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Original Article

Recurrence characteristics after focal salvage HDR brachytherapy in prostate cancer

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ABSTRACT

Background and purpose: Radiorecurrent prostate cancer is often confined to the prostate, predominantly near the index lesion. The purpose of this study was to look at recurrence characteristics in patients treated with focal salvage high dose-rate (HDR) brachytherapy.

Materials and methods: Patients treated with MRI-guided HDR brachytherapy, with a single fraction of 19 Gy from July 2013 to October 2021 as focal salvage treatment, were prospectively included in the current study. Imaging data were collected regarding the occurrence of local, regional and distant recurrences, including location of local recurrences (LR) in relation to the HDR radiotherapy field.

Results: One hundred seventy-five patients were included after focal salvage HDR brachytherapy (median follow-up 36 months (IQR 23–50)). Three-years biochemical recurrence-free survival, LR-free survival, in-field LR-free survival, out-of-field LR-free survival, any-recurrence-free survival and ADT-free survival were 43% (95%CI 34%–52%), 51% (41%–61%), 70% (61%–80%), 92% (88%–97%), 42% (32%–52%) and 86% (80%–92%), respectively. Larger GTV-size and shorter PSA doubling time were associated with in-field LR in multivariable analysis.

Conclusion: After focal salvage HDR brachytherapy with a dose of 1x19 Gy for local prostate cancer recurrence, subsequent recurrences are mostly local and in-field.

In patients with a biochemical recurrence after primary radiotherapy for prostate cancer, local recurrences (LR) in the prostate are found on prostate-specific membrane antigen (PSMA) PET-CT imaging in 52% [1]. Recurrences after primary radiotherapy often occur within the prostate and/or seminal vesicle [2] and are frequently located near the initially largest and/or highest grade index lesion [3–6]. Deferred androgen deprivation therapy (ADT) remains the main approach for patients with radiorecurrent disease, whereas factors as comorbidity, age and risk for additional toxicity are considered [7,8]. Although the role of ADT in the treatment of recurrent or metastasised prostate cancer is crucial, its suppressive effect is not permanent. It is in fact a palliative treatment that is often accompanied by adverse effects that can negatively influence a patient's quality of life.

For selected patients, salvage strategies can be considered, in order to prolong recurrence-free survival, defer ADT and potentially cure disease. Because of increased risk for late toxicity after a second local treatment, focal salvage strategies are usually preferred over whole-gland salvage treatment to minimize chances of toxicity [3]. Focal salvage high dose-rate (HDR) brachytherapy is one of the available focal salvage modalities for radiorecurrent prostate cancer. In our institution focal salvage HDR brachytherapy has been used for this indication since 2013. Compared to recurrence patterns after primary radiotherapy, less is known about recurrence characteristics after focal salvage treatment following radiorecurrent disease, which could provide important information for improvement of this treatment.

The aim of this study was to look at recurrence characteristics in patients treated with focal salvage HDR brachytherapy.

Materials and methods

Patient selection

In this study we included 175 patients with radiorecurrent prostate cancer that were treated at the UMC Utrecht with focal salvage HDR brachytherapy between July 2013 and October 2021. Patients received a single dose of 19 Gy to the local recurrence. All patients were prospectively included, either within a

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study or off-protocol. Firstly, 30 patients were treated in a feasibility study (Netherlands Trial Register number NTR6123) with inclusion criteria PSA doubling time (PSADT) $\geq$ 12 months, tumour stage $\leq$ T2c on MRI, PSA value $\leq$ 10 ng/mL and an International Prostate Symptom Score (IPSS) < 15. We also included 72 patients that participated in a subsequent phase II study ('PRostatE Cancer MRI guided focal SalvagE high-dose-rate brachytherapy' (PRECISE), NTR7014), with expanded inclusion-criteria PSADT $\geq$ 9 months, tumour stage $\leq$ T3b on MRI and PSA value $\leq$ 20 ng/mL. The institutional review board (IRB) approved both studies and these patients all provided informed consent. For patients treated off-protocol, the requirement for informed consent was waived by the IRB. Twelve patients treated off-protocol were excluded: 4 because they had a previous focal HDR salvage treatment and would otherwise participate twice, 5 because of a previous focal LDR salvage treatment, 2 patients primarily treated with focal HDR brachytherapy instead of whole-gland EBRT or LDR and 1 patient because of use of ADT at time of HDR brachytherapy.

