Clinical and Translational Radiation Oncology 56 (2026) 101037

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Review Article

# Salvage stereotactic MR-Guided adaptive radiotherapy (SMART) re-irradiation for locally recurrent prostate Cancer: Clinical and dosimetric outcomes☆

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ARTICLE INFO

*Keywords:*
Re-irradiation
Radiorrecurent disease
Prostate cancer
Stereotactic Ablative Radiation Therapy (SABR)
Adaptive Radiotherapy (ART)
Stereotactic MR-Guided Adaptive Radiation Therapy (SMART)

ABSTRACT

*Introduction:* Stereotactic ablative radiotherapy (SABR) is a salvage option for locally recurrent prostate cancer (LRPC); however, challenges remain. Stereotactic MRguided Adaptive Radiotherapy (SMART) permits daily adaptation, real-time tracking and automated beam gating, allowing critical organ sparing while potentially improving target coverage. Equivalent Dose in 2 Gy fraction (EQD2) calculation allows accurate organs-at-risk (OAR) dose accumulation in re-irradiation.

We report safety and efficacy of daily SMART re-irradiation for LRPC, alongside an EQD2-based OAR tolerance calculation method.

*Methods:* Salvage SMART to histologically proven non-metastatic hormone-sensitive LRPC was retrospectively analysed. Inclusion criteria included: ≥18 months post-RT, prostate-specific antigen (PSA) ≤ 30 ng/mL, PSA doubling-time > 6 months, International Prostate Symptom Score (IPSS) ≤ 19, prostate ≤ 80 cc and cT1–T3a/b. Reirradiation regimens were 30–35 Gy/5 fractions. Dose-boost and hormone therapy were allowed. Rectal spacer was recommended.

Outcomes included toxicity, local control (LC), biochemical relapse-free survival (bRFS), progression free survival (PFS) and overall survival (OS). EQD2-based workflow to estimate OAR cumulative constraints was reported.

*Results:* Between 2019 and 2023, nineteen patients underwent salvage-SMART to whole-gland (n = 12), hemi-gland (n = 5) or seminal vesicle (n = 2) at a median 87 months (range 35–587) from first radiotherapy. All 95 delivered fractions underwent online adaptation, meeting all estimated OAR.

With 21 months follow-up, acute grade 2 genitourinary (GU) toxicity was 21 % with no acute ≥ grade 3 GU or ≥ grade 2 gastrointestinal (GI) toxicity observed. Late GU grade 3 toxicity occurred in 3 patients (15.7 %).

OS was 100%; bRFS 73.7%; LC 84.2%; and median-PFS was not reached. One and two-year PFS were 94.7% and 89.4%. One and two-year LC was 100%. Two contralateral intraprostatic failures followed hemi-gland treatment were observed.

*Conclusion:* Daily adaptive SMART re-irradiation is a feasible, non-invasive salvage option for LRPC, combining high LC with low toxicity. Our experience supports integrating MR- guidance with an individualized EQD2-informed planning.

☆ This article is part of a special issue entitled: 'Reirradiation' published in Clinical and Translational Radiation Oncology.

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https://doi.org/10.1016/j.ctro.2025.101037
Received 29 May 2025; Received in revised form 10 August 2025; Accepted 19 August 2025
Available online 26 August 2025

## Introduction

Following primary radical radiotherapy (RT) for localized prostate cancer (PCa), between 20 % and 50 % of patients will experience biochemical recurrence (BCR) [1]. Across all risk groups, the first clinical site of relapse is most commonly local [2]. Despite this, just 2 % of patients with locally radio-recurrent prostate cancer (LRPC), undergo local definitive therapies [3]. Historically, intermittent or lifelong androgen deprivation therapy (ADT) has been the standard approach [4,5].

Advances in imaging and ultrasensitive prostate-specific antigen (PSA) assays have improved the early detection of recurrence, supporting a more targeted treatment approach [6]. Local salvage therapies include radical prostatectomy (RP), cryotherapy, high-intensity focused ultrasound (HIFU), brachytherapy (BT) and stereotactic ablative radiotherapy (SABR). However, the optimal salvage technique remains debated, emphasizing the need for a personalized, multidisciplinary approach. While all local modalities demonstrated comparable biochemical relapse-free survival (bRFS) rates, toxicity profiles vary significantly [7]. High-dose rate (HDR) BT is one of the most extensively studied modalities, offering favourable dosimetric advantages by enabling steep dose fall-off and organ sparing. However, it is invasive and technically demanding, requiring significant operator expertise and infrastructure, which limits its availability to specialist centres [8]. Repeating external beam RT (EBRT) to the prostate allows control of the disease to be regained with curative intent or at least good control for a period, delaying or avoiding a patient being treated with ADT. However, dose-limiting toxicity (DLT) to organs at risk (OAR) remains the main concern for reirradiation, as historical data on salvage EBRT reported unacceptably high toxicity rates [9]. Technological advances gave re-irradiation a second chance with SABR offering a more accurate, conformal and tolerable approach. Contemporary series of CyberKnife® and computed tomography (CT)-based SABR demonstrated encouraging efficacy and safety in prostate reirradiation [10–14]. Reported 2-year bRFS ranges from 55-81 %, with 5-years around 60 %. Local control (LC) rates vary between 83.4–94 % with a favourable toxicity profile. Nevertheless, prospective clinical trials and expert consensus on the optimal use of salvage SABR remains limited, emphasizing the need for further investigation and standardization [15].

Further enhancement of treatment precision has emerged with stereotactic magnetic resonance guided adaptive radiotherapy (SMART). SMART provides superior soft-tissue visualization, target and OAR contour adaptation to daily anatomical position, plan re-optimization, real time tracking and beam gating. These features not only eliminate the need for fiducial markers but also enhance target coverage and improve OAR sparing by enabling the use of tighter margins. In the primary PCa setting, the MIRAGE phase III trial [16] demonstrated the advantages of Magnetic Resonance Imaging (MRI)-guided SABR over CT-based SABR, with significantly reduced acute physician-scored toxicity and preserved patient-reported quality of life.

