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Online adaptive stereotactic body radiotherapy for localized prostate cancer in patients with lower urinary tract symptoms and/or prostate hyperplasia (X-SMILE)

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Abstract

Background Stereotactic body radiotherapy (SBRT) for localized prostate cancer offers non-inferior oncological outcomes and toxicity profiles compared to conventionally or moderately hypofractioned radiotherapy regimens, with shorter treatment durations. However, SBRT may not be suitable for all patients, particularly those with lower urogenital tract symptoms and/or prostatic hyperplasia.

Methods This study aims to evaluate the safety and efficacy of weekly computed tomography (CT) or magnetic resonance image (MRI)-guided online adaptive SBRT in patients with intermediate to high-risk localized prostate cancer (i.e. ≤ cT3a and Gleason score ≤ 9 and PSA ≤ 20 ng/ml) who present with lower urinary tract symptoms (International Prostate Symptom Score [IPSS] > 12) and/or have prostate hyperplasia (prostate volume > 60 mL). The primary outcome measure is urogenital toxicity grade ≥ 3 within 3 months after completion of SBRT (according to CTCAE V5.0) or treatment-related discontinuation. Our aim is to show an event rate of 3% below a clinically acceptable threshold which is set at 20%. Under the null hypothesis, this design with an alpha of 0.05 and power of 80% results in an expected number of cases of 30.

Discussion In cases of moderate to high IPSS or significant obstructive urodynamics, a pre-emptive transurethral resection of prostate (TURP) may be beneficial. Notably, 10–20% of prostate cancer patients receiving radiotherapy patients have a history of TURP. While TURP can improve obstructive symptoms, its impact on late toxicity, particularly in SBRT, requires further investigation. To mitigate the risk of urogenital toxicity, especially in the case of patients with lower urogenital tract symptoms and/or prostatic hyperplasia, emerging approaches like MR-guided adaptive SBRT and weekly SBRT have shown promise.

Trial registration ClinicalTrials.gov/NCT06834152.

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Protocol version Version 6.0.

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Background and rationale

Prostate cancer is the most prevalent form of cancer among men in both the United States and Europe [1]. In 2023, approximately 288,300 new cases of prostate cancer were diagnosed in the US, and 470,000 in Europe [1]. External beam radiotherapy (EBRT) plays a crucial role in the treatment of localized prostate cancer according to international guidelines [2, 3]. Conventionally fractioned radiotherapy involves the administration of a total dose of 74–78 Gy in 1.8–2 Gy single doses over a period of 7 to 8 weeks [4]. The use of moderately hypofractioned radiotherapy (single doses between 2.4 and 3.4 Gy) has been shown to be non-inferior in clinical outcomes for patients with prostate cancer compared to conventionally fractioned radiotherapy [5]. Further reduction in the number of fractions is referred to as ultrahypofractionated or stereotactic radiotherapy (SBRT), which commonly involves delivering 1–7 fractions with single doses > 6 Gy [6].

Recently, the PACE-A randomized controlled trial (RCT) demonstrated that SBRT, with a total dose to the clinical target volume (CTV) of 40 Gy and to the planning target volume (PTV) of 36.25 Gy delivered in 5 fractions showed less patient-reported urinary incontinence and sexual dysfunction, and slightly more bowel bother than prostatectomy [7]. The PACE-B RCT demonstrated that SBRT results in excellent oncological outcomes with a 5-year biochemical and biochemical progression-free survival rate of 95.8% which was non-inferior to conventionally or moderately hypofractioned radiotherapy [8]. While there was a small increase in genitourinary (GU) toxicity at 12–18 months, no long-term increased toxicity was observed with SBRT [8].

Baseline lower urinary tract symptoms, measurable via the International Prostate Symptom Score (IPSS), are critical in predicting GU toxicity during and after radiotherapy [9, 10]. For example, the impact of higher IPSS on GU toxicity was demonstrated by a French study analyzing predictive factors for GU toxicity and self-reported symptoms after EBRT for prostate cancer [9]. This study included 280 patients treated with conventionally fractioned EBRT for localized prostate cancer [9]. The analysis of self-reported symptoms showed a significant correlation between IPSS baseline values ($P = 0.009$), presence of nocturia ($P = 0.002$), bladder urgency ($P = 0.024$) and incontinence ($P = 0.024$) and development of acute GU toxicity at univariate analysis [9]. At multivariate logistic regression analysis, bladder filling, IPSS value, nocturia, and urinary incontinence retained significant correlation with GU toxicity ($P = 0.0003$)[9]. The correlation of baseline IPSS and GU toxicity was also demonstrated in a secondary analysis of the PACE-B trial [11]. In a univariable analysis factors statistically significantly associated with late grade 2 + GU toxicity were baseline IPSS ($P < 0.0001$), prostate volume ($P = 0.02$), baseline grade 2 + GU events ($P < 0.0001$), baseline EPIC-26 overall urinary bother ($P < 0.0001$), and the use of conventional linac ($P = 0.002$)[11].

