



## Original Research Article

## Single fraction of HDR brachytherapy for prostate cancer: Results of the SiFEPI phase II prospective trial

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## ABSTRACT

**Purpose:** To report the results of the *Single Fraction Early Prostate Irradiation* (SiFEPI) phase 2 prospective trial. **Materials/Methods:** The SiFEPI trial (NCT02104362) evaluated a single fraction of high-dose rate brachytherapy (HDB) for low- (LR) and favorable-intermediate (FIR) risk prostate cancers. After rectal spacer placement, a single fraction of 20 Gy was delivered to the prostate. Oncological outcome (biochemical (bRFS) and local (lRFS) relapses, disease-free (DFS) and overall (OS) survivals and toxicity (acute/late genito-urinary (GU), gastrointestinal (GI) and sexual (S) toxicities were investigated.

**Results:** From 03/2014 to 10/2017, 35 pts were enrolled, of whom 33 were evaluable. With a median age of 66 y [46–79], 25 (76 %) and 8 (24 %) pts were LR and FIR respectively. With a MFU of 72.8 months [64–86], 6y-bRFS, lRFS and mRFS were 62 % [45–85], 61 % [44–85] and 93 % [85–100] respectively while 6y-DFS, CSS and OS were 54 % [37–77], 100 % and 89 % [77–100] respectively. Late GU, GI and S toxicities were observed in 11 pts (33 %;18G1), 4 pts (12 %;4G1) and 7 pts (21 %;1G1,5G2,1G3) respectively. Biochemical relapse (BR) was observed in 11 pts (33 %;7LR,4FIR) with a median time interval between HDB and BR of 51 months [24–69]. Nine of these pts (82 %) presented a histologically proven isolated local recurrence.

**Conclusions:** Long-term results of the SiFEPI trial show that a single fraction of 20 Gy leads to sub-optimal biochemical control for LR/FIR prostate cancers. The late GU and GI toxicity profile is encouraging, leading to consideration of HDB as a safe irradiation technique.

## Introduction

The global prostate cancer (PC) incidence rate is 1 414 259 per year;

it is the second most common cancer in men after lung cancer and the fifth in terms of mortality in the world [1]. In Europe, PC is the most frequent cancer (473 344 new cases in 2020) but ranks third in terms of

**Abbreviations:** ADT, androgen deprivation therapy; bRFS, biochemical relapse free survival; CSS, cancer specific survival; CT, computerized tomography; CTC/AE, common terminology criteria for adverse events; CTV, clinical target volume; D90, dose delivered to 90% of the clinical target volume; DFS, disease-free survival; DNR, dose non-homogeneity ratio; DVH, dose volume histogram; EBRT, external beam radiation therapy; EQD2, equivalent dose at 2 Gy per fraction; GI, gastrointestinal; GTV1, initial gross volume tumor; GTV2, relapse gross volume tumor; GU, genito-urinary; HDB, high-dose rate brachytherapy; HR, high risk; IR, intermediate risk; IIEF, international index of erectile function; IPSS, International prostate symptom score; ISUP, International Society of Urological Pathology; ITPL, index tumor predominant lesion; LDR, low dose-rate; LIR, low-intermediate risk; LR, low risk; lRFS, local relapse free survival; MFU, median follow up; mRFS, metastatic relapse-free survival; mpMRI, multi-parametric magnetic resonance imaging; NCCN, national comprehensive cancer network; OAR, organs at risks; OS, overall survival; PC, prostate cancer; PET, positron emission tomography; PSA, prostate specific antigen; pts, patients; PUF, peak urine flow; PVRV, post-void residual volume; QLQC30, quality of life questionnaire cancer patients; QLQ-PR25, quality of life questionnaire for prostate cancer; QoL, quality of life; SBRT, Stereotactic Body Radiation therapy; SDRT, Single Dose Radiotherapy; TURP, Transurethral resection of the prostate; V100, percentage of the clinical target volume receiving 100% of the prescribed dose; V150, percentage of the clinical target volume receiving 150% of the prescribed dose; V200, percentage of the clinical target volume receiving 200% of the prescribed dose; V85<sub>R</sub>, percentage of the rectal volume receiving 85% of the prescribed dose; V110<sub>U</sub>, percentage of the urethra volume receiving 110% of the prescribed dose.

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mortality. The PC incidence rate in 2040 is expected to rise to 2 260 000 per year, making it a major concern for patients, health care providers and insurance companies.

NCCN guidelines categorize PC according to its biochemical recurrence risk rate at the time of diagnosis [2]. This classification defines 3 risk levels: low (LR), intermediate (IR) and high (HR) according to clinical stage, PSA level and ISUP grading. For LR (T1c/T2a; PSA < 10 ng/ml, ISUP 1) and favorable-intermediate risk (FIR) prostate cancers (LR with one of the following risk factors: T2b/T2c, ISUP 2, PSA 10–20, and < 50 % of positive biopsy), discussion centers on active surveillance, radical prostatectomy, external beam radiation therapy (EBRT) or brachytherapy [3].

Until the last decade, brachytherapy techniques were mainly based on low dose-rate (LDR) permanent implants (iodine/palladium seeds), providing excellent oncological outcomes with 10-year biochemical control and prostate cancer mortality rates of 85 % and 5 % respectively [4]. Initially, toxicity profile appears to be negatively impacted by acute and late genito-urinary (GU) side effects, which could represent a limiting factor in terms of quality of life (QoL) [5]. Moreover, regarding radiobiological considerations, PC appears to be highly sensitive to dose fractionation due to a low  $\alpha/\beta$  ratio. High-dose rate brachytherapy (HDB) could allow better tumor control by offering higher dose per fraction [6]. In addition, due to its possibility of the dual time variation of the stepping source a better optimization of the dose distribution for both clinical target volume (CTV) and organs at risk (OAR) is possible and can limit the side effects [7]. To retain the LDR brachytherapy advantage of a single treatment day, a single fraction of HDB was proposed and from a radiobiological stance, increasing dose per fraction with HDB is favorable. In 2012, Prada et al. reported encouraging oncological outcomes in their first prospective study investigating a single fraction (19 Gy) of HDB for LR and FIR prostate cancer [8]. Based on consistent, rational, promising early results, we conducted a prospective phase I/II trial using a single fraction of 20 Gy for LR and LIR prostate cancer patients.