The database was closed on December 1st 2021.

Brachytherapy procedure

A complete description of the treatment procedure can be found in a previous paper [9]. To summarize: under spinal anesthesia, brachytherapy catheters are perineally placed within the target volume in the prostate and/or seminal vesicles, with TRUS/MR image guidance. The target volume is defined before the treatment by the delineation of a gross tumour volume (GTV) on multiparametric MRI (mp-MRI) and PSMA PET-CT and clinical target volume (GTV + 5 mm margin within prostate). The organs at risk (OAR) that are taken into account are rectum, bladder and urethra. After catheter insertion, a 1.5 T MRI is performed and used for catheter reconstruction, contour adaptions and dose distribution simulation. A coverage of $\geq$ 19 Gy to 95% of the CTV (CTV D95%) is pursued, and of $\geq$ 17 Gy to 90% of the CTV (CTV90%). Prior to the dose administration, another MRI is performed for verification of catheter positions, to enable safe and reliable dose delivery.

Outcome assessment

Data was prospectively collected regarding patient-, tumour- and treatment characteristics, including: Gleason score before primary treatment, pre-treatment PSA value, pre-treatment PSADT, PSA value after treatment, including the lowest value after treatment (nadir), tumour T- and N-stage before treatment, GTV and CTV of the HDR brachytherapy and dose characteristics such as D90 and D95 of the CTV. Patient follow-up was scheduled at 1, 3, 6, 9, 12, 18 and 24 months after treatment and then yearly up to 10 years. In case of increasing PSA values, follow-up was often intensified. Post-treatment imaging with 68 Ga-PSMA PET-CT was not routinely planned, but performed in most patients in case of a biochemical recurrence according to the Phoenix definition (PSA nadir + 2 ng/ml) or in later years systematic PSA increases.

Primary outcome consisted of local recurrences and the occurrence of biochemical recurrence according to the Phoenix definition. In case of a LR, the new imaging was compared to the delineation and treatment plan of the applied focal HDR treatment, in order to determine if the LR was localised in a region of the prostate and/or seminal vesicles corresponding with the target volume of the previous HDR salvage treatment (in-field), not corresponding with the target volume (out-of-field), in an overlapping in-field and out-of-field region, or consisting of multiple separate localizations.

Secondary outcomes were regional and distant recurrences, overall survival, occurrence of regional and/or distant metastases, any recurrence and start of ADT.

Statistical analyses

Analyses were performed using SPSS version 25.0 (IBM Corp, IBM SPSS Statistics for Windows, Armonk, NY) and RStudio version 4.1.2. Descriptive statistics were performed for baseline patient-tumour- and treatment variables. Kaplan-Meier (KM) analyses were used for survival analyses. For all outcomes studied in KM-analyses except for overall survival, competing risk analyses were performed, taking into account competing risks for mortality. R-packages cmprsk and survminer were used. Cox regression analyses was performed for univariable and multivariable regression analyses. Univariable regression analysis was performed for occurrence of LR, in-field LR, out-of-field LR, recurrences both in- and out-of-field, metastases and any recurrence, with covariates time between primary radiotherapy and focal salvage HDR, PSADT, cT- and cN tumour stage pre-focal HDR treatment, GTV- and CTV-size, D90 and D95 dose to the CTV and PSA nadir value after treatment. Subsequently, multivariable regression analysis was performed in the focal salvage cohort with relevant variables, including variables that reached significance in univariate analysis, while respecting the maximum number of variables according to the 1-variable-per-10-events rule-of-thumb [10].