While early reports on salvage SMART for prostate reirradiation are promising, the current evidence remains limited, often involving heterogeneous patient cohorts that may confound outcome interpretation [17–21]. In this context, we present our institutional experience using SMART-based salvage reirradiation for non-metastatic, hormone-sensitive, LRPC evaluating focusing on both efficacy and toxicity outcomes.

## Methodology

### *Study design and population*

This single-institution retrospective analysis evaluated SMART-based salvage re-irradiation for non-metastatic, hormone-sensitive LRPC. All patients provided written informed consent and were assessed by a urology SABR advisory team (USAT) with agreement that SMART reirradiation would be the most appropriate local treatment modality. Key inclusion criteria for prostate salvage SMART are listed in Table 1. Use of a rectal spacer (Barrigel®) was recommended in all patients where feasible [22]. All patients were treated with SMART-based salvage re-irradiation as exclusive local therapy. ADT was prescribed according to clinical judgment.

### *SABR planning and delivery*

Continuous intrafraction adaptive MRI-guided RT with automatic beam triggering was used (*6MV 0.35 T MRIdian Linac, ViewRay Inc, Oakwood Village, OH*). Daily MRI setup images were acquired, followed by re-contouring and plan re-optimisation to account for anatomical variations from the baseline plan in all cases.

Simulation included a true fast imaging with steady-state free precession (TRUFISP) MRI and a CT scan. The CT was deformably registered to the MRI to provide electron density information for dose calculation. The prostate gland was identified as the tracking structure through cine MRI, enabling gated treatment. Additional diagnostic imaging, such as other MRI sequences or prostate-specific membrane antigen (PSMA)-positron emission tomography (PET), could be fused to assist with target contour delineation.

Contouring and prescription were guided by institutional protocol and available literature [7,12–15]:

1. Focal recurrence with dominant lesion: If the recurrence was clearly visible as a dominant intraprostatic lesion (DIL) on MRI and confirmed by biopsy, the gross tumour volume (GTV) was this DIL. Clinical target volume (CTV) was GTV + 2 mm, excluding the urethra where identifiable. The preferred dose regimen was 35 Gy in 5 fractions to the PTV.
2. Non-focal or bilateral recurrence / unclear DIL: If the recurrence was PET-positive but not visible on TRUFISP MRI, GTV was distinct DIL per fused PET. The GTV was rigidly transferred and not adapted daily. CTV was either the whole gland or GTV + 2 mm. A prescription of 30 Gy in 5 fractions to the whole gland PTV was used. An additional partial simultaneous integrated boost (SIB) was given to any lesion visible on MR or PET within the prostate, up to a maximum of 35 Gy /5 fractions.

In all cases, the planning target volume (PTV) was a 3 mm isotropic margin expansion from the CTV.

SABR plans were generated with inverse planning with the following dosimetric aims; PTV V(100 %) $\geq$ 95 %, PTVHigh V(95 %) $\geq$ 98 % and PTV D(1 cc) $<$ 140 %. The minimum PTV V(100 %) threshold was

**Table 1**
Key Inclusion Criteria for Prostate Salvage SMART.

| Criterion | Details |
|---|---|
| Biochemical Failure | Defined by Phoenix criteria*: PSA nadir + 2 ng/mL |
| Recurrence Interval | Occurred $\geq$ 18 months after completion of primary radiotherapy |
| Histological Confirmation | LRPC confirmed by prostate biopsy |
| Prostate Volume | $\leq$80 cc |
| Clinical Stage | T1–T3a/b (with caution in posterior cT3a extension, especially if rectal spacers were used) |
| PSA Level | $\leq$30 ng/mL (at the time of salvage reirradiation) |
| PSA-DT | >6 months |
| LUTS | IPSS $\leq$ 19 (preferably $<$ 14 if no visible DIL) |
| ADT | Bicalutamide 150 mg or LHRH analogues, as clinically appropriate |

ADT: Androgen Deprivation Therapy; DIL: dominant intraprostatic lesion; IPSS: International Prostate Symptom Score; LHRH: luteinizing hormone-releasing hormone; LRPC: Locally recurrent prostate cancer; LUTS: Lower Urinary Tract Symptoms; PSA: Prostatic Specific Antigen; PSA-DT: PSA Doubling Time; SMART: stereotactic magnetic resonance guided adaptive radiotherapy.
* Roach M. IJRBOP 2006.

defined as ≥ 70 %, whilst achieving all individualised OAR tolerances. Treatment plans were normalised to maximise prescription dose coverage while ensuring compliance with all OAR constraints. DLT was recorded to identify factors restricting the planning process.

*EQD2-based workflow for cumulative dose assessment and re-irradiation constraints calculation*

To ensure the safety of the new treatment course, updated OAR dose constraints were calculated based on the previous course(s), and cumulative doses were estimated using a methodology aligned with the United Kingdom (UK) SABR consortium guidance [23,24]. In brief, this involves converting doses from all courses to the equivalent total dose in 2-Gy fraction (EQD2) with suitable alpha–beta ratios (α/β) [25], applying a tissue recovery factor to account for the time since the previous course of treatment, and assessing the remaining OAR tolerance with respect local protocols. In cases with previous EBRT, Digital Imaging and Communications in Medicine (DICOM) RT dose data was available and was used to determine the dose delivered to critical OARs [26]. Where patients received previous low or high-dose rate (LDR or HDR) BT and detailed dosimetric data was not available, previous OAR doses were estimated based on published literature [27]. This process is summarised in Fig. 1 [23,28] with a worked example available in Appendix 1.