## Materials and methods

SiFEPi trial was a phase I/II, interventional open-label prospective single-institution study (ClinicalTrials.gov Identifier: NCT02104362). The primary objective was to investigate early genito-urinary (GU) toxicity during the first 6 months after a single fraction of HDB as monotherapy for LR and LIR prostate cancer. The following items were considered secondary objectives: dosimetric data, late GU, acute/late gastro-intestinal (GI) and sexual (S) toxicities, oncological outcome and Quality of Life (QoL). A micro-costing analysis was conducted in an ancillary study. An amendment was proposed in order to perform long-term oncological outcome and late toxicity analyses (Health data hub Identifier: F20220201113814).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave their informed consent and the relevant investigational review boards (South Mediterranean V Ethical Committee and regulatory agencies) approved the protocol.

### Patient features

Patients with non-metastatic histologically proven adenocarcinoma of the prostate matching the afore mentioned LR or LIR localized prostate cancer criteria were prospectively enrolled in the SiFEPi phase I/II trial. Prostatic biopsies were systematically performed through a transrectal approach for the primary diagnosis (after or before multiparametric prostatic MRI -mpMRI- in 9 and 24 patients respectively). Before inclusion, all patients were screened with prostate mpMRI, abdominal-pelvic CT-scan and bone scan. All patients had clinical stage  $\leq$  T2b, PSA  $\leq$  15, ISUP  $\leq$  2 with a maximum of 3 positive biopsies and had to meet the following criteria: prostate volume (measured by MRI)  $\leq$  60 cc., urinary function investigated before inclusion in accordance

with an international prostate symptom score (IPSS) < 15 with post-void residual volume (PVRV)  $\leq$  50 cc and peak urine flow (PUF) rate  $\geq$  12 ml/s. Patients who underwent large transurethral resection of the prostate (TURP) within the 6 months were excluded of the study. Androgen Deprivation Therapy (ADT) and a history of pelvic irradiation were considered exclusion criteria.

### Treatments

The brachytherapy technique has already been described [9]. Under spinal or general anesthesia, after insertion of a triple-lumen Foley catheter using transrectal ultrasound, the procedure began with the injection of 10 ml of hyaluronic acid used as a rectal spacer (Macrolane VRF30 Q-Med Galderma, Lausanne, Switzerland) (**Video Supplementary data**). Then, depending on the prostate volume and patient anatomic constraints and using a dedicated perineal template, 15 to 17 catheters were implanted into the prostate through a transperineal approach. After leaving the recovery room, patients received a post-implant CT-scan for treatment planning purposes. The CTV was delineated as the prostate capsule. OARs include rectum, and urethra. Dose optimization was performed in order to respect the following dose constraints: D90  $\geq$  105 %, V100  $\geq$  95 %, V150  $\leq$  35 %, V200  $\leq$  15 %, rectum V85<sub>R</sub>  $\leq$  1 %, urethra V110<sub>U</sub> < 1 %. A single fraction of 20 Gy was prescribed on the reference isodose. At the end of the irradiation procedure, all the needles were removed and the patient kept the triple-lumen catheter with continuous irrigation. The day after, the bladder catheter was removed and the patient was discharged after recovering normal urinary function, with a prescription for alpha-blockers and advice to overhydrate (>2 L per day).

### Follow-up and evaluation

After completion of HDB, pts were followed up at 30, 90 and 180 days and then every 6 months for 36 months after brachytherapy. Evaluation included clinical examination, urinary function (IPSS, PVRV, PUF), digestive and sexual functions (International Index of Erectile Function – IIEF) and PSA blood test. Toxicity was assessed according to the fourth version of the Common Toxicity Criteria for Adverse Events (CTCAE v4.0). QoL questionnaires (QLQC30, QLQ-PR25) were used during the first 180 days. After the 36 months of surveillance, pts were followed up every 6 months until the 5th year after brachytherapy, and then annually (clinical examination, urinary, digestive and sexual functions and PSA).

According to the protocol, biochemical relapse was defined by using the Phoenix criteria definition (PSA nadir + 2 ng/ml). However, in the event of rising PSA < nadir + 2, pts underwent prostate MRI and PET-scan in order to detect local and/or distant disease progression followed by prostatic guided biopsies if local relapse was suspected. For histologically proven isolated local failure, a salvage treatment was carefully discussed among the urological board members and proposed to the patient (surgery, external beam re-irradiation or ADT).

For patients who experience local relapse, a dedicated study of recurrence anatomical site was performed in order to consider this oncological event as a “new primary PC” (occurring at distance from the initial site) or a “true recurrence” (occurring into or close to the initial site). For true recurrence, relapse Growth Tumor Volume (GTV2) was partially or totally included into the initial GTV (GTV1). For new primary PC, GTV2 occurred at distance from GTV1. GTV1 was defined by using mpMRI and biopsies performed before the implant while GTV2 definition was achieved with mpMRI, PET-scanner and biopsies.

## A comparative dosimetric analysis was performed between patients who experienced local relapse and patients free of relapse (analysis of EQD2<sub>D90</sub>, V100 and V150 for GTV1).