Results

Median follow-up was 36 months, interquartile range (IQR) 23–50. Baseline patient-, tumour- and treatment characteristics are presented in Table 1 In patients with PSA increases after treatment that resulted in the acquisition of PSMA PET-CT imaging, median PSA (IQR) was 3.3 (2.5–5.5), while median PSA nadir (IQR) in these patients was 0.9 (0.4–1.7).

Fig. 1 displays a Venn diagram with the recurrence distribution.

For patients who developed the recurrence event of interest, median time (IQR) until LR, metastases (regional and/or distant) or any recurrence was 22 (18–34), 22 (14–37) and 22 months (16–34) respectively.

KM-survival analyses for various outcome measures are presented in Fig. 2 and Table 2. Three-years KM-estimates were as follows: biochemical recurrence-free survival (bRFS) 43% (95%CI 34%–52%), LR-free survival 51% (41%–61%), in-field LR-free survival 70% (61%–80%), out-of-field LR-free survival 92% (88%–97%), any-recurrence-free survival 42% (32%–52%) and ADT-free survival 86% (80%–92%). Results after 5 years need to be interpreted with caution because of a limited number of remaining patients at risk for most outcome measures. Compared to the KM-analyses, additional competing risk analyses showed differences in outcome of 3% at most after 3 years (Supplementary Table A.1).

Univariable Cox regression analyses with regards to occurrence of LR and in-field only recurrence are displayed in Table 3 and with regards to occurrence of out-of-field only recurrence, both in- and out-of-field recurrence, metastases and any recurrence in Supplementary Table B. A shorter PSADT and a larger GTV- and CTV-size increased the risk of both LR and in-field recurrence, and additionally a higher cT-stage and higher PSA nadir increased the risk of LR. A higher PSA nadir and higher cT-stage were predictors for out-of-field only recurrence, when higher cT-stage and larger GTV- and CTV-size increased risk of recurrences both in- and out-of-field. Predictors for regional and/or distant metastases were higher cN-stage, larger GTV- and CTV-size and higher PSA nadir, while shorter time between primary treatment and salvage, shorter PSADT, higher cT- and cN-stage, larger GTV- and CTV-size and higher PSA nadir all increased risk of any recurrence.

Subsequent multivariable analyses showed the following significant predictors: higher cT-stage with LR, larger GTV-size and shorter PSADT with in-field LR, a higher cT-stage and higher PSA nadir with out-of-field LR (Supplementary Table C). No significant

Table 1
Baseline characteristics.

	No. patients (%) / median (IQR)
Total	175
Primary setting	
iPSA	11.3 ng/mL (8.3–17.0)
Clinical T-stage	
T1	39 (22.3%)
T2a	54 (30.9%)
T2b	12 (6.9%)
T2c	20 (11.4%)
T3a	36 (20.6%)
T3b	11 (6.3%)
Unknown	3 (1.7%)
Clinical N-stage	
0	81 (46.3%)
1	7 (4.0%)
X	87 (49.7%)
Gleason score	
Sumscore 6	91 (52.0%)
Sumscore 7	64 (36.6%)
Sumscore 8	11 (6.3%)
Sumscore 9/10	6 (3.4%)
Unknown	3 (1.7%)
Primary treatment	
EBRT	95 (54.3%)
I-125 LDR	79 (45.1%)
Whole gland HDR	1 (0.6%)
History of ADT around primary treatment [median duration]	
No	139 (79.4%)
Yes, neoadjuvant	9 (5.1%) [6 months]
Yes, adjuvant	27 (15.4%) [36 months]
PSA nadir after primary treatment	0.56 ng/mL (0.2–1.0)
Interval between primary RT and salvage	91.5 months (62–123)
Recurrent setting	
Age	72 years (68–75)
iPSA	4.4 ng/mL (2.5–6.7)
PSA doubling time	16.6 months (11.6–24.1)
Prostate size on MRI	30.9 cc (24.5–37.7)
iT stage on MRI	
T2a	54 (30.9%)
T2b	27 (15.4%)
T2c	15 (8.6%)
T3a	14 (8.0%)
T3b	62 (35.4%)
T4	2 (1.1%)
Unknown*	1 (0.6%)
Tumour location	
Base	20 (11.4%)
Midgland	34 (19.4%)
Apex	26 (14.9%)
Overlapping regions within prostate	34 (19.4%)
Seminal vesicle	26 (14.9%)
Prostate and seminal vesicle	35 (20.0%)
GTV size	2.9 cc (1.7–5.1)
CTV size	9.9 cc (7.0–14.5)

