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Highly hypofractionated schedules for localized prostate cancer: Recommendations of the GETUG radiation oncology group

Ariane Lapierre, Christophe Hennequin, Amandine Beneux, Sarah Belhomme, Nicolas Benziane, Marie-Claude Biston, Gilles Crehange, Renaud de Crevoisier, Jean-luc Dumas, Maher Fawzi, Albert Lisbona, David Pasquier, Sandra Pelissier, Pierre Graff-Cailleaud, Pascal Pommier, Paul Sargos, Jean-Marc Simon, Stéphane Supiot, Florence Tantot, Olivier Chapet

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Abstract

Stereotactic body radiotherapy (SBRT) has become treatment option for localized prostate cancer but the evidence base remains incomplete. Several clinical studies, both prospective and retrospective, have been published. However, treatment techniques, target volumes and dose constraints lack consistency between studies. Based on the current available literature, the French Genito-Urinary Group (GETUG) suggests that:

- Because large prospective trials are lacking, SBRT could not be considered as a standard, but could be proposed as an option after patients have been given appropriate information and counselling
- Good candidates for SBRT are patients of the favorable or intermediate favorable groups
- 5 fractions of 7.25 Gy, for a total prescribed dose of 36.25 Gy seems both safe and effective.
- Volume of interest delineation (target volume and organs at risk) and margins, dose constraints and radiotherapy techniques that should be used are also discussed.

Keywords

Prostatic Neoplasms; Prostatic Neoplasms /radiotherapy; Radiosurgery/methods;
Radiotherapy Dosage

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Introduction

Moderately hypofractionated radiotherapy regimens are now the standard of care for patients with localized prostate cancer (PCa) [1–3]. The GETUG group has recently published recommendations on dose constraints in this setting [4]. Highly hypofractionated regimens (HHFR) have been evaluated in several retrospective and prospective phase II studies, combined in one meta-analysis [5–10], using stereotactic body radiotherapy (SBRT) techniques, with Cyberknife or Volumetric arc therapy (VMAT). So far, only two randomized trials have been published [11,12]. The first one, used seven fractions of 6.1 Gy and the more recent PCE-B trial used 7.25 Gy fractions. In both trials, there was no significant differences in toxicity between conventional (78 Gy) and highly hypofractionated schedules although the follow-up is rather short in both studies. To date, prostate SBRT cannot be considered as a standard of care, but is a valid treatment option. However, based on the large number of published series and ongoing randomized trials, prostate SBRT may soon be proven to be equivalent to conventional fractionation. This prompts the radiation oncology group of the GETUG to define the best regimen actually available and to propose some recommendations regarding its use within clinical trials or as a treatment option for some patients.

1. Methods

A literature review of the last fifteen years was performed in PubMed/MEDLINE in November 2019. The search strategy used the following MeSH terms: Prostate Neoplasms AND Radiotherapy with the additional terms: stereotactic OR highly hypofractionated. We identified over 30 studies on prostate SBRT. Discussions about indications, SBRT techniques, dosimetry, dose constraints and quality control were conducted within the GETUG group. After careful consideration of each proposition, the subsequent decisions were included in the guidelines when a consensus between all participants was reached.

A first draft was elaborated and proposed to all participants. Remarks and modifications were taken into account to design a second draft. After new modifications, approval by all participants was obtained. The final version of these recommendations is presented here.

