesicles into the target volume is a decision based on tumor characteristics [148]. If the seminal vesicles are included in the target volume without visualized seminal vesicle invasion on mpMRI (<cT3b), we create a second, seminal vesicle CTV. OARs are delineated based on the RTOG consensus guidelines [67]. Dose constraints, based on the pHART6 and pHART7/PATRIOT study (Sunnybrook Hospital) [149,150] and the hypo-FLAME trial, and target volume dose prescriptions of the hypo-FLAME trial are summarized in Table 2. Currently, we treat our trial patients once weekly, however, further investigation of the most optimal OTT regarding treatment outcome, toxicity and patient comfort is needed.

Table 2
Overview of the target volume dose prescriptions and dose constraints for the hypo-FLAME study.

Structure	Volume	Expected dose
CTV prostate		
	≥99%	35 Gy
PTV prostate		
	≥99%	33.25 Gy
GTV focal boost		
	≥99%	35 Gy; aimed up to 50 Gy*
CTV seminal vesicles		
	≥99%	30 Gy
PTV seminal vesicles		
	≥99%	30 Gy
Rectum		
	<1 cc	38 Gy
	<2 cc (if possible < 1 cc)	35 Gy
	≤15%	32 Gy
	≤20%	28 Gy
	0.035 cc (=D_{max})	<40 Gy
PRV rectum		
	0.035 cc (=D_{max})	<42 Gy
Urethra		
	0.035 cc (=D_{max})	<42 Gy
PRV urethra		
	0.035 cc (=D_{max})	<42 Gy
Bladder		
	<1 cc	42 Gy
	<5 cc	37 Gy
	≤15%	32 Gy
	≤20%	28 Gy
Penile bulb		
	≤90%	20 Gy
Femoral head and neck		
	≤5%	28 Gy
Small bowel		
	<5 cc	19.5 Gy
	0.035 cc (=D_{max})	35 Gy

Abbreviations: CTV: clinical target volume; PTV: planned target volume; GTV: gross tumor volume; Gy: Gray; D_{max}: maximum dose; PRV: planning organ at risk volume.

* GTV focal boost is aimed to receive up to 50 Gy, as long as the normal tissue constraints [137,138] are not at risk by adding this focal boost.

Treatment delivery is performed on conventional C-arm linacs using dual-arc VMAT with photon energies >6 MV. Based on earlier results for the prostatic displacements observed during VMAT delivery by Gladwish et al., an isotropic CTV-to-PTV treatment margin of 4 mm is used [89]. To limit high dose exposure to the rectum and urethra, a 2 mm isotropic planning risk volume (PRV) margin is used for both OARs. During treatment planning, additional care is taken to ensure that no hot-spots (D_{max} < 42 Gy) are located inside the PRVs (Table 2). Pre-treatment localization is performed using marker-based alignment of the gold seeds visible in orthogonal on-board kV X-ray images to minimize inter-observer variability [105] and to evaluate inter-fraction prostate rotations. After initial alignment, daily variations in the patient anatomy, especially bladder filling and rectal content, are verified using on-board CBCT. In addition, the relative position of the rectum with respect to the planned focal boost dose is evaluated for lesions located in the posterior peripheral region to avoid exposure of the rectum to the high focal boost dose. A clinical intervention is performed for patients whose rectum is filled with an excessive amount of rectal gas on the pre-treatment CBCT image to mitigate the occurrence of prostate motion during treatment [83,87]. To assess intra-fraction displacements, real-time motion monitoring or post-treatment (volumetric) imaging is performed.

We perform a closer follow-up during and shortly after treatment, as in moderate and extreme hypofractionation trials acute toxicity was shown to occur sooner than with conventional fractionation. The standard long-term follow-up protocols are comparable to conventional fractionation protocols. Specific attention is paid to the occurrence of benign PSA-bounces after extreme hypofractionation.

Conclusion

SBRT represents a valid treatment option for patients with low and intermediate risk PCa. Based on multiple phase II trials and one phase III trial, both the long-term disease free survival and safety of SBRT compare favorably with conventional or moderate hypofractionated regimens. Currently, SBRT with a focal lesion ablative microboost for PCa should be restricted to clinical trials only as 5-year follow-up data of this treatment strategy are not yet available.

Declaration of Competing Interest

None.

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