* : For 1 patient, a reliable iT stage on MRI was not possible due to osteosynthesis artefacts. HDR: high dose rate. IQR: interquartile range. iPSA: (initial) prostate specific antigen. EBRT: external beam radiotherapy. LDR: low dose rate. RT: radiotherapy. GTV: gross tumour volume. CTV: clinical target volume.

predictors remained for development of metastases or any recurrence in multivariable analyses.

Re-salvage

Four patients with an out-of-field LR underwent another focal salvage HDR treatment (as mentioned previously), one patient with an in-field recurrence had a salvage prostatectomy and nine patients underwent cryotherapy, seven of which had (at least partially) an in-field recurrence and two of which received a second salvage cryoablation eventually. As far as the results of these re-salvages were known: all four patients experienced PSA increases after the second focal salvage HDR, the patient that had a prostatectomy had unmeasurable PSA levels. After salvage cryotherapy five patients had subsequent PSA increases (including the two patients with a second cryotherapy), two did not have a PSA increase and for two patients this information was not available yet.

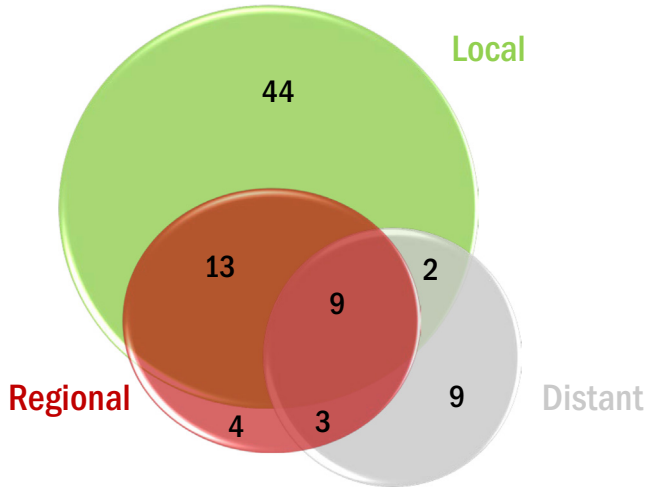

Fig. 1. Venn diagram with the recurrence distribution. Every patient is included only once. Patients in the green circle had a local recurrence, patients in the red circle had a regional lymph node recurrence and patients in the grey circle had distant metastases. Patients who had recurrences in more than one category, are displayed in the overlapping areas of the circles. In these patients, different categories of disease progression were not necessarily detected at the same time.

Discussion

The current study focuses on the oncologic outcome following focal salvage HDR brachytherapy for radiorecurrent prostate cancer. After 3 years, bRFS was 43%, LR-free survival 51% and metastases-free survival 74%. In around 2/3 of patients with a LR, it concerned at least partially an in-field recurrence.