### Micro-costing analysis

A micro-costing analysis was considered an ancillary study. The cost of one day was calculated in the following way: an analysis of the analytical operating income statement of our surgical department, including all direct personnel, medical, hotel and logistics expenses, general management, structural real estate and financial expenses was carried out. Indirect expenses, equal to the French national accounting median of 40 % of direct expenses (medical, medico-technical and overall structural expenses) were then added. The last step consisted in separating the cost of brachytherapy stays from overall surgery department costs and computing expenses according to the number of hospitalization days.

### Statistical analysis

Quantitative data were described by median and range and qualitative data by absolute and relative frequencies. Survival data were defined as between the date of inclusion and the event onset date. Survival curves and 6-year biochemical (bRFS), local (lRFS) and metastatic (mRFS) relapse-free survival and disease-free (DFS), cancer specific (CSS), overall survival (OS) rates (confident intervals 95 %) were estimated according to the Kaplan-Meier method and estimated with 95 % confidence interval (95 %CI). Median follow-up with a 95 % confidence interval was calculated using the reverse Kaplan-Meier method. All statistical analyses were performed using R.3.0.2 software for Windows. Data entry and management were based on the capture system (Ennov Clinical).

## Results

### Patient features

From March 2014 to October 2017, 35 pts were enrolled, of whom 33 were evaluable (2 pts were not implanted owing to pubic arch interference). With a median age of 66.1 years [46.3–79], 25 (76 %) and 8 (24 %) pts were LR and FIR respectively (Table 1). Median biopsy number/pt and tumor size were 14 [7–22] and 6.7 mm [1–15] respectively. Median MRI prostatic volume was 40.8 cc [18.7–84]. Median pre-HDB IPSS score, PUF and PVRV were 5 [0–14], 16.5 ml/s [7.6–24.8] and 18.8 cc [0–165] respectively while 30 pts (90.9 %) had an IIEF score between 16 and 25.

### Dosimetric results

With a median CTV of 50 cc [29–92], median V100% was 98 % [96–99] (e-Table 1, Supplementary data). Median Dose non-homogeneity ratio was 0.23 [0.16–0.36]. With a median D90% of 106 % [104–109], median EQD2<sub>D90</sub> (assuming an  $\alpha/\beta$  ratio of 1.5) was 122 Gy [119–130]. Median urethra volume was 3.2 cc [2.3–3.7] with median D<sub>2cc</sub> of 94 Gy [60–103] and median EQD2<sub>D2u</sub> of 81 Gy [23–96]. Median rectum volume was 47 cc [23–88] with median D<sub>2cc</sub> of 53 Gy [38–65] and median EQD2<sub>D2u</sub> of 30 Gy [16–42].

### Oncological outcome

With a MFU of 72.8 months [63.8–86], 6y-bRFS, lRFS and mRFS rates were 62 % [95 %CI: 45–85], 61 % [95 %CI: 44–85] and 93 % [95 %CI: 85–100] respectively. Six year-DFS, CSS and OS rates were 54 % [95 %CI: 37–77], 100 % and 89 % [95 %CI: 77–100] (Fig. 1). Median nadir PSA was 0.76 ng/ml [0.05–1.97] and was reached 60 months after brachytherapy. A bounce with a median PSA of 1.31 ng/ml [0.08–4.33]

**Table 1**

Patient and tumor features.

| Patient/tumor features                               | # pts | [min–max]  |
|--|-------|------------|
| Median age (y)                                       | 66.1  | [46.3–79]  |
| Median BMI (kg/m <sup>2</sup> )                      | 26.8  | [22–40.8]  |
| Median Karnofsky index (%)                           | 92.3  | [80–100]   |
| MFU (months)   | 72.8  | [63.8–86]  |
| NCCN classification                                  |       |            |
| LR   | 25    | 76         |
| FIR  | 8     | 24         |
| cT (clinical TNM)                                    |       |            |
| 1C   | 24    | 72.7       |
| 2A   | 9     | 30.3       |
| ISUP classification                                  |       |            |
| 1  | 29    | 87.9       |
| 2  | 4     | 12.1       |
| Median PSAi (ng/ml)                                  | 8     | [3.2–14.7] |
| Biopsies   |       |            |
| Median biopsy number/pt                              | 14    | [7–22]     |
| Median positive biopsy number                        | 2     | [1–5]      |
| Median tumor size (mm)                               | 6.7   | [1–15]     |
| Total positive biopsy length/total biopsy length (%) | 24.4  | [3.8–62.5] |
| Median MRI prostatic volume (cc)                     | 40.8  | [18.7–84]  |
| Initial urinary status                               |       |            |
| IPSS   | 5     | [0–14]     |
| PUF (ml/s)   | 16.5  | [7.6–24.8] |
| PVRV (cc)  | 18.8  | [0–165]    |
| Initial erectile status                              |       |            |
| 16 ≤ IIEF < 25                                       | 30    | 90.9       |
| 5 ≤ IIEF < 16  | 3     | 10.1       |

BMI: body mass index; MFU: median follow-up; NCCN: National Comprehensive Cancer Network; LR: low-risk prostate cancer; FIR: favorable intermediate-risk prostate cancer; ISUP: International society of urological pathology; IPSS: International Prostatic Symptom Score; PUF: peak urine flow; PVRV: post-void residual volume; IIEF: international index of erectile function (5 items).

was observed between 36 and 48 months after HDB (e-Fig. 1, Supplementary data). This “late” PSA bounce also described after permanent seed implants was associated in few patients with an early-one, occurring about 1 month after the implant probably induced by a small quantity of hyaluronic acid injected into the prostatic gland.