The impact of larger prostate volumes on late GU toxicity was demonstrated in a study conducted at the Veteran's Affairs Medical Center [12]. In this study patients with localized prostate cancer treated with moderately hypofractioned radiotherapy between 2008 and 2018 were included [12]. Patients with a larger prostate target volume (corresponding to median prostate volume of 76 mL) were at increased risk and earlier onset of late grade 2 + GU toxicity [12]. Another prospective study assessing the quality of life and satisfaction with outcome among 1201 prostate cancer survivors showed that large prostate size exacerbated urinary irritation after radiotherapy and was associated with worse quality of life scores [13].

Therefore, many studies evaluating SBRT for localized prostate cancer have excluded patients with lower urinary tract symptoms, defined by IPSS > 12 [14], >15 [15]–[17], or > 19 [18], or with prostatic hyperplasia defined as prostate volume > 60 mL [15], > 70 mL [16], > 80 mL [14], or > 90 mL [18] (Table 1).

In cases of moderate to high IPSS or significant obstructive urodynamics, a pre-emptive transurethral resection of the prostate (TURP) may be beneficial [19]. Notably, 10–20% of prostate cancer patients receiving radiotherapy patients have a history of TURP [20]. While TURP can improve obstructive symptoms, its impact on late GU toxicity, particularly in the era of hypofractionated radiotherapy, requires further investigation. The impact of TURP on late GU toxicity has been demonstrated by study including 141 patients treated with cyberknife SBRT for localized prostate cancer between 2010 and 2020 [21]. Among the included patients, 13.5% had a history of TURP. Multivariate analysis revealed that a history of TURP was significantly associated with late 2 + GU toxicity [21]. However, another retrospective cohort study showed no association between late GU toxicity and SBRT or moderately hypofractioned radiotherapy in patients with prior TURP, or TURP cavity volume in univariable or multivariable analysis [22].

The urogenital toxicity associated with SBRT in patients with lower urinary tract symptoms or prostate hyperplasia could potentially be mitigated by administering

Table 1 Inclusion criteria of important trials in the field of definitive SBRT for localized prostate cancer

Author, year	Study name	Treatment	Study type	Inclusion criteria				
				IPSS	Prostate volume	T stage	Gleason	PSA (ng/ml)
Van As, 2024 [19]	PACE-B	MHRT or CRT vs. SBRT	Phase III	ns	ns	T1c-T2c	≤ 7a	≤ 20
Van As, 2024 [7]	PACE-A	P vs. SBRT	Phase III	ns	ns	T1c-T2c	≤ 7a	≤ 20
Draulans, 2024 [14]	Hypo-FLAME	SBRT	Phase II	≤ 15	ns	T2b-T3b	≥ 7	≤ 30
Fink, 2024 [11]	SMILE	SBRT	Phase II	≤ 12	< 80 mL	T1-3a	≤ 8a	≤ 20
Lukka, 2023 [29]	NRG RTOG 0938	SBRT: 12 Fx vs. 5 Fx	Phase II	ns	ns	T1-2a	≤ 6a	≤ 10
Widmark, 2019 [6]	HYPO-RT-PC	SBRT	Phase III	ns	ns	T1-3a	≥ 7a	≤ 20
Kinshan, 2019 [28]	MIRAGE	CT vs. MRI SBRT	Phase II	ns	ns	T1-3a	≥ 7a	≤ 20
Quon, 2018 [15]	PATRIOT	Weekly vs. EOD SBRT	Phase II	≤ 19	≤ 90 mL	T1-2b	≤ 7a	≤ 20
Zelefsky, 2018 [12]	MSKCC	SBRT	Phase I	≤ 15	≤ 60 mL	T1-3a	≤ 7a	≤ 20
NCT03367702 [13]	NRG GU005 (ongoing)	SBRT vs. MHRT	Phase III	< 15	< 70 mL	T1-2b	≤ 7a	≤ 20

CRT: conventional radiotherapy, CT: computed tomography, EOD: every other day, IPSS: international prostate symptom score, MHRT: moderately hypofractioned radiotherapy, MRI: magnetic resonance imaging, ns: not specified P: prostatectomy, PSA: prostate specific antigen, SBRT: stereotactic body radiotherapy

SBRT on a weekly basis. The PATRIOT RCT has shown that weekly SBRT for prostate cancer is associated with reduced acute GU and gastrointestinal (GI) toxicity compared to SBRT delivered every other day [18, 23]. Notably, weekly SBRT did not result in differences in biochemical failure rates [23]. This reduction in acute GU toxicity for weekly SBRT was also demonstrated in the phase II hypo-FLAME 2.0 trial which showed reduced acute grade 2 GU toxicity with weekly SBRT compared to SBRT delivered every other day (34.0% versus 47.5%) [24]. Importantly, this improvement in acute GU and GI toxicity associated with weekly SBRT in the PATRIOT trial did not translate to improvement in long-term GU or GI toxicity [23].