2. Results

2.1 Indications

2.1.1 Review of the literature

A literature review was performed and summarized in table 1

Article	Inclusion years	N	Study type	Number of fraction	Dose per fraction (Gy)	Total dose (Gy)	Radiotherapy device	Tracking method	Patient characteristics (d'Amico risk classification)			Median follow up time (months)	Early toxicity ≥ grade3		Late toxicity ≥ grade 3		Actuarial FFBF
									Low risk	Intermediate risk	High risk		GI	GU	GI	GU	
King [13]	2003-2011	1100	phase II	5	7-8	35-40	CyberKnife®	implanted gold markers	58%	30%	11%	36	NA	NA	NA	NA	93% at 5 yrs
Friedland [14]	2005-2006	112	retrospective	5	7-7.2	35-36	CyberKnife®	implanted gold markers	NA	NA	NA	24	0%	0%	1%	0%	97% at 3 yrs
Widmark [12]	2005-2015	602	phase III	7	6.1	42.7	NA	implanted gold markers	0%	89%	11%	60	NA	NA	1.5%	4.2%	84% at 5 yrs
Bolzicco [15]	2006-2009	100	prospective	5	7	35	CyberKnife®	implanted gold markers	41%	42%	17%	36	0%	0%	0%	1%	94.40% at 3 yrs
Katz [16]	2006-2010	477	retrospective	5	7-7.25	35-36.25	CyberKnife®	implanted gold markers	68%	32%	0%	72				1.70%	93.70% at 7 yrs
Mantz [17]	2007-2009	102	retrospective	5	8	40	Truebeam®	Calypso®	68%	32%	0%	60	0%	2%	0%	0%	100% at 5 yrs
Bernetich [18]	2007-2012	142	retrospective	5	7-7.5	35-37.5	CyberKnife®	implanted gold markers	43%	44%	13%	38	0%	2%	0%	2%	92.70% at 5 yrs
Meier [7]	2008-2010	309	phase II	5	8	40	CyberKnife®	implanted gold markers	56%	44%	0%	61	0%	0%	0%	1.30%	95.60% at 5 yrs
Chen [19]	2008-2010	100	retrospective	5	7-7.25	35-36.25	CyberKnife®	implanted gold markers	37%	55%	8%	28	0%	0%	0%	1%	99% at 2 yrs
Zelevsky [20]	2011-2016	136	phase I	5	6.5-8	32.5-40	Varian LINAC	implanted gold markers	NA	NA	0%	46	0%	0.70%	0%	0.70%	89.20% at 3 yrs
Quon [8]	2012-2013	152	phase II	5	8	40	LINAC	implanted gold markers	14%	86%	0%	48	0%	2%	0.70%	5%	NA
Brand [11]	2012-2018	415	phase III	5	7.25	36.25	CyberKnife® or LINAC	implanted gold markers	7%	93%	0%	3	2.4%	0.2%	NA	NA	NA

Table 1: Major studies (over 100 patients) on stereotactic body radiotherapy for localized prostate cancer

N: patient number, NA: unavailable data, GI: gastrointestinal, GU: genitourinary, FFBF: freedom from biochemical failure, yrs: years

Although mostly non-randomized and including patients of different risk groups, these studies show good results in terms of biochemical control, over 90% at 3-5 years [5,7–10,12,11,21,14–18,20,22,23]. Early and late toxicity rates (both genitourinary and gastrointestinal) were also low, under 2% in most studies.

Only two randomized trials have been published so far [11,12]. They both compared 78 Gy in 39 fractions to a SBRT regimen (42.7 Gy in 7 fractions or 36.25 Gy in 5 fractions, 3 days per week). One thousand and fifty-four patients were enrolled in the HYPO-RT-PC trial, and 874 in the PACE-B trial. Most of the patients were of intermediate risk in both studies (89% and 93% respectively). Unfortunately, no distinction was made between favorable and unfavorable intermediate risk groups. No androgen deprivation treatment (ADT) was allowed. With a median follow-up of 5 years, there was no difference between the two regimens (biochemical and/or clinical control: 84% in both groups) in the HYPO-RT-PC trial. Initially designed as superiority trial, with a one-sided comparison test, the study was secondarily transformed in a non-inferiority trial, with a pre-specified margin of 4%, corresponding to a critical hazard ratio of 1.338. Thus, the authors drew the conclusion that this regimen is not inferior to conventional fractionation. Regarding toxicity, although early urinary toxicity was higher for the hypofractionated regimen (6% vs 2% grade 2 or more toxicity at 1 year, $p=0.0037$), there was no significant difference in late urinary symptoms, or in gastrointestinal symptoms, whether early or late [12].

The PACE-B trial has recently published preliminary results which only included acute toxicity results. In this study, there was no significant difference in either urinary or gastrointestinal acute toxicity in the SBRT group (27% vs 23% grade 2 or more urinary toxicity, 12% vs 10% grade 2 or more gastrointestinal toxicity) [11].

Another randomized trial (NCT03367702), comparing SBRT (5 fractions of 7.25 Gy) to hypofractionated IMRT (28 fractions of 2.5 Gy) is currently recruiting and additional results should soon be published.

2.1.2 Indications

All participants agree that the level of proof for prostate SBRT regarding efficacy is good but not strong.

HHFR cannot be considered as a standard of care yet, but can be offered as a therapeutic option to the patients, after information on the limited number of randomized trials in this setting.

Most of the studies have included patients of low- or favorable intermediate-risk groups, according to NCCN classification [24]. Due to the lack of data in higher-risk groups and the lack of specific studies in this subset of patients, all participants agree that only low- or favorable intermediate-risk groups should be considered for prostate SBRT.

As such, GETUG participants advise against the use of prostate SBRT in ISUP 3 prognostic group patients. Moreover, short-term ADT should be discussed in the unfavorable intermediate-risk group.

Furthermore, active surveillance should be proposed to low-risk patients whenever possible.

In conclusion, patients in the intermediate favorable prognostic group are the best candidates for a SBRT regimen.

All participants strongly agree that enrollment in clinical trials should be encouraged whenever available.

2.1.3 Contraindications

History of trans-urethral resection of the prostate (TURP) does not contra-indicate prostate SBRT. However, a delay of at least 3 months between TURP and radiotherapy must be observed.