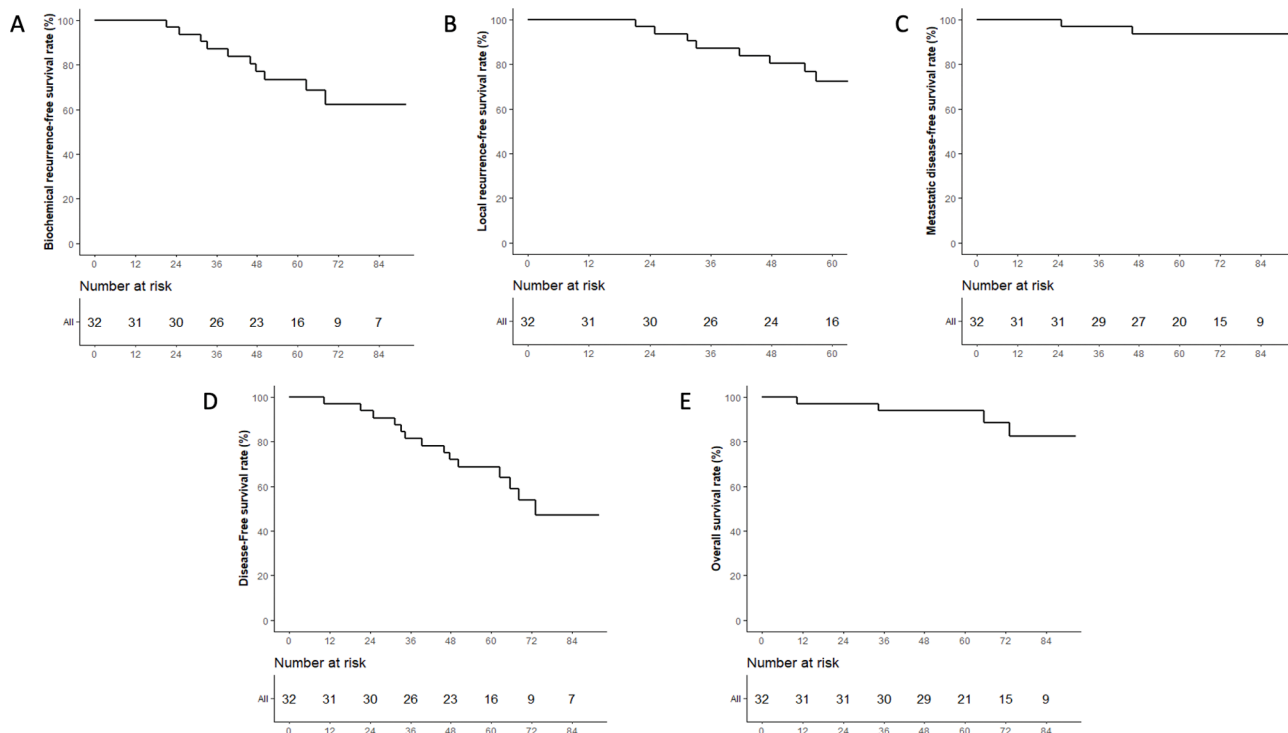
Biochemical relapse (bR) was observed in 11pts (33 %; 7 LR & 4 FIR) with a median time interval between HDB and bR of 51 months [24–69]. Nine of these pts (82 %) presented a histologically proven isolated local recurrence and underwent salvage prostate re-irradiation delivering a median dose of 78 Gy [78–78] (2 Gy/f) (1pt underwent salvage radical prostatectomy [pT3B, pN+, R1] followed by adjuvant EBRT [73 Gy]). With a MFU from salvage EBRT of 27 months [3–59], the 2nd bRFS rate was 100 %. One pt presented a G3 GU toxicity (hematuria) while no G ≥ 3 GI complication was observed.

Two patients presented concomitant local and metastatic relapse. They received ADT and 1pt underwent prostate re-irradiation. Tumor and treatment features for patients who experienced biochemical relapse are presented in e-Table 1, (Supplementary data).

For patients who experience PC local relapse (N = 11), the anatomical recurrence site (GTV2) was partially or totally included into the initial GTV (GTV1) in 100 % of the cases leading to consider all the patients with a “true recurrence”. Comparative dosimetric analysis of EQD2<sub>D90</sub>, V100 and V150 for GTV1 performed between patients who experienced local relapse and patients free of relapse did not show significant difference (e-Table 3 and e-Fig. 2, Supplementary data).

### Toxicity profile

Acute GU, GI and S toxicities were observed in 27 pts (82 %; 36 G1 & 8 G2), 5 pts (15 %; 7 G1 & 3 G2) and 5 pts (15 %; 3 G1 & 2 G2) respectively (Table 2). No acute G3 toxicity was observed. Although the rate of acute GI toxicity remained stable from d30 to d180 (number of patient and number & grade of complication per patient), the number of patients with GU and S acute side effects increased from d30 (GU: 39.4



**Fig. 1.** Oncological outcome: bRFS: 6-year biochemical free survival rate (A); lRFS: 6-year local recurrence free survival rate (B); mRFS: 6-year metastatic free survival rate (C); DFS: 6-year disease free survival rate (D); OS: 6-year overall survival rate (E).

**Table 2**

Acute and late genito-urinary (GU), gastro-intestinal (GI) and sexual dysfunction.

| Toxicity |      | GU   |      |    |    | GI   |      |    |    | Sexual |      |    |    |    |
|----------|------|------|------|----|----|------|------|----|----|--------|------|----|----|----|
|          |      | #pts | %    | G1 | G2 | #pts | %    | G1 | G2 | #pts   | %    | G1 | G2 | G3 |
| Acute    | d30  | 13   | 39.4 | 14 | 4  | 5    | 15.2 | 5  | 3  | 2      | 6.1  | 2  | 0  | 0  |
|          | d90  | 22   | 66.7 | 28 | 8  | 5    | 15.2 | 6  | 3  | 3      | 9.1  | 3  | 0  | 0  |
|          | d180 | 27   | 81.8 | 36 | 8  | 5    | 15.2 | 7  | 3  | 5      | 15.2 | 3  | 2  | 0  |
| Late     |      | 11   | 33.3 | 18 | 0  | 4    | 12.1 | 4  | 0  | 7      | 21.2 | 1  | 5  | 1  |

GU: genito-urinary; GI: gastro-intestinal; G1: grade 1; G2: grade 2; G3: grade 3; d30: toxicity evaluation @day 30; d90: toxicity evaluation @day 90; d180: toxicity evaluation @day 180.