*Statistical analysis*

Descriptive data were presented as median (range) for continuous variables, and percentage for categorical and dichotomous variables. The primary objective of this study was to assess the incidence of salvage SMART re-irradiation related acute (<3 months) and late (>3 months) genitourinary (GU) and gastrointestinal (GI) toxicity, graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A secondary objective was to evaluate time-to-event outcomes, measured from the first day of SMART, including bRFS, LC, progression free survival (PFS) and overall survival (OS). Given there is no universally accepted consensus for bRFS following re-irradiation, it was clinical judgement-based PSA rise (2–3 consecutive PSA rising). PFS was determined using the date of any progression or death from any cause, with those lost from follow-up censored. OS was determined using the date of death from any cause, with those lost from follow-up censored. The Kaplan-Meier method was used to estimate bPFS, PFS, and OS, with log-rank for subgroup comparisons. Fisher's exact test was used for associations between categorical variables.

## Results

Between December 2019 and June 2024, nineteen patients underwent SMART-based salvage re-irradiation for non-metastatic hormone-sensitive LRPC. The median interval between the primary RT course and SMART re-irradiation was 87 months (range 35—587 months). First treatments were EBRT (conventional fractionation n = 9, moderate hypofractionation n = 2, SABR n = 1) and BT (n = 7). Two patients had prior locoregional lymph-nodes (LN) disease (cN1). ADT was administered during initial therapy in 68.4 % cases.

At SMART re-irradiation, the median age was 74 years (range 63–83 years ), and median PSA 3 ng/mL (range 0–16 ng/mL). Local relapse was within the prostate gland in 17 patients (89.5 %) and in the prostate base-seminal vesicles (SSVV) in 2 patients (10.5 %). ADT was prescribed in 47.4 % of patients at salvage setting. Table 2 lists patients' characteristics.

All patients were treated with curative/salvage intention in 5-fraction regimen delivered on alternate days. The target volume included partial-gland (n = 5), the involved SV (n = 2) or the whole gland (n = 12 patients, among them 3 cases received SIB to the DIL). All cases fulfilled the European Society for Radiotherapy and Oncology (ESTRO)- European Organisation for Research and Treatment of Cancer (EORTC) type 1 re-irradiation criteria (geometric overlap) [29]. The total dose prescribed was 30 Gy/5 fractions (Biologically Effective Dose $[BED]_{1.5}$ 150 Gy) in 12 patients, receiving SIB up to 35 Gy/5 fractions ($BED_{1.5}$ 198.3 Gy) 3 of them, while 7 patients received a total dose of 35 Gy/5 fractions. All partial-gland treatments used the 35 Gy regimen. (Table 3).

Online plan adaptation was performed in 100 % of delivered fractions (95 fractions) and all patients completed the planned treatment schedule. All patients achieved the mandatory aim of PTV High V95%> 98 % and all estimated OAR constraints were met. Table 4 shows the EQD2-converted doses for each patient, using suitable α/β and recovery factors [24,25].

With a median follow-up from salvage SMART re-irradiation of 21 months (range 6–48), no patients were lost to follow-up, and all were alive at the time of analysis. The cumulative incidence of any acute GU toxicity was 68.1 %, with 21 % experiencing grade 2 and the most common acute GU side effect was urgency/frequency (15,8%). No acute ≥ grade 3 GU events occurred. Late grade 3 GU toxicity was recorded in three patients (15.7 %). Two patients developed obstructive symptoms managed with local ablative therapies. Notably, one with prior intermittent self-catheterization and transurethral resection of the prostate (TURP) before salvage SMART. The third patient experienced severe urinary incontinence managed with botulinum toxin (Botox®).

Acute and late GI toxicity was limited to grade 1 in 15.7 % and 10.5 % of patients, respectively; no ≥ grade 2 GI toxicity was observed.

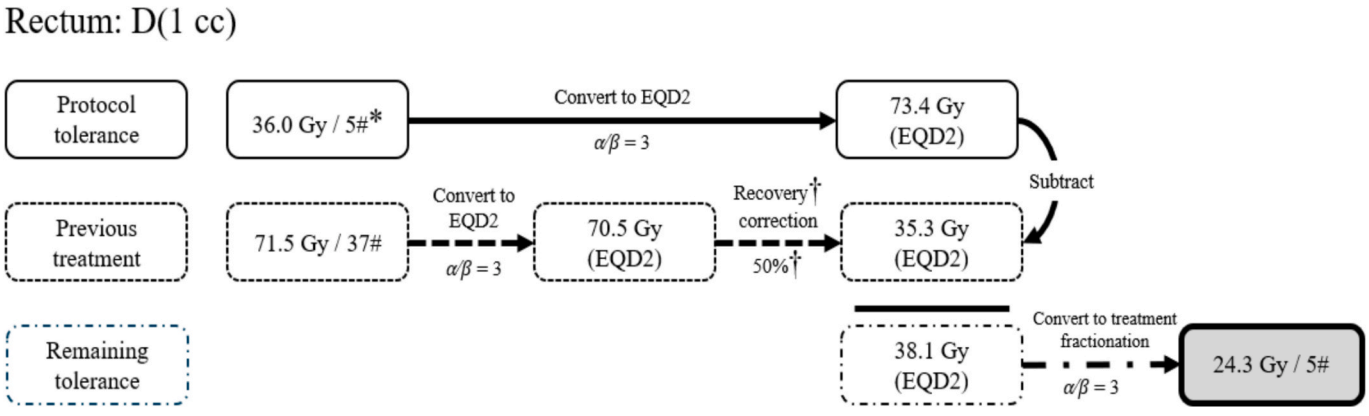


**Fig. 1.** Relative biological effectiveness (RBE) calculation example of rectal constraint. *D(1 cc) constraint per PACE-B trial recommendations (van As N et al. NEJM 2024). †8.6 years of recovery, therefore 50 % recovery as per UK SABR consortium guidelines (NHS England and Moreno-Olmedo et al. TipsRO (2025). α/β ratio = 3 (Joiner, M.C., & van der Kogel, A. Basic Clinical Radiobiology CRC Press; 2009).