Another method to reduce the rate of GU toxicity is with use the of MR as opposed to CT guidance [25]. The phase III MIRAGE trial has shown that MRI-guided SBRT versus CT-guided SBRT was associated with significantly lower cumulative incidence of late grade 2 toxicity at 2 years for both GU toxicity (27% vs. 51, $p = 0.004$) and GI toxicity (1.4 vs. 9.5%, $p = 0.025$) [25]. Importantly, the PTV margins used for MRI-guided SBRT were smaller than for CT-guided SBRT (2 mm versus 4 mm) which could also have impacted results [25].

The aim of this phase II international multicenter study is to evaluate the safety, feasibility, and efficacy of adaptive definitive SBRT, delivered in five weekly fractions, in patients with newly diagnosed localized prostate cancer who have lower urinary tract symptoms and/or prostatic hyperplasia.

Methods

This study protocol was written in accordance with SPIRIT checklist [26].

Study setting

This observational international multicenter prospective phase II study, conducted in collaboration with several academic hospitals in Switzerland and Germany, will include patients with histologically confirmed intermediate to high risk localized prostate cancer (i.e. ≤ cT3a, Gleason ≤ 9 and PSA ≤ 20) with lower urinary tract symptoms (i.e. IPSS > 12) and/or prostate hyperplasia (i.e. > 60 mL). These patients are planned to receive weekly CT or MRI online adaptive SBRT for localized prostate cancer. Patients with seminal vesicle involvement (i.e. cT3b) or very high-risk localized disease defined by Gleason ≥ 8 score combined with extra prostatic extension (cT3a) will excluded. Figure 1 provides a schematic overview of the study. Supplementary File S1 provides NCCN initial risk stratification for localized prostate cancer in relation to eligibility for X-SMILE.

Eligibility

Inclusion criteria

- Patients with histologically confirmed intermediate to high risk localized prostate cancer according to NCCN guidelines (i.e. ≤ cT3a, Gleason score ≤ 9, and PSA ≤ 20 ng/ml)[2].
- IPSS > 12 and/or with prostate volume > 60 mL.
- Age ≥ 18 years.
- ECOG performance status of 0–2.
- Written informed consent.
- For patients with high-risk localized disease (i.e. cT3a or Gleason ≥8) a PSMA PET/CT or PSMA PET/MRI scan is mandatory.

Exclusion criteria

- Seminal vesicle involvement (i.e. cT3b disease).
- Very high-risk localized disease according to NCCN guidelines defined by Gleason ≥ 8 score combined with extra prostatic extension (cT3a).
- Gleason score 10.
- PSA > 20 ng/ml.