%; S: 6.1 %) to d180 (GU: 81.8 %; S: 15.2 %). Acute GU toxicity was maximal 1 month after HDB (Fig. 2).

Late GU, GI and S toxicities were observed in 11 pts (33 %; 18 G1), 4 pts (12 %; 4 G1) and 7 pts (21 %; 1 G1, 5 G2 & 1 G3) respectively. Except for S toxicity, no  $G \geq 2$  late toxicity was observed.

*Quality of life*

In the SiFEPI trial, QoL was investigated using QLQ-C30 and QLQ-PR25. By comparing QLQ-C30 recorded at 1, 3 and 6 months after HDB compared to baseline, significant changes were observed at 1 month for Global quality of life ( $p < 0.001$ ), role ( $p = 0.01$ ) and social ( $p < 0.001$ ) function and fatigue ( $p < 0.001$ ) (e-Table 4 Supplementary data). However, for Global quality of life, ( $p = 0.02$ ) all the items reverted to baseline as of the 3rd month after HDB (e-Fig. 3 Supplementary data).

Regarding QLQ-PR25 sexual functioning (libido and erectile function) ( $p < 0.001$ ) significantly decrease at 1 month (e-Table 5 Supplementary data) but for patients having an active sexual function, there sexual activity did not change significantly at 1, 3 and 6 months after HDB, urinary symptoms ( $p < 0.001$ ). However, while urinary symptoms returned to baseline as of the 3rd month after HDB, sexual function ( $p < 0.001$ ) remained significantly deteriorated ( $p < 0.001$ ) at 6 months (e-

Fig. 4 Supplementary data).

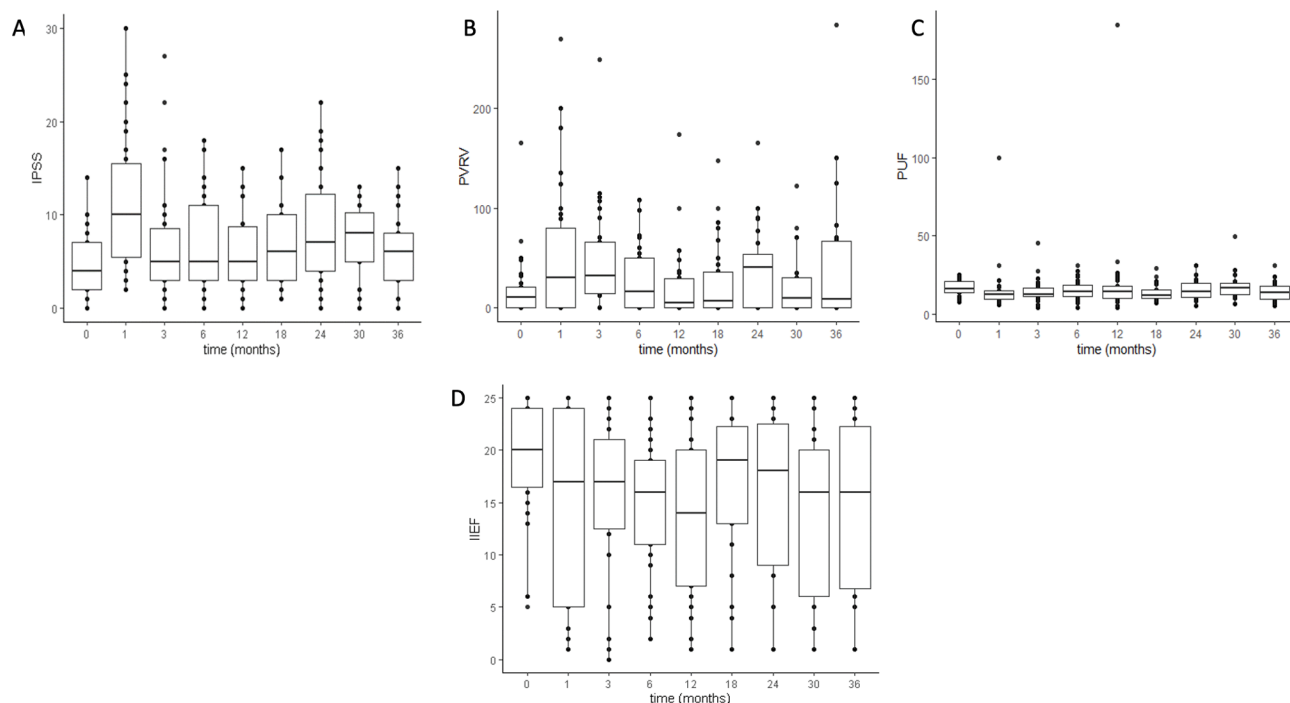
*Micro-costing analysis*

This analysis used the 2021 cost for each parameter considered in this ancillary study (e-Table 6 Supplementary data). The total cost of material used during the SiFEPI trial was 21 093 €, that is 639 € per patient The total cost of human resources during the SiFEPI trial was 41 477 €, that is 1 257 € per patient. In sum, in the SiFEPI trial, the total cost of the procedure was 62 570 €, that is 1 896 € per patient.