**Table 2**
Demographic parameters.

| Patients, n (%) | 19 (100) |
|---|---|
| **First treatment** | |
| **Age (years), median (range)** | 62 (33–76) |
| **iPSA (ng/mL), median (range)** | 17 (5–113) |
| **RT technique** | |
| **LDR BT, n (%)** | 6 (31.6) |
| **HDR BT, n (%)** | 1 (5.2) |
| **EBRT, n (%)** | 12 (63.2) |
| **Conventional (74 Gy/37#), n (%)** | 9 (47.4) |
| **Moderate hypo (55–60 Gy/20#), n (%)** | 2 (10.5) |
| **SABR (36.25/5#), n (%)** | 1 (5.3) |
| **Gleason Score (GS)** | |
| **≤3 + 4** | 10 (52.6) |
| **7 (4 + 3)** | 4 (21.1) |
| **≥8** | 5 (26.3) |
| **ADT, n (%)** | 13 (68.4) |
| **Salvage SMART-based reirradiation** | |
| **Age (years), median (range)** | 74 (63–63) |
| **IPSS, median (range)** | 6 (2–15) |
| **iPSA (ng/mL), median (range)** | 3 (0–16) |
| **SMART schedule** | |
| **1 DL, n (%)** | 15 (78.9) |
| 30 Gy/5#, n (%) | 9 (47.4) |
| 35 Gy/5#, n (%) | 6 (31.6) |
| **2 DL (30 + 35 Gy SIB), n (%)** | 4 (21.1) |
| **Target volume** | |
| **Whole gland** | 12 (63.2) |
| **Partial gland** | 5 (26.3) |
| **Seminal Vesicle** | 2 (10.5) |
| **ADT** | |
| **No** | 8 (42.1) |
| **Yes** | 9 (47.4) |
| **Unknown** | 2 (10.5) |

ADT: Androgen deprivation therapy; BT: brachytherapy; EBRT: External bean radiotherapy; Gy: Gray; HDR: High dose rate; IPSS: International Prostate Symptom Score; iPSA: initial prostatic specific antigen; LDR: Low dose rate; n: number; SIB: simultaneous integrated boost; SMART: Salvage Stereotactic MR-Guided Adaptive Radiotherapy; #: fraction/s;

At analysis, bRFS was 73.7 % and OS remained 100 %. The median-PFS was not reached and 1 and 2-year PFS were 94.7 % and 89.4 %, respectively. The 3-year estimated PFS was 33.7 %, with most events occurring after 24 months. 1 and 2-year LC rates were 100 %, with an estimated 3-year LC of 84.2 %.

Five patients (26.3 %) experienced BCR (Fig. 2**)**. Of these, two had contralateral in-field intraprostatic recurrence following partial-gland salvage SMART, at 26 and 29 months. Although a higher proportion of local relapses occurred in partial gland (33.3 % vs 9.1 %), this difference did not reach statistical significance ($p = 0.23$). Another patient had intraprostatic recurrence with concurrent locoregional nodal progression 26-month after SMART re-irradiation. Two other patients developed isolated nodal relapses but showed a complete response within the prostate gland.

No significant difference in 2-year PFS was observed between patients treated with and without ADT (78 % vs 70 %; $p = 0.49$). However, patients achieving a nadir PSA $\leq$ 0.2 ng/mL ($n = 12$) correlated with improved 2-year PFS (91.7 % vs 42.9 %; $p = 0.045$). ADT use was significantly associated with reaching a PSA nadir $\leq$ 0.2 ($p = 0.04$).

## Discussion

Despite the growing indication, prostate re-irradiation remains challenging, mainly due to DLT to OAR. Historically, salvage EBRT resulted in unacceptable toxicity [9]. While SABR renewed the interest in local salvage, cross-study comparisons remain difficult due to heterogeneity in patient selection, treatment technique, ADT use, endpoints' criteria and variable follow-up. Given these limitations, high-quality real-world data collection remains essential to guide clinical practice and contribute toward standardization.

Our study sought to highlight the feasibility, safety profile, and promising outcomes of salvage SMART re-irradiation in LRPC, while also presenting an individualized EQD2-based workflow for cumulative dose summation and OAR constraint evaluation.

With a follow-up of 21 months, although with a modest number of patients, SMART prostate re-irradiation achieved excellent LC (84.2 %) and favourable bRFS (73.7 %), comparable to or slightly higher than previously reported salvage SABR series using CT-based platforms [10–14]. As far as toxicity is concerned, outcomes in our study align well with previously published data [13]. We observed no acute $\geq$ G3 GU, with acute G2 GU toxicity in 21 % and late G3 GU events in 15.7 %. GI toxicity was mild, limited to G1 events only. Prior studies reported acute GU grade 2 + rates around 13 % and late up to 25 %, with grade 3 + rates up to 9.4 %.