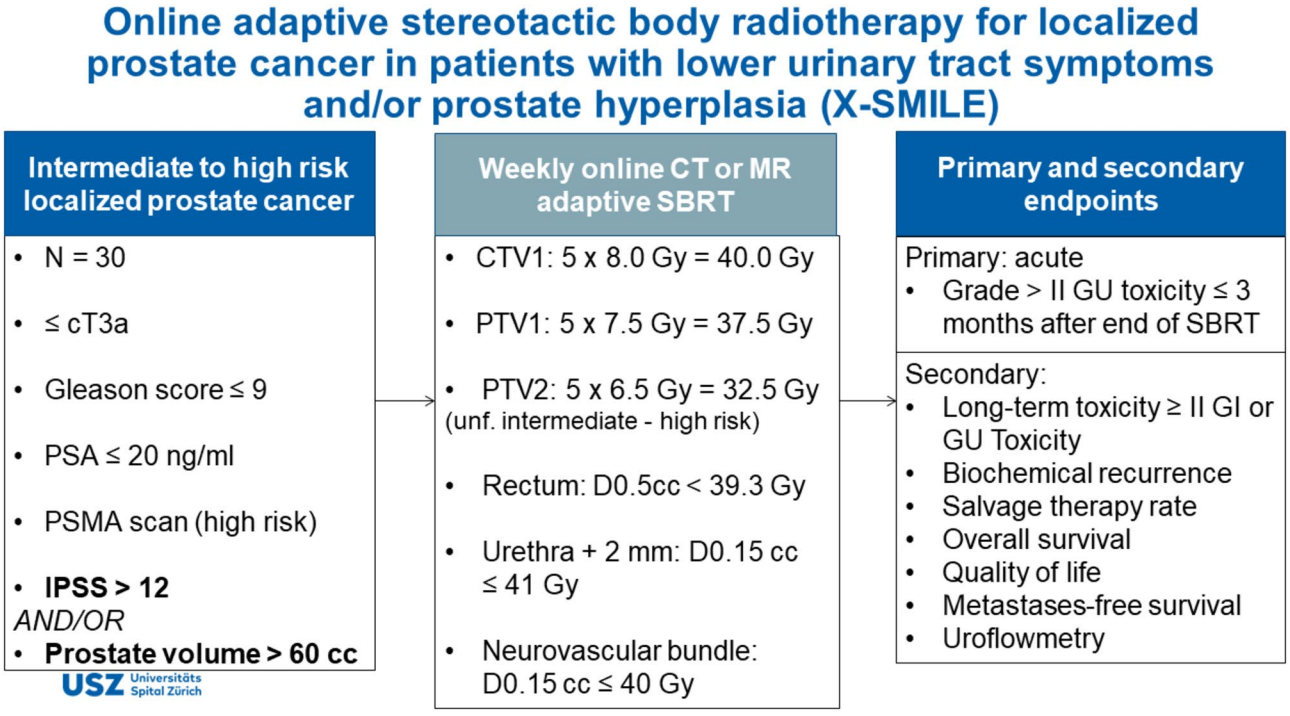

Fig. 1 Schematic overview of the X-SMILE study

- Patients with contraindications against definitive CT or MRI-adaptive radiotherapy of the prostate, e.g. inflammatory bowel disease, previous radiotherapy in the pelvis, previous local radiotherapy of the prostate.
- Severe obstructive genitourinary symptoms (e.g. recent urinary retention ≥ grade 3 according CTCAE v.5.0).
- Lymph node metastases (i.e. cN1 disease).
- Distant metastases (i.e. cM1 disease).

Intervention

SBRT will be according to standard of care and consist of definitive CT or MRI online adaptive SBRT of the prostate according to the PACE trial [27] which includes a total dose to CTV 1 (i.e. prostate and proximal 1 cm of the seminal vesicle) of 40.0 Gy in 5 weekly fractions (single dose of 8.0 Gy) and total dose to PTV 1 of 37.5 Gy in 5 weekly fractions (single dose of 7.5 Gy) with a compromise for bowel sparing allowed. For patients with unfavorable intermediate risk or high risk disease a total dose to the PTV2 (i.e. PTV1 + proximal 2–2.5 cm of the seminal vesicle) of 32.5 Gy in 5 weekly fractions (single dose of 6.5 Gy) will be delivered. The inclusion of the proximal 2–2.5 cm of the seminal vesicle for unfavorable intermediate risk or high risk was based on a retrospective study on 344 prostatectomy samples [28]. In this study, the median length of seminal vesicles involvement was 1.0 cm and only 1% of their patients had a risk of seminal vesicles involvement beyond 2.0. [28] Table 2 provides radiation dose and target volumes for X-SMILE based on NCCN risk groups. Figure 2 provides a schematic illustration of the seminal vesicle inclusion. Tables 3 and 4 provides recommendations for organs at risk (OAR) constraints.

Neoadjuvant, concomitant, or adjuvant systemic therapy (e.g. androgen deprivation therapy [ADT] or androgen receptor pathway inhibitors [ARPI]) is not part of this study and will be administered at the discretion of the treating physician, following a shared decision-making process with the patient.

Outcomes

Primary outcome

The primary endpoint is a composite endpoint in which the occurrence of one of the following is considered an event:

- the presence of GU toxicity of grade ≥ 3 within 3 months after completion of radiotherapy (according to CTCAE v5.0).
- Treatment-related discontinuation.

A subgroup analysis for acute urogenital toxicity will be performed for patients with and without a history of TURP.

Table 2 Radiation dose and target volumes for X-SMILE based on NCCN risk groups

NCCN risk group	Volume	Dose
Favorable intermediate risk	CTV1 = prostate + proximal 1 cm of seminal vesicles	5 x 8 Gy = 40 Gy (V100%>95%, compromise for OAR sparing allowed V100%>90%)
	PTV1 = CTV1+ 5 mm margin, 3 mm to posterior	5 x 7.5 Gy = 37.5 Gy weekly (V100%>95%, compromise for OAR sparing allowed D99%>36.25 Gy for PTV_PH = PTV1-(Bowel+3mm)
Unfavorable intermediate risk or high risk	CTV1 = prostate + proximal 1 cm of seminal vesicles	5×8 Gy=40 Gy (V100%>95%, compromise for OAR sparing allowed V100%>90%)
	PTV1 = CTV1 + 5 mm margin, 3 mm to posterior	5 x 7.5 Gy = 37.5 Gy weekly (V100%>95%, compromise for OAR sparing allowed D99%>36.25 Gy for PTV_PH = PTV1-(Bowel+3mm)
	CTV2 =CTV1 + proximal 1 cm to 2.0-2.5 cm of seminal vesicles	-
	PTV2 = CTV2 + 5 mm margin, 3 mm to posterior	5 x 6.5 Gy = 32.5 Gy (V95%>95%, compromise for OAR sparing allowed))