Satisfactory urinary function (IPSS (International Prostatic symptom score) ≤ 15) and a prostate volume ≤ 80 cc are recommended. Patients with larger prostate volumes (over 100 cc) or recent history of TURP show a higher level of grade 3 urinary toxicity in studies [25,26]. As such, although not a strict contra indication as long as OAR constraints are met, authors advise caution in treating large prostates with SBRT.

Classical contra-indications of pelvic radiotherapy must be observed in SBRT setting as well (previous history of pelvic irradiation, chronic inflammatory bowel disease, ...).

2.2 Technical aspect: Target volumes

2.2.1 Necessary imaging techniques for radiotherapy planning and planning: CT-scan acquisition protocol

Prostate MRI (with T2-weighted and gadolinium enhanced T1-weighted images) is mandatory for local PCa staging (i.e. to ensure the lack of extracapsular, seminal vesicles or pelvic nodes involvement) and highly recommended for the delineation of the clinical target volume (CTV). Implantation of three fiducial markers in the prostate before MRI evaluation and treatment is highly recommended [27].

Registration with MRI images, after fiducial markers implantation, is strongly recommended, although not mandated. In both HYPO-RT-PC and PACE-B randomized trials, fiducial-based registration was performed [11,12]. IGRT can be performed using either fiducial markers or CT-based approaches with soft-tissue matching, although a combination of the two is strongly advised [28]. When available, intrafraction motion tracking must also be considered.

Most of the following recommendations are identical to those used in moderately hypofractionated schedules [4].

For the planning CT, patients should be placed in a supine position, arms folded on the chest. Different immobilization systems can be used (leg and foot rests, customized mattress). CT-scan images must be acquired in 2-mm or less slice thickness acquisition, beginning at L5 vertebra to below the lesser trochanters of both femoral heads.

If an MRI-CT-scan registration is not performed, contrast enhancement is recommended, in order to better visualize the prostate-bladder interface for segmentation.

The rectum must be empty. This must be thoroughly checked before every treatment fraction. If necessary (rectal distension ≥ 4 cm in anterior-posterior diameter [29]), a rectal enema can be performed before the CT-scan acquisition, but must be, in this case, repeated before every treatment fraction to ensure reproducibility. The bladder must be “comfortably full”, i.e. bladder dome should exceed the upper limit of femoral heads [30].

2.2.2 Volumes

CTV definition differs between studies, with some including 1 cm of seminal vesicle for intermediate risk patients [11]. However, since the participants recommend that SBRT be limited to patients of low- or favorable intermediate-risk, GETUG members agree that the clinical target volume (CTV) should only include the prostate gland.

The planning target volume (PTV) is an automatic expansion of the CTV with a 5 mm margin in all directions, except for the posterior margin, which must be reduced to 3 mm, as recommended by the ASTRO [31], and used in most studies (except for the HYPO-RT-PC trial, where the CTV to PTV margin was 7mm).

2.2.3 Doses

Based on the literature review, 5 fractions of 7.25 Gy, for a total prescribed dose to the PTV of 36.25 Gy seems both safe and effective. This schedule can be delivered either daily or every other day, although toxicity appears slightly higher when treatment is delivered on a daily

basis [7]. Although used in only one trial, the fractionation regimen of the HYPO-RT-PC study (7 fractions of 6.1 Gy, every other day) is the only regimen proven to be safe and effective in a phase III study, and cannot be overlooked [12].

The PACE-B trial suggested an additional CTV dose target of 40 Gy, but this cannot be considered as a standard procedure yet as it was only used in one trial [11].

As per ICRU guidelines, GETUG members recommend that the dose be prescribed on the 100% isodose, which means that the dose to the PTV is to be kept between 95 and 107%. Although several dose-escalation studies in prostate SBRT show promising results with acceptable toxicity rates [12,32], this point needs to be further assessed by prospective studies, and GETUG members agree that dose escalation within the PTV cannot be advised outside of clinical trial settings.

Based on the literature review, GETUG members suggest two types of dose-constraints for the PTV. Validation constraints have to be strictly respected: if not, the treatment planning must be rejected. Optimization constraints must be searched to obtain the best treatment planning compromise.

Validation constraints:

- For the PTV: $V_{95\%} \geq 95\%$ of the prescribed dose: the 95% isodose must cover at least 95% of the PTV
- The CTV must be covered by the 100% isodose
- $D_{1cc} < 120\%$: Maximal dose (D_{1cc}) must not exceed 120%
- *The 107% isodose shall be comprised in the CTV, with particular attention to the bladder and rectal volumes*

Optimization constraints for the PTV:

- $D_{98\%} \geq 100\%$
- $D_{1cc} < 107\%$ (for VMAT technique)

Optimization and OAR dose constraints for the major trials are summarized in Table 2.