**Table 3**
Key dosimetric parameters.

| | Dose prescription (Gy) | | PTV prostate (30 Gy) | | | PTV SIB (35 Gy) | | | PTV high (30 Gy) | | PTV high (SIB) | | Plan quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| re-RT volume | Primary (Gy) | Secondary (Gy) | V(100 %) (%) | vol. (cc) | D(98 %) (Gy) | V(100 %) (%) | vol. (cc) | D(98 %) Gy | V(95 %) (%) | vol. (cc) | V(95 %)% | vol. (cc) | PDS |
| Hemi gland | 35 | | 72.7 | 4.1 | 24.0 | | | | 96.2 | 2.8 | | | 1.19 |
| SV | 30 | | 73.3 | 8.3 | 13.23 | | | | 99.7 | 4.7 | | | 1.16 |
| Whole gland | 30 | | 89.0 | 63.2 | 24.3 | | | | 99.8 | 54.3 | | | 1.11 |
| Whole gland | 30 | | 85.7 | 71.8 | 26.6 | | | | 99.2 | 56.4 | | | 1.03 |
| Whole gland | 30 | | 83.2 | 60.9 | 12.6 | | | | 99.8 | 49.7 | | | 1.08 |
| Whole gland | 30 | 35 | 89.6 | 98.2 | 26.1 | 89.9 | 29.6 | 31.0 | 99.3 | 54.9 | 99.6 | 26.9 | 1.06 |
| Whole gland | 30 | | 95.0 | 89.6 | 28.6 | | | | 99.8 | 77.2 | | | 1.09 |
| Whole gland | 30 | 35 | 80.5 | 61.3 | 19.2 | 85.6 | 22.4 | 26.3 | 100.0 | 43.0 | 99.9 | 19.0 | 1.18 |
| Whole gland | 35 | | 78.9 | 58.9 | 26.7 | | | | 99.8 | 43.5 | | | 1.10 |
| Hemi gland | 35 | | 95.0 | 16.9 | 34.3 | | | | 100.0 | 13.2 | | | 1.19 |
| Hemi gland | 35 | | 89.5 | 19.2 | 25.1 | | | | 99.3 | 17.5 | | | 1.04 |
| Hemi gland | 35 | | 87.8 | 29.7 | 29.1 | | | | 99.9 | 20.6 | | | 1.09 |
| Whole gland | 30 | 35 | 89.9 | 60.1 | 26.9 | 97.8 | 8.2 | 34.9 | 99.7 | 39.1 | 99.3 | 8.1 | 1.13 |
| Whole gland | 30 | | 92.2 | 61.5 | 26.6 | | | | 99.9 | 50.3 | | | 1.12 |
| Left SV | 30 | | 95.0 | 7.6 | 28.6 | | | | 99.9 | 6.7 | | | 1.16 |
| Whole gland | 35 | | 74.2 | 59.0 | 19.9 | | | | 98.4 | 46.7 | | | 1.06 |
| Whole gland | 30 | | 80.0 | 43.2 | 22.9 | | | | 99.7 | 27.3 | | | 1.07 |
| Hemi gland | 35 | | 95.0 | 11.9 | 32.7 | | | | 99.9 | 10.4 | | | 1.25 |
| Whole gland + L SV | 30 | | 79.5 | 39.3 | 18.1 | | | | 99.4 | 27.7 | | | 1.05 |

PDS: Prescription dose spillage; re-RT: reirradiation; SIB: Simultaneous integrated boost; SV: Seminal Vesicle.