**Discussion**

In recent years, because of its low  $\alpha\beta$ , hypofractionation for prostate cancer irradiation is increasingly used [10]. A higher dose per fraction could increase the therapeutic ratio. In order to decrease late toxicity and increase the dose delivered to the CTV, HDB appears to be a smart technical option. Multi fraction ( $\geq 4f$ ) HDB used as monotherapy appears safe and effective [4]. After the encouraging results published by Prada et al., the SiFEPI trial aimed to evaluate a single fraction monotherapy [8].

With a 6y-bRFS of 62 % (MFU: 72.8 months), our results are consistent with those already published in literature (Table 3). In studies



**Fig. 2.** Urinary and sexual function evolution during the first 36 months after brachytherapy: A) International prostate symptom score (IPSS); B) post-void residual volume (PVRV); C) peak urine flow (PUF); D) international index of erectile function (IIEF).

**Table 3**

Literature analysis of extreme hypofractionated regimen (1 or 2 fractions) with HDR brachytherapy for prostate cancer.

| Authors                     | #pts | Risk (%) |      |    | MFU (mths) | Dose/f (Gy)         | EQD2 (Gy) | ADT (%)       | LGUT (%) |     | LGIT (%) |    | LST (%) |     | BC (%) |
|-----------------------------|------|----------|------|----|------------|---------------------|-----------|---------------|----------|-----|----------|----|---------|-----|--------|
|                             |      | L        | I    | H  |            |                     |           |               | G2       | G3  | G2       | G3 | G2      | G3  |        |
| Prada PJ et al. [8]         | 60   | 73       | 27   | 0  | 72         | 19                  | 111       | 33            | 0        | 0   | 0        | 0  | –       | –   | 66@6y  |
| Prada PJ et al. [20]        | 60   | 37       | 57   | 7  | 51         | 20.5                | 129       | 43 (3 m)      | 1        | 0   | 0        | 0  | 67      | 7   | 82@6y  |
| Xu MJ et al. [21]           | 124  | 21       | 44.4 | 35 | 26         | 19                  | 111       | 0             | 47.6     | 0   | –        | –  | 37.9    | 4   | 97@2y  |
| Siddiqui ZA et al. [12]     | 68   | 59       | 41   | 0  | 47         | 19                  | 111       | 0             | 14.7     | 0   | 1        | 0  | –       | –   | 77@5y  |
| Barnes JM et al. [11]       | 28   | 50       | 50   | 0  | 24         | 19                  | 111       | 1             | 18       | 0   | 0        | 0  | –       | –   | 81@3y  |
| Gomez-Iturriaga et al. [13] | 44   | 57       | 43   | 0  | 48         | 19                  | 111       | –             | –        | –   | –        | –  | –       | –   | 68@4y  |
| Tharmalingam et al. [22]    | 441  | 10       | 65   | 25 | 26         | 19                  | 111       | 37.6 (6/24 m) | 9        | 0   | 3        | 0  | –       | –   | 88@3y  |
| Alayed Y et al. [14]        | 87   | 23       | 77   | 0  | 62         | 19                  | 111       | 0             | 59.8     | 2.3 | 11.5     | 0  | 36.8    | 4.6 | 68@5y  |
|                             | 60   | 8        | 92   | 0  | 50         | 23                  | 161       | 0             | 28.3     | 0   | 5        | 0  | 46.7    | 10  | 70@5y  |
| Hoskin P et al. [23]        | 23   | 0        | 57   | 43 | 49         | 19                  | 111       | 74            | 2.6      | 2.6 | 0        | 0  | –       | –   | 94@4y  |
|                             | 26   | 0        | 57   | 43 | 49         | 20                  | 123       | 74            | –        | –   | 0        | 0  | –       | –   | 94@4y  |
|                             | 138  | 0        | 50   | 50 | 63         | 13x2 <sup>a</sup>   | 108       | 76            | 2.4      | 1   | 3.5      | 0  | –       | –   | 93@4y  |
|                             | 106  | 0        | 46   | 54 | 108        | 10.5x3 <sup>a</sup> | 108       | 87            | 11.6     | 2.2 | 2.1      | 0  | –       | –   | 91@4y  |
| Morton G et al. [15]        | 87   | 24       | 76   | 0  | 60         | 19                  | 111       | 0             | 45       | 1   | 1        | 0  | 36      | 4   | 74@5y  |
|                             | 83   | 15       | 85   | 0  | 60         | 13.5x2 <sup>b</sup> | 116       | 0             | 45       | 1   | 0        | 0  | 45      | 2   | 95@5y  |
| Tsang YM et al. [16]        | 78   | 4        | 96   | 0  | 48.5       | 19                  | 111       | 21            | 30       | 0   | 0        | 0  | –       | –   | 69@5y  |
|                             | 64   | 5        | 95   | 0  | 107.9      | 13x2 <sup>a</sup>   | 108       | 72            | 5        | 3   | 2        | 0  | –       | –   | 95@5y  |
|                             | 43   | 5        | 95   | 0  | 48.9       | 7.25x5 <sup>c</sup> | 88        | 19            | 6        | 0   | 4        | 0  | –       | –   | 92@5y  |
| SiFEPI trial                | 33   | 76       | 24   | 0  | 72         | 20                  | 123       | 0             | 0        | 0   | 0        | 0  | 15.2    | 3   | 62@6y  |

#pts: number of patients; LR: Low-risk prostate cancer; IR: Intermediate-risk prostate cancer; HR: High-risk prostate cancer; MFU: median follow-up (months); Dose/f: dose per fraction (Gy); EQD2: equivalent dose at 2 Gy; ADT: Androgen deprivation therapy; LGUT: late genito-urinary toxicity, Grade 2 and Grade 3; LGIT: late gastrointestinal toxicity, Grade 2 and Grade 3; LST: late sexual toxicity, Grade 2 and Grade 3; BC: Biochemical control (%) according to the median follow-up (@).

a 2 HDR brachytherapy sessions in 2 weeks.

b 2 HDR brachytherapy sessions in 2 days.

c 5 fractions of stereotactic external beam radiation therapy.

using a single fraction (19–20 Gy) as monotherapy for LR and FIR, bRFS ranged from 80 % at 3 years to 65 % at 6 years [8,11,16].