Article	Number of fraction	Dose per fraction (Gy)	Total dose (Gy)	Radiotherapy device	Prescription isodose	CTV to PTV margins	Optimization constraints				OAR dose constraints			
							CTV	PTV	Bladder	Rectum	Femoral Heads	Penile Bulb	Urethra	Sigmoid colon
King [13]	5	7-8	35-40	CyberKnife®	90%	5mm (3mm post)	NA	V100% ≥ 95%	V50% < 40% V100% < 10%	V50% < 50% V80% < 20% V90% < 10% V100% < 5%	V40% < 5%	NA	NA	NA
Friedland [14]	5	7-7.2	35-36	CyberKnife®	NA	5mm (3mm post)	NA	V100% ≥ 95%	V37Gy < 10cc	V36Gy < 1cc	NA	NA	NA	NA
Widmark [12]	7	6.1	42.7	NA	NA	7mm	Dmin ≥ 95% Dmin ≥ 40.6 Gy	V95% ≥ 95% V40.6Gy ≥ 95% D99% ≥ 90% D99% ≥ 38.4 Gy	NA	V90% ≤ 15% V38.4Gy ≤ 15% V75% ≤ 35% V32Gy ≤ 35% V65% ≤ 45% V28Gy ≤ 45%	Dmax ≤ 70% Dmax ≤ 29.9 Gy	NA	NA	NA
Bolzicco [15]	5	7	35	CyberKnife®	80%	5mm (3mm post)	NA	V100% ≥ 95%	V40Gy < 5%	V38Gy < 5%	V25Gy < 25%	V29Gy < 25%	V40Gy < 5%	NA
Katz [16]	5	7-7.25	35-36.25	CyberKnife®	83-87%	5mm (3mm post)	NA	V100% ≥ 95%	V50% < 40% V100% < 10%	V50% < 50% V80% < 20% V90% < 10% V100% < 5%	V40% < 5%	NA	NA	NA
Mantz [17]	5	8	40	Truebeam®	NA	2mm	V100% 100% ≥	V100% ≥ 98%	D15% < 34.9Gy	D15% < 32.7Gy	NA	Dmean < 22.9Gy	NA	NA
Bernetich [18]	5	7-7.5	35-37.5	CyberKnife®	75-85%	5mm (3mm post)	NA	V100% ≥ 95%	V37Gy < 10cc	D1cc < 36Gy	NA	D50% < 29.5Gy	NA	V30Gy < 1cc
Meier [7]	5	8	40	CyberKnife®	NA	5mm (3mm post)	NA	NA	V37Gy < 5-10cc	V36Gy < 1cc	NA	V29.5Gy < 50%	V47Gy < 20%	NA
Chen [19]	5	7-7.25	35-36.25	CyberKnife®	75-81%	5mm (3mm post)	NA	Dmax < 48.33Gy V36.25Gy ≥ 95%	V37 Gy < 5 cc V100% < 10% V50% < 40%	V36 Gy < 1 cc V100% < 5% V80% < 20% V75% < 25% V50% < 50%	NA	V29.5 Gy < 50%	V37 Gy < 50%	V30Gy < 1cc
Zelevsky [20]	5	6.5-8	32.5-40	Varian LINAC	100%	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quon [8]	5	8	40	LINAC	NA	5mm	V40Gy > 99%	V38Gy > 99% V42Gy < 1cc Dmax ≤ 42.8Gy	V28Gy ≤ 20% V32Gy ≤ 15%	V28Gy ≤ 20% V32Gy ≤ 15%	V28Gy ≤ 5%	NA	NA	NA
Brand [11]	5	7.25	36.25	CyberKnife® or LINAC	65-85%	4-5mm (3-5mm post)	V40Gy ≥ 95%	V36.25Gy ≥ 95% D98% ≥ 34.4Gy Dmax < 48Gy D2% ≤ 42.8 Gy	V18.1 Gy < 40% V37 Gy < 10cc	V18.1 Gy < 50% V29 Gy < 20% V36 Gy < 1cc	V14.5Gy < 5%	V29.5Gy < 50%	V42Gy < 50%	NA

Table 2: Optimization and dose constraints for the major studies on stereotactic body radiotherapy for localized prostate cancer
Constraints in italic are optional
Gy: Gray, OAR: Organs at risk

2.3 Organs at risk

The participants agree on using the dose-constraints used in the PACE-B trial (Table 2) [11]. Dose reporting should be carried out according to the recommendations of ICRU Report 91 [33].

2.3.1 Rectum

Unlike previous recommendations of the GETUG, we recommend that the rectum be delineated as a full organ, rather than the rectal wall only. This change in organ definition was made to conform to other studies. Furthermore, delineation of the whole organ instead of the rectal-wall has little to no impact on dose constraints to prevent rectal toxicity [34]. Rectal segmentation should begin at the anal margin and end at the sigmoid flexure.