**Table 4**
Organ at Risk (OAR) dosimetric reporting from baseline plans.

| # | Rectum | | | | | Bladder | | | | | Urethra | | | | | Dose limiting OAR | RF (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | In 5 fractions (Gy) | | reRT course EQD2(Gy) | | Summed doses† EQD2 (Gy) | In 5 fractions (Gy) | | reRT course EQD2(Gy) | | Summed doses† EQD2 (Gy) | In 5 fractions (Gy) | | reRT course EQD2(Gy) | | Summed doses† EQD2 (Gy) | | |
| | Remaining tolerance* | Dose delivered | RBE constraint | Dose delivered | | Remaining tolerance* | Dose delivered | RBE constraint | Dose delivered | | Remaining tolerance* | Dose delivered | RBE constraint | Dose delivered | | | |
| **1** | D(5.0 cc) ≤ 22.4 | 1 | D(5.0 cc) ≤ 33.5 | 0.6 | 44.1 | D(1.0 cc) ≤ 20.9 | 20.8 | D(1.0 cc) ≤ 30.0 | 29.8 | 73.3 | D(0.1 cc) ≤ 30.0 | 29.9 | D(0.1 cc) ≤ 54.0 | 53.7 | 109.7 | Bladder, urethra | 50 |
| **2** | D(0.5 cc) ≤ 14.1 | 9.9 | D(0.5 cc) ≤ 16.4 | 9.9 | 46.2 | D(0.5 cc) ≤ 22.6 | 20.2 | D(0.5 cc) ≤ 34.0 | 28.4 | 63.7 | No urethra included within plan | | | | | None | 50 |
| **3** | D(1.0 cc) ≤ 24.3 | 21.7 | D(1.0 cc) ≤ 38.2 | 31.9 | 67.4 | D(5.0 cc) ≤ 25.4 | 12.7 | D(5.0 cc) ≤ 41.1 | 14.1 | 63.8 | No urethra included within plan | | | | | Bladder | 50 |
| **4** | D(0.1 cc) ≤ 30.6 | 30.5 | D(0.1 cc) ≤ 55.8 | 55.5 | 68.7 | D(0.1 cc) ≤ 30.9 | 30.9 | D(0.1 cc) ≤ 56.7 | 56.7 | 77 | No urethra included within plan | | | | | Bladder, Rectum | 75 |
| **5** | D(1.0 cc) ≤ 20.1 | 20 | D(1.0 cc) ≤ 28.2 | 28 | 73.2 | D(0.5 cc) ≤ 22.6 | 20.9 | D(0.5 cc) ≤ 34.0 | 30 | 76.6 | D(50 %) ≤ 29.4 | 29 | D(50 %) ≤ 52.2 | 51 | 94.7 | Urethra, bladder | 0± |
| **6** | D(1.0 cc) ≤ 24.7 | 22.4 | D(1.0 cc) ≤ 39.2 | 33.5 | 67.8 | D(10.0 cc) ≤ 25.7 | 21.7 | D(10.0 cc) ≤ 41.8 | 31.9 | 67 | D(50 %) ≤ 31.9 | 30.9 | D(50 %) ≤ 59.8 | 56.7 | 92.7 | Urethra | 50 |
| **7** | D(1.0 cc) ≤ 28.0 | 27.7 | D(1.0 cc) ≤ 48.2 | 47.3 | 61.9 | D(5.0 cc) ≤ 30.4 | 29.3 | D(5.0 cc) ≤ 55.2 | 51.9 | 63 | D(50 %) ≤ 32.5 | 31.5 | D(50 %) ≤ 61.8 | 58.6 | 92.6 | Rectum | 75 |
| **8** | D(0.1 cc) ≤ 26.2 | 25.9 | D(0.1 cc) ≤ 43.2 | 42.4 | 80.1 | D(0.1 cc) ≤ 24.3 | 24.3 | D(0.1 cc) ≤ 38.2 | 38.2 | 76.8 | No urethra included within plan | | | | | Bladder, Rectum | 50 |
| **9** | D(1.0 cc) ≤ 26.3 | 26 | D(1.0 cc) ≤ 43.5 | 42.6 | 72.6 | D(5.0 cc) ≤ 27.6 | 27 | D(5.0 cc) ≤ 47.0 | 45.4 | 75.4 | D(50 %) ≤ 33.7 | 33 | D(50 %) ≤ 65.6 | 63.4 | 93.4 | Urethra, Rectum | 50 |
| **10** | D(0.1 cc) ≤ 28.7 | 27.6 | D(0.1 cc) ≤ 50.2 | 47 | 55.1 | D(1.0 cc) ≤ 36.25 | 36 | D(1.0 cc) ≤ 74.3 | 73.4 | 82.2 | D(0.5 cc) ≤ 38.3 | 36.8 | D(0.5 cc) ≤ 81.7 | 76.2 | 96.8 | None | 90 |
| **11** | D(1.0 cc) ≤ 25.7 | 18.5 | D(1.0 cc) ≤ 41.8 | 24.8 | 56.2 | D(10.0 cc) ≤ 27.0 | 10.3 | D(10.0 cc) ≤ 45.4 | 10.4 | 42.1 | D(50 %) ≤ 33.2 | 21.7 | D(50 %) ≤ 64.0 | 31.9 | 70.6 | None | 50 |
| **12** | D(1.0 cc) ≤ 23.6 | 20.8 | D(1.0 cc) ≤ 36.4 | 29.8 | 66.7 | D(5.0 cc) ≤ 24.9 | 21.3 | D(5.0 cc) ≤ 39.7 | 30.9 | 68.1 | D(50 %) ≤ 31.4 | 31.2 | D(50 %) ≤ 58.3 | 57.7 | 95 | Urethra | 50 |
| **13** | D(1.0 cc) ≤ 25.6 | 23 | D(1.0 cc) ≤ 40.8 | 35 | 66.9 | D(10.0 cc) ≤ 24.8 | 15.9 | D(10.0 cc) ≤ 39.5 | 19.7 | 57.1 | D(50 %) ≤ 31.3 | 30.7 | D(50 %) ≤ 58.0 | 56.1 | 93.8 | Rectum | 50 |
| **14** | D(0.1 cc) ≤ 28.9 | 28.7 | D(0.1 cc) ≤ 50.8 | 50.2 | 68.1 | D(0.1 cc) ≤ 28.9 | 28.8 | D(0.1 cc) ≤ 50.8 | 50.5 | 68.2 | D(mean) ≤ 30.0 | 29.9 | D(mean) ≤ 54.0 | 53.7 | 95.4 | Urethra, Rectum | 50 |
| **15** | D(1.0 cc) ≤ 20.9 | 18 | D(1.0 cc) ≤ 30.0 | 23.8 | 67.3 | D(5.0 cc) ≤ 22.4 | 11.2 | D(5.0 cc) ≤ 33.5 | 11.7 | 55.2 | No urethra included within plan | | | | | Rectum | 50 |
| **16** | D(0.1 cc) ≤ 25.7 | 25.3 | D(0.1 cc) ≤ 41.8 | 40.8 | 68 | D(0.1 cc) ≤ 24.8 | 24.8 | D(0.1 cc) ≤ 39.5 | 39.5 | 76.9 | D(50 %) ≤ 30.5 | 30.5 | D(50 %) ≤ 55.5 | 55.5 | 95.6 | Rectum, Bladder, Urethra | 50 |
| **17** | D(1.0 cc) ≤ 22.2 | 13.3 | D(1.0 cc) ≤ 33.0 | 15.1 | 47.2 | D(10.0 cc) ≤ 21.5 | 21 | D(10.0 cc) ≤ 30.7 | 30.2 | 65.6 | D(50 %) ≤ 31.4 | 30.9 | D(50 %) ≤ 58.3 | 56.7 | 94.1 | Urethra | 50 |
| **18** | D(1.0 cc) ≤ 23.5 | 18.9 | D(1.0 cc) ≤ 36.2 | 25.6 | 62.9 | D(5.0 cc) ≤ 26.1 | 3.5 | D(5.0 cc) ≤ 42.9 | 2.6 | 39.1 | D(50 %) ≤ 31.4 | 23 | D(50 %) ≤ 58.3 | 35 | 71.9 | None | 50 |
| **19** | D(5.0 cc) ≤ 22.4 | 16.9 | D(5.0 cc) ≤ 33.5 | 21.6 | 65.1 | D(1.0 cc) ≤ 20.9 | 20.9 | D(1.0 cc) ≤ 30.0 | 30 | 62.2 | D(50 %) ≤ 21.0 | 32.6 | D(50 %) ≤ 30.2 | 62.1 | 105.1 | Bladder, Urethra | 50 |

RBE: Relative biological effectiveness; RF: Recovery Factor; reRT: reirradiation; #: patient number.
All OARs alpha/beta ratio were considered 3.
*Remaining tolerance calculated based on RBE workflow Fig. 1; †Cumulative doses from both RT courses; ±Due to < 6 months between courses.