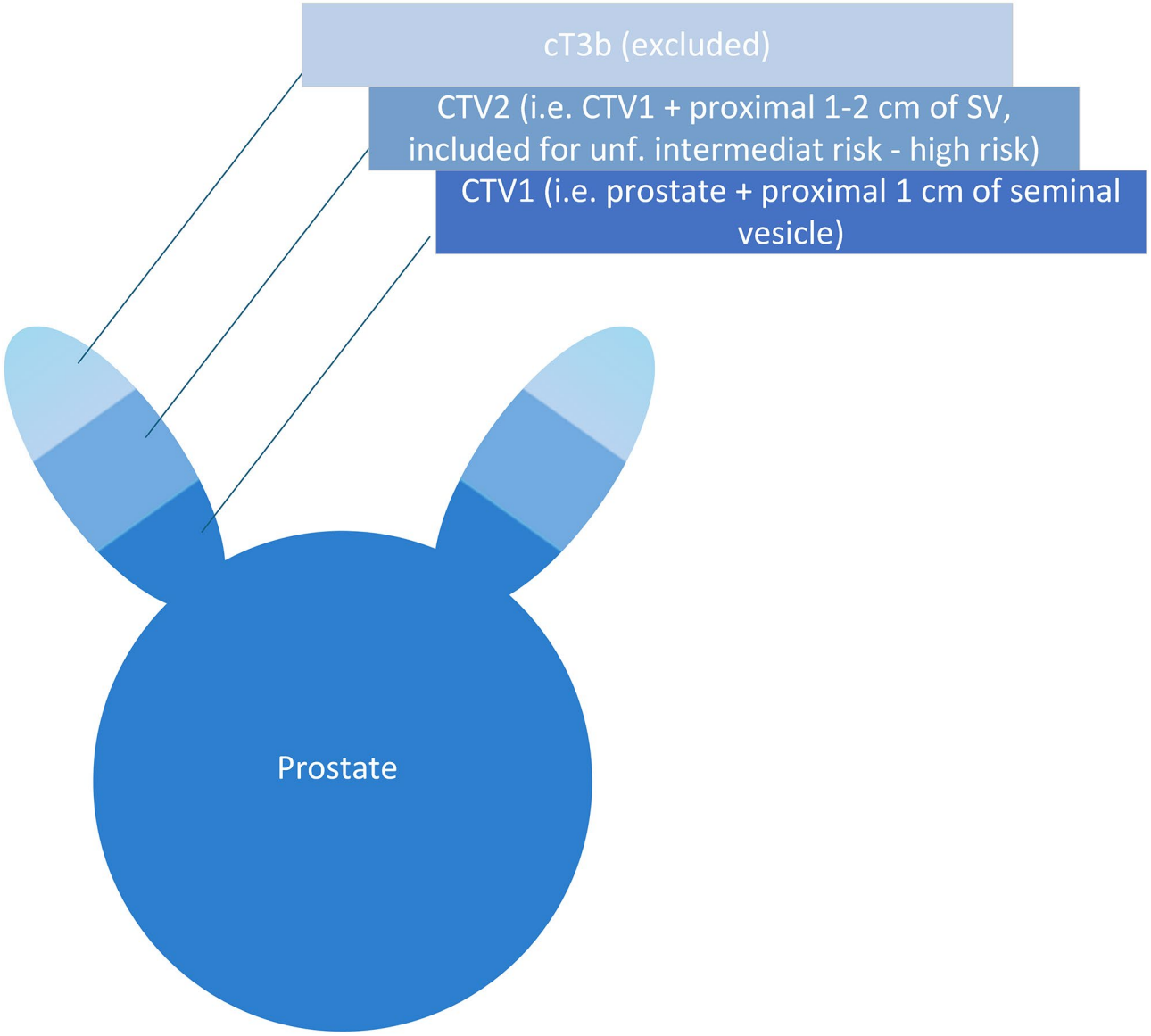

Fig. 2 Schematic illustration of CTV analog the PACE study [27]