The dose constraints for modestly hypofractionated RT have recently been established for the first time with data from the CHHiP trial using clinician and patient-reported outcomes (V20Gy <85%, V30Gy <57%, V40Gy <38%, V50Gy <22%, and V60Gy <0.01%) [35]. However, there is no consensus for highly hypofractionated schedules to date. Rectal toxicity has been assessed in several large series, most of which used similar dose constraints for the rectum [5,14,16]. These showed that, following these dose constraints, the occurrence of grade 3 or higher radiation proctitis could be maintained under 3%.

Dose constraints for the rectum could summarize as follows:

- D50%<50%: 50% of the rectal volume should receive less than 50% of the prescribed dose
- D20%<80%: 20% of the rectal volume should receive less than 80% of the prescribed dose
- V 36.25 Gy (volume of rectum receiving 36.25 Gy) < 1cc

The use of a prostatic spacer such as hyaluronic acid or hydrogel spacer injection has shown promising results in terms of rectal protection. It is a rather safe and minimally invasive procedure that allows a significant decrease of the dose to the rectum [36,37]. As such, it can be considered an option before prostate SBRT, although some authors have expressed reservations about general applicability [38].

2.3.2 Urinary tract and Bladder

We recommend that the bladder be delineated as a full organ as well.

Suggested dose constraints for the bladder are as follows [5,16]:

D40%<50%: 40% of the bladder volume should receive less than 50% of the prescribed dose
D100%<10%: 100% of the bladder volume should receive less than 10% of the prescribed dose

Optimization constraints [21]:

- V40 Gy < 1.5 cc
- V37 Gy < 10 cc (with an optimal constraint of V37Gy < 5cc).

There is no consensus on the dose constraint for the urethra. As such, we consider its delineation optional. If easily seen on the CT-scan, the following optimization constraint can be useful: D50% ≤ 42 Gy.

2.3.3 Other organs

Femoral heads: V14.5 Gy < 5%

The penile bulb should be delineated, although it should not be subjected to specific dose constraints (although V29.5 Gy < 50% appears to be the most frequent dose constraint used in published studies). However, thorough dose record should be ensured, for future recommendations.

The testis must also be delineated to ensure that they are fully spared, especially in case of Cyberknife® treatment.

Given the localized nature of SBRT, the small intestine should stay clear of radiation fields in most cases. In case of bowel irradiation, strict dose constraints must be kept to avoid severe toxicity. In that case, the following constraints are suggested: D10cc and D5cc (dose received by 10cc and 5cc of the organ) under 18 Gy and 36 Gy, respectively.

Table 3 summarizes of suggested optimization and OAR dose constraints.

Dose constraints	Optimization constraints
Schedule: 36.25 Gy in 5 fractions of 7.25 Gy	
Target volumes	
- V95% \geq 95%(PTV)	- D98% \geq 34.4Gy (PTV)
- D100% \geq 100% (CTV)	- D1cc < 107% (VMAT technique)
- Maximum dose (D1cc) \leq 120%	
Rectum	
- D50% < 18.1 Gy	
- D20% < 29 Gy	
- D1cc < 36 Gy	
Bladder	
- D40% < 18.1 Gy	- V40Gy < 1.5 cc
- V100% < 10%	- V37Gy < 5 cc

D%: % of the prescribed dose

V %: % of organ volume; VxGy: volume of the organ receiving dose x

Table 3: Dose constraints for prostate SBRT: GETUG recommendations, based on the PACE-B trial [39]

2.4 Image-guided radiotherapy

In case of Cyberknife® treatment, continuous intra-fraction imaging (with a minimum frequency of 15 seconds), based on implanted fiducial markers is required.

In case of VMAT irradiation, kV/kV and CBCT imaging must be used. When available, an automated fiducial detection and registration on kV images should be used. Otherwise, treatment position should always be based on soft-tissue matching using CBCT registration. Additional kV and CBCT image acquisition can also be performed between each treatment arc. When available, intra-fraction tracking should be used (ie: using gold markers or Calypso® tracking system).

3. Discussion

SBRT is a rapidly developing treatment option for localized prostate cancer, with good results in terms of local control and toxicity. Although several studies on prostate SBRT have been published over the last decade, there is a lack of clear guidelines and, as such, no consistency in prescribed dose levels, dose constraints and treatment modalities. The goal of these guidelines is to set the standard for future studies, as well as be a framework for routine prescription of prostate SBRT.

All the participants agree that this technique must be performed in centers with sufficient expertise in prostate irradiation and SBRT techniques. Although no recommendation on the actual treatment technique can be made, implementation of the chosen technique must follow a rigorous quality control program [40].