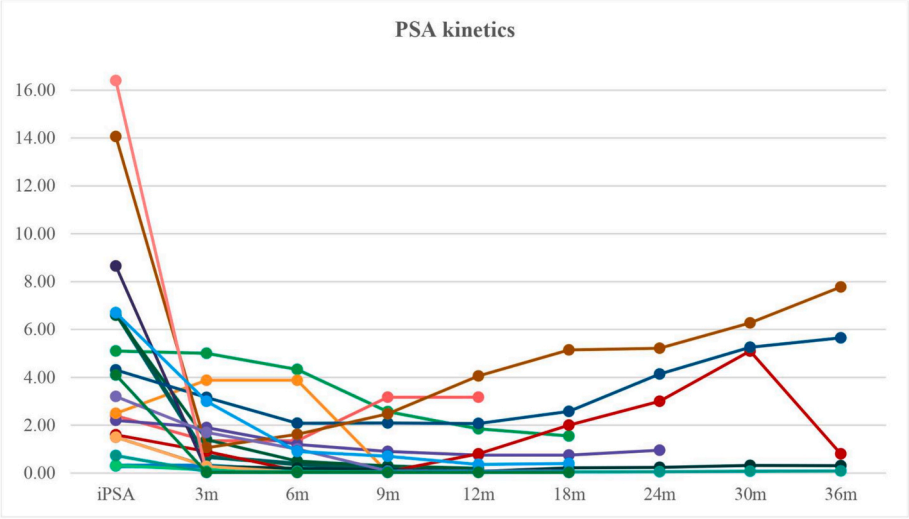


**Fig. 2.** Individual patient PSA kinetics following salvage SMART reirradiation for locally recurrent prostate cancer. Each coloured line reprents one patient's PSA trajectory, plotted from pre-reirradiation baseline (iPSA) through serial follow-up intervals up to 36 months.

In terms of oncologic outcomes, the median PFS was not reached and 1 and 2-year PFS rates were 94.7 % and 89.4 %, respectively, which remain relatively high, likely due to most progression events occurring beyond 24 months. The probability of remaining progression-free dropped below 50 % at approximately 29 months, with an estimated 3-year PFS of 33.7 %. These findings suggest that while early disease control following salvage SMART is excellent, late failures may still occur, emphasizing the need for extended follow-up.

The DIL is recognized as the most common site of local relapse, making it a key target for dose-escalation strategies. MRI offers superior visualization, allowing for image-guided focal dose-escalation to enhance tumour control. However, optimal dose regimen and the cumulative OAR constraints remain challenging and not standardized, as highlighted in a recent international survey [30].

In Corkum et al. *meta*-analysis [10], higher EQD2 doses (median $EQD2_{1.5}$ 77.1 Gy), predominantly delivered with SABR (92 %), were associated with improved LC and bRFS, albeit with increased GU and GI toxicity. In our study, the prescribed 30 Gy and 35 Gy in five fractions correspond to EQD2 of 64.3 Gy and 85 Gy, respectively ($\alpha/\beta = 1.5$), supporting the feasibility of achieving dose-escalation beyond 77 Gy within acceptable toxicity. These regimens are consistent with prior literature [7,12–15], including the UK SABR Consortium updated guidance for salvage pelvic re-irradiation, which proposes 30 Gy in 5 fractions as a standard dose based on the NHS Commissioning through Evaluation (CtE) program [24]. Similarly, the ESTRO ACROP Delphi consensus [15] recommended dose ranges of 30–36 Gy in 5–6 fractions, with individualization based on prior exposure and proximity to OARs. Additional supporting evidence employs 30 Gy/5 or 35 Gy/5 schedules [7,12–14].

Given the lack of consensus, the minimum dose to the PTV in salvage SABR is often constrained by the calculated cumulative OAR doses and the corresponding dose fall-off required to meet safety thresholds. Literature data suggested that the accepted cumulative re-irradiation dose should not exceed 120 Gy for bladder and 70–100 Gy for rectum [31,32]. In our series, the EQD2-converted tolerance doses fall within these recommended thresholds (Table 4). Only three cases exceeded 70 Gy to the rectum, but all remained well < 100 Gy upper limit, which is consistent with our observed GI toxicity rates. In this context, our individualized EQD2-based dose accumulation workflow (Fig. 1, Appendix 1), developed in alignment with the UK SABR Consortium guidance [24], provided a feasible method and supports safe planning. Though prospective validation is required, this approach is consistent with recently published findings from an international survey on re-irradiation constraints [30].

Partial gland re-irradiation is an attractive approach to minimize toxicity, while early results showed no apparent negative impact on disease control outcomes [12]. However, our findings suggest that greater caution may be warranted in patient selection. In our cohort, partial gland re-irradiation delivered 35 Gy/5# to the DIL with three local recurrences (33.3 %) versus one in whole-gland treatments (9.1 %), though not statistically significant ($p = 0.23$). Notably, two recurrences occurred contralaterally to the hemi-irradiated gland, highlighting the risk of undertreating microscopic disease outside the visible target and the trade-off between focal and whole-gland salvage.

This underscores the potential limitations of current imaging modalities in fully characterizing the extent of recurrent disease. Despite all patients in our cohort undergoing both multiparametric MRI and PSMA-PET, microscopic or multifocal disease may remain undetected, particularly at low PSA levels. PSMA-PET, while highly specific, has a sensitivity that increases as PSA levels raise, and may miss lesions with low PSMA expression or a small tumour burden [6,33]. Similarly, multiparametric MRI may fail to detect small or diffuse lesions in the salvage setting, particularly after prior RT, which alters prostate anatomy and contrast enhancement patterns [34,35].