Other studies have described oncologic outcome after whole-gland or focal salvage strategies for prostate cancer recurrences. Biochemical recurrence-free survival is commonly reported. For HDR salvage (focal and whole-gland combined), 2- and 5-year bRFS of 74% (range 63–89%) and 51% (range 45–65%) are documented [11]. For other salvage modalities low dose-rate brachytherapy (LDR), stereotactic body radiation therapy (SBRT), cryotherapy, high intensity focused ultrasound (HIFU), median 2-year bRFS outcomes are between 54–81%, while median 5-year bRFS outcomes are between 50–60% (focal and whole-gland combined) [11,12]. Focusing only on focal HDR salvage, as is the scope of the current study, other series report a 3-year bRFS of 42–62% [11,13]. With 43%, our results are on the lower side of this range. It should however be noted that about half of the patients were treated off-protocol, with relatively more high-risk tumour characteristics (e.g. 43% had iT3a/b disease), providing an explanation for the relatively high number of patients developing lymph node- or distant metastases.

While disease progression is often first detected biochemically, the exact location of recurrence is of interest, but little is known about recurrence patterns after local salvage treatments. In some studies on focal or whole-gland HDR salvage with a median follow-up between 13 and 73 months and 8–83 patients included, few distant recurrences are reported (2–23%) [13–22]. In line with that, our results show that disease progression after focal salvage HDR is primarily a problem of local recurrences and to a lesser extent of regional or distant metastases.