In the literature, prescribed dose ranges from 35 to 50 Gy, while dose per fraction ranges between 6 and 8 Gy (Table 1). While this may not seem like much of a difference, it has a significant impact on treatment tolerance. In studies where the total dose exceeds 40 Gy, late grade ≥ 3 genitourinary toxicity is higher, up to 5% [8,12]. As such, we recommend that total dose should be 36.25 Gy and that dose per fraction should not exceed 7.25 Gy.

Regarding dose constraints, our recommendations are based on the data found in the studies published over the last decade, and in particular the PACE-B study [11]. While early toxicity is not much of a concern in SBRT, late toxicity can be severe at such high doses, and can significantly alter the quality of life. Therefore, given the excellent prognosis of localized prostate cancer, quality of life is a major concern, and late toxicities rates must be kept as low as possible. In most studies, late grade ≥ 3 genitourinary toxicity rate is under 2%, which is acceptable. However, longer follow-up of patients treated with prostate SBRT revealed much

higher toxicity rated, compared with IMRT (43.9% vs 36.3% at 2 years after treatment completion) [41].

Gastrointestinal toxicity is even less frequent, and no grade ≥ 3 was reported in most of the published studies (Table 1). Based on these observations, we came up with a set of validation constraints, which must be reached for treatment plan validation, and optimization constraints, which are not considered mandatory because of their more strenuous nature (Table 3).

Conclusion

Comprised of French experts, both radiation oncologists and medical physicists, the GETUG group has a valid claim at setting guidelines for prostate cancer radiotherapy on both French and international level. With an exhaustive literature review, this is one of the first set of guidelines on prostate SBRT to be published so far [42]. We have come up with a dose fractionation schedule with appropriate dose constraints for the treatment of localized prostate cancer, as well as discuss treatment preparation and delivery.

Based on the current available literature, the GETUG group suggests that:

- Because large prospective trials are lacking, SBRT could not be considered as a standard of care, but could be proposed as an option after patient information
- Good candidates for SBRT are patients of the favorable or intermediate favorable groups
- 5 fractions of 7.25 Gy, for a total prescribed dose of 36.25 Gy seems both safe and effective
- Dose constraints for PTV and OAR are summarized Table 3

However, due to the lack of published data, some of the issues discussed here, such as immobilization procedures, are still open to debate. As such, there still is a need for large prostate SBRT trials, and patient should be enrolled in clinical trials whenever possible.

References:

- [1] Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. *J Clin Oncol Off J Am Soc Clin Oncol* 2017;35:1884–90. <https://doi.org/10.1200/JCO.2016.71.7397>.
- [2] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;17:1047–60. [https://doi.org/10.1016/S1470-2045\(16\)30102-4](https://doi.org/10.1016/S1470-2045(16)30102-4).
- [3] Incrocci L, Wortel RC, Alemany WG, Aluwini S, Schimmel E, Krol S, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2016;17:1061–9. [https://doi.org/10.1016/S1470-2045\(16\)30070-5](https://doi.org/10.1016/S1470-2045(16)30070-5).
- [4] Langrand-Escure J, de Crevoisier R, Llagostera C, Créhange G, Delaroche G, Lafond C, et al. Dose constraints for moderate hypofractionated radiotherapy for prostate cancer: The French genito-urinary group (GETUG) recommendations. *Cancer Radiother J Soc Francaise Radiother Oncol* 2018;22:193–8. <https://doi.org/10.1016/j.canrad.2017.11.004>.
- [5] King CR, Collins S, Fuller D, Wang P-C, Kupelian P, Steinberg M, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *Int J Radiat Oncol Biol Phys* 2013;87:939–45. <https://doi.org/10.1016/j.ijrobp.2013.08.019>.
- [6] Kishan AU, Katz AJ, Mantz C, Chu F-I, Appelbaum L, Loblaw A, et al. Long-term outcomes of stereotactic body radiotherapy for low- and intermediate-risk prostate adenocarcinoma: A multi-institutional consortium study. *J Clin Oncol* 2018;36:84–84. https://doi.org/10.1200/JCO.2018.36.6_suppl.84.
- [7] Meier RM, Bloch DA, Cotrutz C, Beckman AC, Henning GT, Woodhouse SA, et al. Multicenter Trial of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer: Survival and Toxicity Endpoints. *Int J Radiat Oncol • Biol • Phys* 2018;102:296–303. <https://doi.org/10.1016/j.ijrobp.2018.05.040>.
- [8] Quon HC, Ong A, Cheung P, Chu W, Chung HT, Vesprini D, et al. Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): A phase 2 randomized trial. *Radiother Oncol* 2018;127:206–12. <https://doi.org/10.1016/j.radonc.2018.02.029>.
- [9] Alayed Y, Cheung P, Chu W, Chung H, Davidson M, Ravi A, et al. Two StereoTactic ablative radiotherapy treatments for localized prostate cancer (2STAR): Results from a prospective clinical trial. *Radiother Oncol* 2019;135:86–90. <https://doi.org/10.1016/j.radonc.2019.03.002>.
- [10] Jackson WC, Silva J, Hartman HE, Dess RT, Kishan AU, Beeler WH, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. *Int J Radiat Oncol* 2019;104:778–89. <https://doi.org/10.1016/j.ijrobp.2019.03.051>.
- [11] Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol* 2019;20:1531–43. [https://doi.org/10.1016/S1470-2045\(19\)30569-8](https://doi.org/10.1016/S1470-2045(19)30569-8).