As already reported in other series, in the SiFEPI trial local relapse occurred in or close to the initial anatomical site [12,13,15,17]. However, no significant difference in terms of dosimetric data were observed between patients with and without local relapse (e-Table 2 and 3 and e-Fig. 2, Supplementary data). In the same line, Armstrong et al. [17] did not reported significant difference for dosimetric data (CTV, dominant intraprostatic nodule and OAR) between patients with or without local

relapse after a single dose of 19 Gy. In contrast, Gomez-Iturriaga et al. [13] considered PSA > 10 ng/ml and ISUP 2–3 as independent prognostic factors for biochemical relapse in multivariate analysis and proposed dose constraints for biochemical control (V100 ≥ 96 %; V150 ≥ 20 %; D90 ≥ 105 %). In the SiFEPI trial, we observed that the risk of biochemical relapse was almost double in the case of FIR (4/8; 50 %) versus LR (7/25; 28 %).

Patients who experienced local relapse were offered salvage re-irradiation with encouraging biochemical control and a low rate of G

≥ 3 toxicity. Different salvage treatments (radical prostatectomy, brachytherapy, HIFU) are reported in literature [12,14,15].

HDR brachytherapy provides for dual time stepping source variation, leading to better optimization of dose distribution in order to decrease the risk of OAR over-irradiation and consequently the risk of late side effects. Regarding late GU side effects, we reported no  $G \geq 2$  toxicity. In literature, G2 and G3 late GU toxicities ranged between 0 and 59.8 % and 0 to 2.6 % respectively (Table 3). In a recent systematic review, Viani GA et al. [18] reported a cumulative rate of G2 and  $G \geq 3$  late GU toxicity of 22.4 % and 1.4 %, respectively. Dose escalation (simultaneous integrated boost) is described by Alayed Y et al. [14] as a significant prognostic factor for late GU toxicity.

Regarding late GI side effects, we reported no  $G \geq 2$  toxicity. In literature, G2 late GI toxicity ranges between 0 and 11.5 % while no G3 toxicity was observed (Table 3). Viani GA et al. [18] reported a cumulative rate of G2 and  $G \geq 3$  late GU toxicity of 22.4 % and 1.4 %, respectively. In the SiFEPI trial, we used a rectal spacer (hyaluronic acid) in order to increase rectal mucosa protection. Compared to other studies without rectal spacer, we did not observe better results in terms of GI toxicities. In contrast with LDR brachytherapy [19], it seems that the rapid dose fall-off represents the key factor for decreasing the dose to the anterior rectal wall with no need of rectal spacer for very hypofractionated regimen HDB. We reported G2 and G3 late sexual toxicity of 15.2 % and 3 % respectively. Erectile dysfunction remains imperfectly described in literature with G2 and G3 toxicity ranging between 15.2 % and 67 % and 2 % to 10 % respectively. Viani GA et al. [18] reported a cumulative rate of G2 and  $G \geq 3$  late erectile dysfunction of 29.2 % and 9 %, respectively.

Although the interpretation of oncological results remains debatable due to considerable heterogeneity in patient selection (studies included HR prostate cancer treated by HDB + ADT [8,16,20,23]), a single HDR fraction (19 to 20.5 Gy) leads to biochemical control that drops from 80 % at 3 years to 64 % at 6 years (Table 3). In case of biochemical relapse due to intra-prostatic recurrence, one of the first explanations remains that the dose delivered to the index tumor predominant lesion (ITPL) has not been sufficient. The second hypothesis (possibly combined with the first one) is a potential “geographic miss” of ITPL. Such unacceptable biochemical results may be explained in part by the dose–response relationship as proposed by Gomez-Iturriaga et al. [13], while patients treated with cooler implants have a higher incidence of local failure. Indeed, in this study, on multivariate analysis, with a single fraction of 19 Gy, a  $V100 < 96$  % appears an independent predictor of biochemical failure.

However, Alayed Y et al. [14] proposed a MRI-guided focal dose-escalation to the dominant intraprostatic lesion (up to 23 Gy) and failed to improve local control. Nevertheless, the Washington University opened a phase I/II prospective trial evaluating dose escalation from 21 Gy to 25 Gy (ClinicalTrials.gov Identifier: NCT03424850). Assuming that total delivered dose does not appear to be a crucial factor, the number of fractions is more likely key. Indeed, delivering a total dose of 26/27 Gy in 2 fractions makes it possible to increase the 5-y biochemical control rate to up to 95 % [15,16,23].

Finally, it is also important to note that technical irradiation aspects may also play a key role. PROSINT Phase 2 Randomized Trial Patients compared 5 × 9 Gy Stereotactic Body Radiation therapy (SBRT) vs 1 × 24 Gy Single Dose Radiotherapy (SDRT) with encouraging results [24].

## Conclusion

The SiFePi phase 2 prospective trial confirmed that a single fraction of 20 Gy leads to unacceptable biochemical control rates for LR and FIR prostate cancers. The reasons why a single fraction is not efficient remain under debate and are probably multi-factorial (dose level, patient selection, radiobiological considerations ...). As this treatment appears well tolerated, however, a HDB two-fraction regimen may be considered an attractive therapeutic approach.