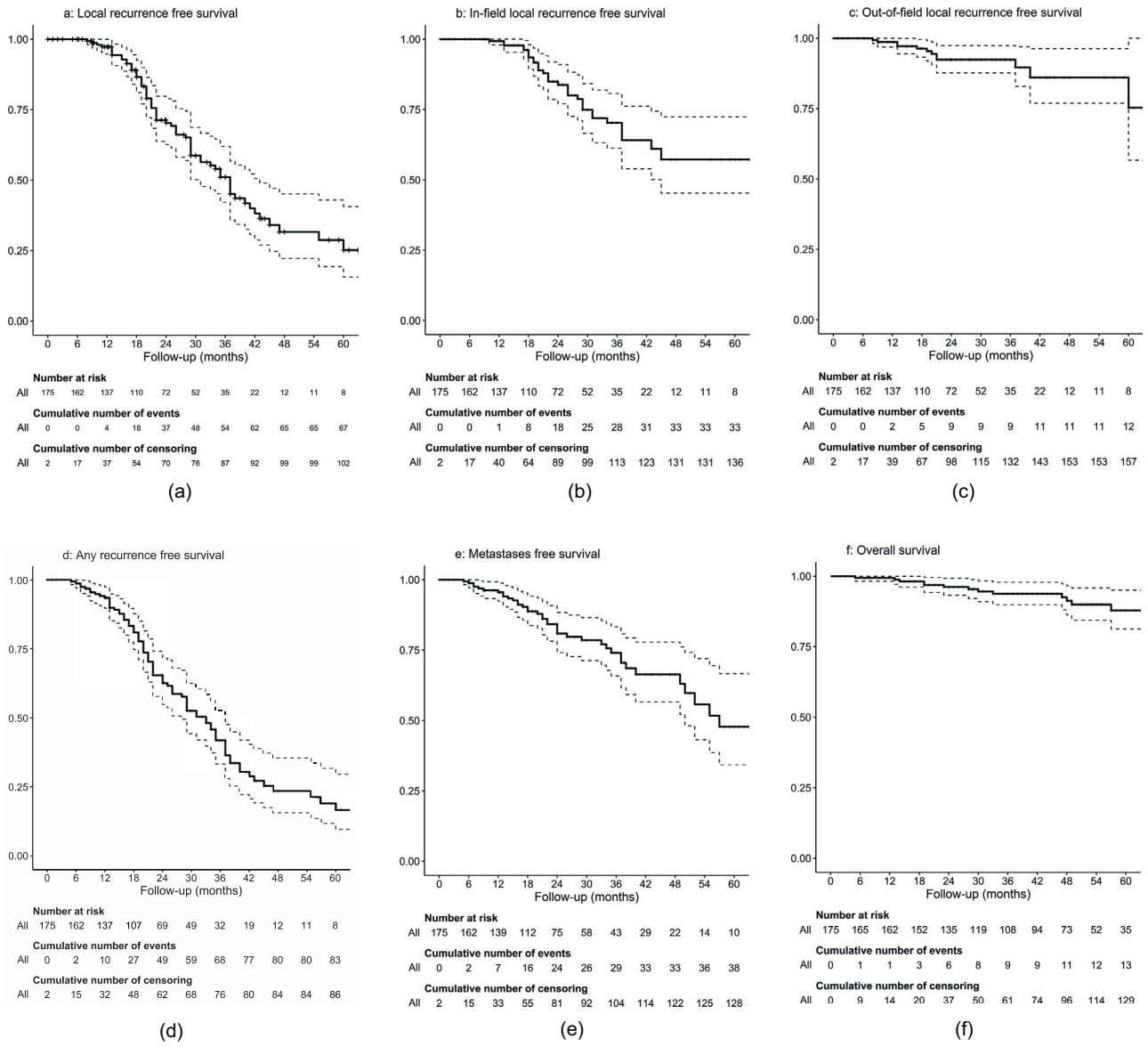

Fig. 2. Graphs of Kaplan-Meier survival analyses in months, for local recurrence-free survival (A), in-field local recurrence-free survival (B), out-of-field local recurrence-free survival (C), any recurrence-free survival (local and/or regional and/or distant recurrence, D), metastases free survival (E) and overall survival (F).

Most studies do not include details on localization of LR. Regarding focal salvage HDR studies, one small study (n = 15, median follow-up 36 months), described that 3 of 13 patients developed a new lesion in the prostate, of which 1 contralaterally and 2 ipsilaterally [23]. Another study (n = 43, median follow-up 26 months) mentioned that of the patients that underwent restaging of the 17 patients with progression, 7 had a LR [18]. Chitmanee et al (n = 50, median follow-up 21 months) stated that 3 of 13 patients with a biochemical recurrence had a LR in the prostate, 3 had distant metastases and in the other patients no site of recurrence could be identified, or no imaging tests were undertaken [19].

When comparing Fig. 2A and E, one can observe the curve showing metastatic disease progression descending earlier than the LR-curve, i.e. some patients show metastatic disease progression before/without local recurrences. In hindsight, these patients were not ideal patients for focal salvage treatment. Other patients developed metastases later on and can have benefit of focal salvage treatment, mostly in regard to postponement of ADT as shown in this paper.

Of interest are the found predictors in multiple regression analyses: larger GTV-size and shorter PSADT for in-field LR and higher cT-stage and higher PSA nadir for out-of-field LR. Since GTV-size corresponds with number of prostate cancer cells, a correlation with in-field recurrences is plausible. And a higher PSA nadir after salvage treatment might indeed be a sign of residual disease outside of the GTV. Although cT-stage was not found as a predictor for regional/distant metastases in this study, seminal vesicle involvement is a known predictor for metastases and 35% of our study population had cT3b stage in the pre-salvage setting [24]. However, some cT3b cases in our cohort were the result of a local recurrence in the prostate base / seminal vesicle area in patients without cT3b disease in the primary setting, potentially representing a different prognostic population. A previous publication of our research group presented two prediction models for biochemical failure after focal salvage HDR brachytherapy in which two models adopting age, GTV, pre-salvage PSA and PSADT, seminal vesicle involvement, post-salvage time to PSA nadir, and percentage PSA reduction were predictive [25]. For example, according to the pre-salvage model, a seventy-year-old patient with a PSADT of

Table 2
Kaplan-Meier analyses.