- [12] Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet Lond Engl* 2019;394:385–95. [https://doi.org/10.1016/S0140-6736\(19\)31131-6](https://doi.org/10.1016/S0140-6736(19)31131-6).
- [13] King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2013;109:217–21. <https://doi.org/10.1016/j.radonc.2013.08.030>.
- [14] Friedland JL, Freeman DE, Masterson-McGary ME, Spellberg DM. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat* 2009;8:387–92. <https://doi.org/10.1177/153303460900800509>.
- [15] Bolzicco G, Favretto MS, Satariano N, Scremin E, Tambone C, Tasca A. A single-center study of 100 consecutive patients with localized prostate cancer treated with stereotactic body radiotherapy. *BMC Urol* 2013;13:49. <https://doi.org/10.1186/1471-2490-13-49>.
- [16] Katz AJ, Kang J. Stereotactic Body Radiotherapy as Treatment for Organ Confined Low- and Intermediate-Risk Prostate Carcinoma, a 7-Year Study. *Front Oncol* 2014;4. <https://doi.org/10.3389/fonc.2014.00240>.
- [17] Mantz C. A Phase II Trial of Stereotactic Ablative Body Radiotherapy for Low-Risk Prostate Cancer Using a Non-Robotic Linear Accelerator and Real-Time Target Tracking: Report of Toxicity, Quality of Life, and Disease Control Outcomes with 5-Year Minimum Follow-Up. *Front Oncol* 2014;4. <https://doi.org/10.3389/fonc.2014.00279>.
- [18] Bernetich M, Oliai C, Lanciano R, Hanlon A, Lamond J, Arrigo S, et al. SBRT for the Primary Treatment of Localized Prostate Cancer: The Effect of Gleason Score, Dose and Heterogeneity of Intermediate Risk on Outcome Utilizing 2.2014 NCCN Risk Stratification Guidelines. *Front Oncol* 2014;4. <https://doi.org/10.3389/fonc.2014.00312>.
- [19] Chen LN, Suy S, Uhm S, Oermann EK, Ju AW, Chen V, et al. Stereotactic Body Radiation Therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. *Radiat Oncol* 2013;8:58. <https://doi.org/10.1186/1748-717X-8-58>.
- [20] Zelefsky MJ, Kollmeier MA, McBride S, Pei X, Happersett L, Lin M, et al. 5-Year Outcomes of a Phase 1 Dose Escalation Study Using Stereotactic Body Radiosurgery for Patients with Clinically Localized Prostate Cancer. *Int J Radiat Oncol • Biol • Phys* 2017;99:S156–7. <https://doi.org/10.1016/j.ijrobp.2017.06.361>.
- [21] Chen LN, Suy S, Uhm S, Oermann EK, Ju AW, Chen V, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. *Radiat Oncol Lond Engl* 2013;8:58. <https://doi.org/10.1186/1748-717X-8-58>.
- [22] Kang J-K, Cho CK, Choi CW, Yoo S, Kim M-S, Yang K, et al. Image-Guided Stereotactic Body Radiation Therapy for Localized Prostate Cancer. *Tumori J* 2011;97:43–8. <https://doi.org/10.1177/030089161109700109>.
- [23] McBride SM, Wong DS, Dombrowski JJ, Harkins B, Tapella P, Hanscom HN, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer* 2012;118:3681–90. <https://doi.org/10.1002/cncr.26699>.
- [24] National Comprehensive Cancer Network. Prostate Cancer (Version 2.2021). NCCN n.d. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed July 15, 2021).