## 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.2022.08.007>.

## References

- [1] Global Cancer Observatory. International Agency for Research on Cancer. World Health Organization. [https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=27&single\\_unit=50000](https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=27&single_unit=50000). Access on line 21/03/22.
- [2] National Comprehensive Cancer network. Prostate Cancer. [https://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Access on line 21/03/22.
- [3] D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; 280(11):969–74.
- [4] Henry A, Pieters BR, André Siebert F, Hoskin P. UROGEC group of GEC ESTRO ith endorsement by the European association of urology. GEC-ESTRO ACROP prostate brachytherapy guidelines. *Radiother. Oncol.* 2022;167:244–51.
- [5] Grills IS, Martinez AA, Hollander M, Huang R, Goldman K, Chen PY, et al. High dose rate brachytherapy as prostate cancer mono therapy reduces toxicity compared to low dose rate palladium seeds. *J Urol* 2004 Mar;171(3):1098–104.
- [6] King CR. LDR vs. HDR brachytherapy for localized prostate cancer: the view from radiobiological models. *Brachytherapy* 2002;1(4):219–26.
- [7] Hsu I-C, Pickett B, Shinohara K, Krieg R, Roach M, Phillips T. Normal Tissue dosimetric comparison between HDR prostate implant boost and conformal external beam radiotherapy boost: potential for dose escalation. *Int J Radiat Oncol Biol Phys* 2000;46(4):851–8.
- [8] Prada PJ, Cardenal J, Blanco AG, Anchuelo J, Ferri M, Fernández G, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: toxicity and long-term biochemical results. *Radiother Oncol* 2016;119(3):411–6.
- [9] Falk AT, Demontoy S, Chamorey E, Chand ME, Gautier M, Azria D, et al. High-dose-rate brachytherapy boost for prostate cancer: Comparison of three different fractionation schemes. *Brachytherapy* 2017;16(5):993–9.
- [10] 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* 2019;394(10196):385–95.
- [11] Barnes JM, Gabani P, Sanders M, Chundury A, Altman M, Garcia-Ramirez J, et al. Single fraction high-dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: toxicities and early outcomes from a single institutional experience. *J Contemp Brachytherapy* 2019;11(5):399–408.
- [12] Siddiqui ZA, Gustafson GS, Ye H, Martinez AA, Mitchell B, Sebastian E, et al. Five-year outcomes of a single-institution prospective trial of 19-gy single-fraction high-dose-rate brachytherapy for low- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2019;104(5):1038–44.
- [13] Gomez-Iturriaga A, Buchser D, Mayrara E, San Miguel I, Gonzalez A, Suarez F, et al. Pattern of relapse and dosimetric analysis of a single dose 19 Gy HDR-brachytherapy phase II trial. *Radiother Oncol* 2020;146:16–20.
- [14] Alayed Y, Loblaw A, McGuffin M, Chung HT, Tseng CL, D'Alimonte L, et al. Single-fraction HDR brachytherapy as monotherapy in low and intermediate risk prostate cancer: Outcomes from two clinical trials with and without an MRI-guided boost. *Radiother Oncol* 2021;154:29–35.
- [15] Morton G, McGuffin M, Chung HT, Tseng CL, Helou J, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. *Radiother Oncol* 2020;146:90–6.
- [16] Tsang YM, Tharmalingam H, Belessiotis-Richards K, Armstrong S, Ostler P, Hughes R, et al. Ultra-hypofractionated radiotherapy for low- and intermediate risk prostate cancer: high-dose-rate brachytherapy vs stereotactic ablative radiotherapy. *Radiother Oncol* 2021;158:184–90.
- [17] Armstrong S, Tsang Y, Lowe G, Tharmalingam H, Alonzi R, Ostler P, et al. Dosimetry of local failure with single dose 19 Gy high-dose-rate brachytherapy for prostate cancer. *Radiother Oncol* 2021;157:93–8.
- [18] Viani GA, Arruda CV, Assis Pellizzon AC, De Fendi LI. HDR brachytherapy as monotherapy for prostate cancer: a systematic review with meta-analysis. *Brachytherapy* 2021;20(2):307–14.
- [19] Lin YH, Loon W, Tacey M, Bolton D, Tan A, Chan Y, et al. Impact of hydrogel and hyaluronic acid rectal spacer on rectal dosimetry and toxicity in low dose rate prostate brachytherapy: a multi institutional analysis of patients outcomes. *J Contemp Brachytherapy* 2021;13(6):605–14.
- [20] Prada PJ, Ferri M, Cardenal J, Blanco AG, Anchuelo J, Díaz de Cerio I, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results. *Brachytherapy* 2018;17(6):845–51.

- [21] Xu MJ, Chen KS, Chang AJ, Lazar A, Shinohara K, Cunha JAM, et al. Single-fraction brachytherapy as monotherapy for early-stage prostate cancer: the UCSF experience. *Brachytherapy* 2019;18(4):470–6.
- [22] Tharmalingam H, Tsang Y, Ostler P, Wylie J, Bahl A, Lydon A, et al. National UK HDR prostate brachytherapy database. single dose high-dose rate (HDR) brachytherapy (BT) as monotherapy for localized prostate cancer: Early results of a UK national cohort study. *Radiother Oncol* 2020;143:95–100.
- [23] Hoskin P, Rojas A, Ostler P, Hughes R, Alonzi R, Lowe G. Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer. *Radiother Oncol* 2017;124(1):56–60.
- [24] Greco C, Pares O, Pimentel N, Louro V, Santiago I, Vieira S, et al. Safety and efficacy of virtual prostatectomy with single-dose radiotherapy in patients with intermediate-risk prostate cancer: results from the PROSINT phase 2 randomized clinical trial. *JAMA Oncol* 2021;7(5):700–8.