These findings emphasize the risk of undertreatment with partial-gland salvage, despite the use of advanced imaging, and reinforce the importance of accurate disease mapping, and the need for robust selection criteria when considering focal salvage strategies. For these uncertainties, ADT may contribute control microscopic disease and achieve better outcomes. However, in our results, no significant difference in 2-year PFS was observed with or without ADT (78 % vs 70 %; $p = 0.49$). Despite the lack of statistical significance, the absolute difference in PFS suggests a potential benefit of ADT that may not be fully captured due to the limited sample size and retrospective design.

Interestingly, achieving a post-treatment PSA nadir $\leq 0.2$ ng/mL was significantly associated with improved 2-year PFS (91.7 % vs. 42.9 %, $p = 0.045$), and the ADT use was significantly correlated with reaching this threshold ($p = 0.04$). This suggests that post-therapy PSA kinetics, particularly PSA nadir, may serve as a valuable predictor of sustained disease-free status and stratification factor in salvage re-irradiation. While modest, our data endorse this PSA nadir utility as a prognostic threshold.

Advances in modern RT technologies have enabled highly precise and adaptive treatments, which are key in the re-irradiation scenario. MRL enables excellent visualization with soft tissues discrimination: MRI sequences can reduce the daily uncertainties in identifying the

exact interface between the posterior part of the prostate gland and the anterior rectal wall or between the prostate apex and the penile bulb, allowing a better definition of the daily critical structures and consequently the possible reduction of PTV margins [36–38]. Our results build on the MIRAGE trial's demonstration of reduced acute toxicity with MRI guidance, extending its benefits to the re-irradiation setting. While MIRAGE achieved this through tighter margins alone, our approach further incorporated daily adaptive planning and gated treatment, which may contribute to enhanced target conformity and additional OAR sparing.

Early clinical evidence supports the feasibility of MR-guided salvage re-irradiation for prostate cancer. Cuccia et al.[19] reported 1-year bRFS and PFS rates of 85.9 % in 22 patients with prostate or prostate bed recurrences, following initial EBRT or BT, with minimal late toxicity, although median follow-up was 8 months. Michalet et al.[18] analysed 37 patients treated on MRIdian®, reporting 1-year bRFS of 65 %, using internal PSA progression criteria. Toxicity was low, with only one acute G3 GU event (haematuria) and no $\geq$ grade 2 late GU or GI toxicity. Notably, 22 % of this cohort were prostate bed relapses and 6 castration-resistant PCa. Boldrini et al. [20] retrospectively analysed 18 patients (50 % post-prostatectomy relapse), reporting 1- and 2-year LC of 88.9 % and 66.7 %, respectively, although the median follow-up was 4 months.

In our series, which exclusively included intraprostatic relapses, bRFS was 73.7 %, 1 and 2-year PFS were 94.7 % and 89.4 %, respectively. 1 and 2-year LC rates were 100 %, with an estimated 3-year LC of 84.2 %. Importantly, we reported a standardized EQD2-based workflow to perform cumulative dose summation and OAR constraint evaluation, enabling individualized re-irradiation planning and enhancing safety. Despite growing interest in salvage SMART, several challenges remain. First, the risk of DLT due to prior RT. Our EQD2-based workflow provides a practical solution to guide safe re-irradiation. Second, fractionation remains non-standardized. By reporting outcomes from two commonly used regimens (30 Gy and 35 Gy in 5 fractions), we contribute relevant real-world evidence. Third, patient selection and target delineation remain heterogeneous across studies. We focused on intraprostatic-only relapses to ensure cohort homogeneity and support focal salvage approaches. Finally, we explored prognostic factors such as PSA nadir and ADT use, which may inform future risk stratification.

However, we must acknowledge certain limitations in our study, including its retrospective design, small cohort size and heterogeneity in prior treatments and ADT use. Although the median follow-up was relatively short, it was sufficient to meaningfully assess acute-mid toxic effects, but longer surveillance is needed to capture late effects. These factors inherently limit the statistical power and generalizability of our findings. Therefore, while our results are encouraging, and to our knowledge, this represents one of the largest reported series of SMART re-irradiation to non-metastatic hormone sensitive LRPC, they should be interpreted with appropriate caution, particularly when considering their application to broader patient populations. Further prospective studies with larger cohorts are needed to validate these outcomes.

Regarding future directions, we are hopeful that tools like genomic classifiers (i.e. Decipher®), which have shown promise in stratifying risk among patients with radiorecurrent prostate cancer, will help to identify those at higher risk of progression. This can guide personalized decision-making for salvage treatment versus observation, and inform potential intensification strategies, such as combining local salvage with systemic therapies [39].

In the meantime, the growing number of ongoing clinical trials underscores the salvage SABR re-irradiation emerging role as a valuable local treatment option within the clinical community [40].

## Conclusion

Daily adaptive salvage SMART re-irradiation is a feasible, non-invasive salvage option for LRPC, combining high LC with low toxicity. Our experience supports the integration of MR-guidance and individualized, EQD2-informed planning to overcome traditional re-irradiation challenges. Future prospective trials and standardized outcome reporting will be essential to define optimal practice and validate these encouraging results.

## CRediT authorship contribution statement

**Elena Moreno-Olmedo:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Dan Murray:** Conceptualization, Methodology, Data curation, Writing – original draft. **Ben George:** Conceptualization, Methodology, Data curation, Writing – original draft. **Daniel Ford:** Conceptualization, Methodology, Resources. **Nicola Dallas:** Conceptualization, Methodology, Resources. **Prantik Das:** Conceptualization, Methodology, Resources. **Ami Sabharwal:** Resources. **Yoodhvir Nagar:** Resources. **Jamie Mills:** Resources. **Carla Perna:** Conceptualization, Methodology, Resources, Resources, Writing – review & editing. **Yae-eun Suh:** Conceptualization, Methodology, Resources. **Alex Martin:** Resources. **Philip Camilleri:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2025.101037.

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