- [25] Syed YA, Patel-Yadav AK, Rivers C, Singh AK. Stereotactic radiotherapy for prostate cancer: A review and future directions. *World J Clin Oncol* 2017;8:389–97. <https://doi.org/10.5306/wjco.v8.i5.389>.
- [26] Wang K, Mavroidis P, Royce TJ, Falchook AD, Collins SP, Sapareto S, et al. Prostate Stereotactic Body Radiation Therapy: An Overview of Toxicity and Dose Response. *Int J Radiat Oncol Biol Phys* 2021;110:237–48. <https://doi.org/10.1016/j.ijrobp.2020.09.054>.
- [27] O’Neill AGM, Jain S, Hounsell AR, O’Sullivan JM. Fiducial marker guided prostate radiotherapy: a review. *Br J Radiol* n.d.;89. <https://doi.org/10.1259/bjr.20160296>.
- [28] Ghadjar P, Fiorino C, Munck af Rosenschöld P, Pinkawa M, Zilli T, van der Heide UA. ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer. *Radiother Oncol* 2019. <https://doi.org/10.1016/j.radonc.2019.08.027>.
- [29] de Crevoisier R, Tucker SL, Dong L, Mohan R, Cheung R, Cox JD, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. *Int J Radiat Oncol* 2005;62:965–73. <https://doi.org/10.1016/j.ijrobp.2004.11.032>.
- [30] Braide K, Kindblom J, Lindencrona U, Månsson M, Hugosson J. The value of a bladder-filling protocol for patients with prostate cancer who receive post-operative radiation: results from a prospective clinical trial. *Acta Oncol* 2019;58:463–8. <https://doi.org/10.1080/0284186X.2018.1554261>.
- [31] Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. *J Clin Oncol* 2018;36:3411–30. <https://doi.org/10.1200/JCO.18.01097>.
- [32] Zelefsky MJ, Kollmeier M, McBride S, Varghese M, Mychalczak B, Gewanter R, et al. Five-Year Outcomes of a Phase 1 Dose-Escalation Study Using Stereotactic Body Radiosurgery for Patients With Low-Risk and Intermediate-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2019;104:42–9. <https://doi.org/10.1016/j.ijrobp.2018.12.045>.
- [33] Report 91. *J Int Comm Radiat Units Meas* 2014;14:1–160. <https://doi.org/10.1093/jicru/ndx017>.
- [34] Tucker SL, Dong L, Cheung R, Johnson J, Mohan R, Huang EH, et al. Comparison of rectal dose-wall histogram versus dose-volume histogram for modeling the incidence of late rectal bleeding after radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;60:1589–601. <https://doi.org/10.1016/j.ijrobp.2004.07.712>.
- [35] Wilkins A, Naismith O, Brand D, Fernandez K, Hall E, Dearnaley D, et al. Derivation of Dose/Volume Constraints for the Anorectum from Clinician- and Patient-Reported Outcomes in the CHHiP Trial of Radiation Therapy Fractionation. *Int J Radiat Oncol Biol Phys* 2020;106:928–38. <https://doi.org/10.1016/j.ijrobp.2020.01.003>.
- [36] Chapet O, Udrescu C, Tanguy R, Ruffion A, Fenoglietto P, Sotton M-P, et al. Dosimetric implications of an injection of hyaluronic acid for preserving the rectal wall in prostate stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2014;88:425–32. <https://doi.org/10.1016/j.ijrobp.2013.10.039>.
- [37] Boissier R, Udrescu C, Rebillard X, Terrier J-E, Faix A, Chapet O, et al. Technique of Injection of Hyaluronic Acid as a Prostatic Spacer and Fiducials Before Hypofractionated External Beam Radiotherapy for Prostate Cancer. *Urology* 2017;99:265–9. <https://doi.org/10.1016/j.urology.2016.09.045>.
- [38] Hall WA, Tree AC, Dearnaley D, Parker CC, Prasad V, Roach M, et al. Considering benefit and risk before routinely recommending SpaceOAR. *Lancet Oncol* 2021;22:11–3. [https://doi.org/10.1016/S1470-2045\(20\)30639-2](https://doi.org/10.1016/S1470-2045(20)30639-2).

- [39] Hanna GG, Murray L, Patel R, Jain S, Aitken KL, Franks KN, et al. UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy. *Clin Oncol* 2018;30:5–14. <https://doi.org/10.1016/j.clon.2017.09.007>.
- [40] Seung SK, Larson DA, Galvin JM, Mehta MP, Potters L, Schultz CJ, et al. American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) Practice Guideline for the Performance of Stereotactic Radiosurgery (SRS). *Am J Clin Oncol* 2013;36:310–5. <https://doi.org/10.1097/COC.0b013e31826e053d>.
- [41] Yu JB, Cramer LD, Herrin J, Soulos PR, Potosky AL, Gross CP. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *J Clin Oncol Off J Am Soc Clin Oncol* 2014;32:1195–201. <https://doi.org/10.1200/JCO.2013.53.8652>.
- [42] Draulans C, De Roover R, van der Heide UA, Haustermans K, Pos F, Smeenk RJ, et al. Stereotactic body radiation therapy with optional focal lesion ablative microboost in prostate cancer: Topical review and multicenter consensus. *Radiother Oncol* 2019;140:131–42. <https://doi.org/10.1016/j.radonc.2019.06.023>.