Table 3 Organs at risk (OAR) constraints

Bladder	D 0.1 cc < 41.4 Gy and D 5 cc < 39.3 Gy, Compromise of CTV and PTV coverage allowed
Sigma/Bowel	D 1 cc < 30 Gy and D 0.1 cc < 33 Gy (hard constraints); Compromise of CTV and PTV coverage allowed
Neurovascular bundle (NVB)	D 0.15 cc ≤ 40.0 Gy. No overlap with CTV; if Tumor directly abuts the NVB → no dose constraint on the affected side Tumor does not directly abuts the NVB→ constraint on both sides, compromise of CTV and PTV coverage allowed
Posterior rectal wall	D 0.1 cc < 10.9 Gy
Rectum	D 0.5 cc < 39.3 Gy, Compromise of CTV and PTV coverage allowed
Urethra + 2 mm	D 0.15 cc ≤ 41 Gy, Compromise of CTV coverage allowed

Secondary outcomes

- GI toxicity of grade ≥ 3 within 3 months after completion of radiotherapy (according to CTCAE V5.0 determined by treating physician),
- mortality within one year of radiotherapy initiation (related to treatment and/or disease),
- number of GU and GI toxicities within 5 years after completion of radiotherapy and their severity,
- biochemical progression-free survival (determined from the start of therapy until the occurrence of PSA recurrence according to the Phoenix criteria i.e. post-therapeutic PSA nadir + 2 ng/ml),
- hormonal therapy-free survival (HTFS) is defined separately for different patient groups:
  - For patients receiving concomitant hormonal therapy, HTFS is measured from the start of SBRT until the initiation of the next line of hormonal therapy.
  - For patients where hormonal therapy is introduced after SBRT (not concomitant), HTFS is calculated as the time from the start of SBRT until the initiation of hormonal therapy.
- overall survival (defined from the start of therapy until death or censoring),
- quality-of-life measured using the EORTC QLQ-C30 and QLQ-PR25 questionnaires during and after treatment,
- uroflowmetry (optional).

A subgroup analysis will be performed for patients with and without a history of TURP.

Participant timeline

Recruitment for the study will take place over a period of approximately 2 years. The end of the study is defined as the end of the follow-up period of the last patient (regular end of the treatment phase: approx. 2 weeks after the start of radiotherapy; regular end of radiotherapy; regular end of study participation: after a follow-up period of five years).

Enrolment of 1st participant	Enrolment of last participant	Completion of treatment of last participant	End of follow-up
1st quarter of 2024	1st quarter of 2026	2nd quarter of 2026	3rd quarter of 2026 (primary endpoint) 2nd quarter of 2031 (secondary endpoints)

1) Baseline

- Medical history (incl. surgical report, surgical histology, data on anti-hormonal therapy and medications improving voiding problems if applicable).
- Documentation of staging examinations (staging according to S3 guideline).
- Quality of life questionnaires (EORTC QLQ-C30 and QLQ-PR25).
- Data on severe obstructive genitourinary symptoms, e.g. date of TURP.
- Assessment of symptoms (prostate specific) according to CTCAE (version 5.0), IPSS and RTOG criteria.
- PSA measurement within 6 weeks prior to the start of radiotherapy.
- Standard planningMRI.
- Uroflowmetry within 6 weeks prior to the start of radiotherapy (optional).

2) During radiotherapy During radiotherapy, the patient is monitored according to standard of care and internal guidelines at the respective project site.

On the last day of radiotherapy (+/- 3 days), the following data are collected:

- Symptoms and toxicities (CTCAE, RTOG).
- PRO questionnaires (QLQ-C30 and QLQ-PR25, study procedure).

3) Follow-up At regular intervals (3, 6, 9, 12, 18, 24, 36, 48, and 60 months after completion of radiotherapy, +/- 2 weeks), outpatient appointments should be scheduled at the treating project site as part of standard of care follow-

Table 4 Data collection

	Baseline	End of RT	Year 1				Year 2				Year 3		Year 4		Year 5		In case of recurrence
			3	6	9	12	15	18	21	24	30	36	42	48	54	60	
	within 6 weeks prior RT start	(+/- 3 days)	months after end of RT (+/- 2 weeks)														
Medical history and documentation of staging	X																
Planning MRI	X																
PSA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival status			X	X	X	X		X		X		X		X		X	X
Hormonal therapy status			X	X	X	X		X		X		X		X		X	X
Symptoms (IPSS)	X		X														
On-site visit / telephone contact possible (X)*	X	X	(X)	(X)	(X)	(X)		(X)		(X)		(X)		(X)		(X)	(X)
Toxicities (CTCAE, RTOG)	X	X	X	X	X	X		X		X		X		X		X	X
PROM (QLQ-C30, QLQ-PR25)	X	X	X	X	X	X		X		X		X		X		X	X
Uroflowmetry**	X		X														

*: if possible should be visit at project site, alternatively telephone visit possible; **: optional

Bold: study procedure

up. If a patient is unable to attend the appointment in person, it is possible to conduct the consultation by telephone and send the questionnaires by mail. At follow-up appointments, symptoms will be evaluated according to RTOG and CTCAE criteria (version 5.0) specific for prostate as well as quality of life using EORTC QLQ C30 and QLQ PR25.

Survival status and use of hormonal therapy or medications improving voiding problems will be assessed at every visit. IPSS and an optional uroflowmetry will be assessed only at 3 months after completion of RT.

PSA values are measured in accordance with the current S3 guidelines for prostate cancer: quarterly during the first two years after completion of radiotherapy (at 3, 6, 9, 12, 15, 18, 21 and 24 months, +/- 2 weeks), then every six months (at 30, 36, 42, 48, 54 and 60 months, +/- 2 weeks) until 5 years after completion of radiotherapy. If PSA is measured by the treating urologist or general practitioner, the patient (or his treating urologist or general practitioner) is asked to submit the results to the project site within 4 weeks. Alternatively, PSA measurement can be done at the project site. However, it is strongly recommended that PSA is measured at the same laboratory at each time point to avoid fluctuation errors due to different measurement methods.

Consent

Participation in the project may be prematurely terminated in the following cases:

a) Prior or during radiotherapy

- the patient (no longer) fulfills the eligibility criteria for the project

b) At any time during the course of the project

- withdrawl of consent

In case of premature termination of the participation in the project, e.g. in case of withdrawal of consent, the data collected up to that timepoint will still be used for the project in pseudonymized form.

Sample size

We assume that around 3% of patients have acute grade ≥ 3 GU toxicity according to CTCAE version 5 (i.e. 1 patient). The rate of treatment discontinuation within 3 months is considered negligible. Our aim is to show with high probability, that the event rate is below a clinically acceptable threshold, which is set at 20%. Under the null hypothesis, this design with an alpha of 0.05, power of 80%, results in an expected number of cases of 30. Dropouts prior to treatment start will be replaced. The protocol population (PP) comprises all patients who have received the planned treatment in full according to the protocol and for whom all relevant data are fully documented. A subgroup analysis will be performed for patients with and without history of TURP.

Recruitment

Patients according to the eligibility criteria will be informed about the project, its objectives, data collection procedures and timepoints, as well as their rights and obligations by a project physician. To participate in the project, patients must provide written informed consent prior any project-specific data collection (i.e. patient reported outcomes measures and optional uroflowmetry).

Data collection

All data collected in this study must be entered into the eCRFs by appropriately authorized persons. The database checks the data using programmed value ranges, validity and consistency checks. If necessary, queries can be made, which are processed by authorized persons via the database. Using these queries, authorized project staff at site can check, answer or correct the discrepancies that have arisen.

For quality assurance, the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents will be granted on such occasions.

Statistical methods

The analysis is carried out for the per-protocol population. The data are analyzed descriptively by determining the mean, standard deviation, minimum, maximum, median, interquartile range and absolute and relative frequencies according to the data distribution. Kaplan-Meier curves are created for the survival endpoints (e.g. biochemical progression-free survival). Regression models are created for the various endpoints to analyze potential influencing factors on the respective endpoint. Reasons for treatment discontinuation and cases of discontinuation or loss to follow-up will be analyzed. Missing values are not imputed, i.e. not replaced or supplemented.

Data monitoring

Not applicable for this observational cohort study with risk category A according to Swiss regulations.

Harms

Definite CT or MRI online adaptive SBRT can be considered a standard of care for the project population in all participating centers, where CT or MRI guided online adaptive SBRT is available. However, its safety and feasibility for the project population (patients with lower urinary tract symptoms and/or prostatic hyperplasia) has not yet been shown. This research project mostly uses data collected in clinical routine. The only data collected specifically for the project is quality of life (QoL) assessed by QLQ-C30 and QLQ-PR25; participants will need 15–20 min per visit to complete the QoL questionnaires. An uroflowmetry is optional.

Auditing

Not applicable for this observational cohort study with risk category A according to Swiss regulations.

Discussion

This phase II international multicenter study aims to evaluate the safety, feasibility, and efficacy of online adaptive definitive SBRT, delivered in five weekly fractions, in patients with newly diagnosed intermediate or high risk localized prostate cancer who present with lower urinary tract symptoms and/or prostatic hyperplasia. Given the increasing adoption of SBRT [29] for localized prostate cancer and its potential advantages in reducing treatment duration, it is crucial to assess its suitability in a population often excluded from previous trials due to concerns over GU toxicity.

The rationale for this study is supported by prior evidence demonstrating the association between baseline lower urinary tract symptoms, prostate volume, and the risk of acute and late GU toxicity following SBRT. Studies such as the secondary analysis of the PACE-B trial [11]

and research from the Veteran's Affairs Medical Center [12] have highlighted the significant association between higher baseline IPSS, increased prostate volume, and the development of GU toxicity. Additionally, a history of TURP has been suggested as a potential risk factor for increased late GU toxicity [21], although conflicting findings indicate the need for further investigation.

Our approach, utilizing a weekly fractionation schedule, is informed by the PATRIOT RCT [18] and hypoFLAME 2.0 trial [24], both of which demonstrated reduced acute GU and GI toxicity with weekly SBRT compared to every-other-day SBRT. This strategy may be particularly beneficial in patients with lower urinary tract symptoms or larger prostate volumes, potentially mitigating the risk of treatment-related toxicities while maintaining oncological efficacy.

Another key aspect of our study is the incorporation of MR-guided SBRT, as MRI guidance has been shown to significantly reduce late grade 2 + GU and GI toxicities compared to CT-guided SBRT [25]. These improved outcomes were likely due to improved visualization of soft tissue structures and enhanced adaptive radiotherapy capabilities [25].

By addressing a population with significant baseline urinary dysfunction and/or prostatic hyperplasia, our study seeks to fill a critical gap in the literature. The findings will provide essential insights into whether weekly adaptive MR-guided SBRT can serve as a viable treatment modality for this subset of patients. If successful, this approach may expand the eligibility criteria for SBRT in localized prostate cancer, offering a safe and effective alternative for patients traditionally considered at higher risk for radiotherapy-related toxicity. Limitations of this study include lack of a comparator group (e.g., conventional fractionation or non-adaptive SBRT), limiting direct causal inferences about efficacy/safety improvement.

Conclusion

SBRT is a highly effective treatment for localized prostate cancer. However, the safety and efficacy of SBRT in patients with lower urinary tract symptoms and/or prostatic hyperplasia has not yet been demonstrated. This phase II international multicenter observational study aims to evaluate the role of weekly CT- or MR-guided online-adaptive SBRT in treating localized intermediate to high-risk prostate cancer in patients with lower urinary tract symptoms (i.e. IPSS > 12) and/or prostate hyperplasia (i.e. prostate volume > 60 mL) who are at increased risk for GU toxicity. Emerging approaches like MR adaptive SBRT and weekly fractionation have shown promise to mitigate the risk of urogenital toxicity.

Abbreviations

CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIL	Dominant intraprostatic lesion
ECOG	Eastern cooperative oncology group
EORTC	European Organisation for Research and Treatment of Cancer
IBD	Inflammatory bowel disease
IPSS	International Prostate Symptom Score
MRI	Magnetic resonance Imaging
NVB	Neurovascular bundle
PROM	Patient reported outcome measures
PSA	Prostate specific antigen
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RTOG	Radiation therapy oncology group
SBRT	Stereotactic body radiation therapy
SIB	Simultaneous integrated boost
TURP	Transurethral resection of prostate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-025-02653-4.

Supplementary Material 1

Author contributions

T.K. and M.M wrote the main manuscript text. All authors reviewed the manuscript.

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Data availability

All data collected in this study must be entered into the eCRFs by appropriately authorized persons. Authorization is given in writing by the principal investigator (signature log). Access to the database is only intended for authorized persons and may not be passed on to third parties. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The final protocol was approved by the Ethics Committee of the University of Zurich, Zurich, Switzerland (Zurich: 2024 – 00115). The X-SMILE study complies with the Helsinki Declaration in its recent German version, the principles of Good Clinical Practice (GCP) and the General Data Protection Regulation (GDPR) as well as the Federal Data Protection Act (FDPA). The trial will also be carried out in accordance with local legal and regulatory requirements. The ClinicalTrials.gov identifier is NCT06834152.

Consent for publication

Not applicable.

Protocol amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation.

Roles and responsibilities

The sponsor had a role in the study design, but not in the collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The funder had no role in the study design, collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Confidentiality

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within

the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. The project site personnel maintain a participant identification list, in which the participant identification numbers are linked to the full participant names and dates of birth. This list will be kept strictly confidential and must not leave the project site. After completion of the project, the participant identification list will be archived for 15 years. All clinical data entered into the database, including electronic case report forms (eCRFs), radiation treatment plans and imaging data, will only be transmitted in pseudonymized form.

Ancillary and post-trial care

The insurance costs will be covered by the sponsor. Local insurance will be arranged in accordance with local regulations, where applicable. Policy Number: 14.970.888.

Dissemination policy

Responsibility for the publication of the results lies with the project management. Until this time, all information on the research project must be treated confidentially. The final publication is planned for after the end of the project. All participating centers will be included in the publication, either as named authors or to the extent that the number of possible co-authors allows. Authors agree to make data and materials supporting the results or analyses presented in their paper available upon reasonable request.

Competing interests

J.L. declares Speaker fee from Accuary and Traveling costs from Micropos Medical and from RaySearch Laboratories. The remaining authors declare no conflict of interest.

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