	KM-estimate (%)	Number of events	Number at risk
Overall survival			
1 y	99 (98–100)	1	161
3 y	94 (90–98)	9	107
5 y	88 (81–95)	13	34
BR-free survival			
1 y	93 (89–97)	11	147
3 y	43 (34–52)	75	39
5 y	19 (10–28)	92	6
LR-free survival			
1 y	97 (95–100)	4	136
3 y	51 (41–61)	54	34
5 y	25 (13–37)	67	7
In-field LR-free survival†			
1 y	99 (98–100)	1	136
3 y	70 (61–80)	28	34
5 y	57 (44–71)	33	7
Out-of-field LR-free survival†			
1 y	99 (97–100)	2	136
3 y	92 (88–97)	9	34
5 y	75 (54–97)	12	7
Metastases-free survival			
1 y	96 (92–99)	7	138
3 y	74 (65–83)	29	42
5 y	48 (32–64)	38	9
Any recurrence*-free survival			
1 y	94 (90–98)	10	136
3 y	42 (32–52)	68	31
5 y	17 (7–26)	83	6
ADT-free survival			
1 y	98 (95–100)	4	155
3 y	86 (80–92)	18	83
5 y	70 (59–80)	29	20

BR: biochemical recurrence (PSA nadir + ≥2). LR: local recurrence. ADT: androgen deprivation therapy. *: local and/or regional and/or distant recurrence. †: apart from LRs solely in-field or out-of-field, 10 patients had a LR in an overlapping region in- and out-of-field and 12 had a LR in multiple regions in- and out-of-field.

24 months, a 2 cm^3 GTV-size and a PSA value of 3 ng/mL pre-salvage, would have a 91% chance of 3-years biochemical disease-free survival (bDFS), while a seventy-year-old patient with a PSADT of 6 months, a 6 cm^3 GTV-size and a PSA value of 6 ng/mL has a 35% probability. There are similarities between the predictors for biochemical failure and LR as found in this study, further assisting in proper selection of patients for this treatment.

Knowledge about predictors of biochemical control and (in-field) local recurrence can guide in estimating the chance of a successful salvage beforehand and therefore help select patients that benefit most. Other factors to take into account are preexisting genitourinary or gastrointestinal complaints, time between primary radiotherapy and recurrence/salvage, life expectancy and patient preferences. For patients with increased risk of recurrence (such as those with simultaneous oligometastases), adequate follow-up should be ensured or even intensified and patients should be counseled as to whether treatment is applicable in their situation.

The current study does not elaborate on our experiences with radiation toxicity; however a previous publication of our group does [26]. A new toxicity analyses is planned several years after the former. Other series have also published on toxicity after focal salvage HDR brachytherapy [11,12]. Desired benefits in oncologic outcome need to be carefully weighed against possible additional toxicity.

Out-of-field local recurrences were relatively uncommon. In focal salvage HDR treatments, target volumes are deliberately kept small because of the reirradiation setting, and surrounding areas of the prostate already received a high radiation dose during primary treatment. With adequate staging as used in this study, we expect out-of-field local recurrences to remain uncommon.

For patients experiencing another LR following focal salvage HDR brachytherapy, sometimes a second focal salvage treatment is considered. Even more so compared to the consideration of a first focal salvage, risk of additional toxicity must be critically taken into account. In our institution, a second focal salvage HDR treatment is usually not performed in case of an in-field recurrence, because of expected dose limitations regarding the OAR and hypothesised radioresistance. These patients are occasionally referred for salvage cryotherapy, although severe toxicity has been documented for salvage cryotherapy as well [12,27–29].

However, even in case of disease progression after focal salvage, the start of subsequent ADT and potential further toxic treatment seems to be adequately deferred. In fact, three-years ADT-free survival was 86%, similar to the findings of Corkum et al. [13].

A strength of our study is the large number of treated patients, with a median follow-up duration that is sufficient for developing potential recurrent disease. Furthermore, survival analyses and Cox regression analyses were added to descriptive information regarding recurrences. The single-center character of this study could be mentioned as a limitation, although patients are referred to our institution for focal salvage HDR brachytherapy from other hospitals around The Netherlands, reflecting a national, adequate case-mix.

Future research might focus on further improving oncologic outcome. With GTV-size as a predictor of in-field recurrences, the focus should be on improving local control. Increasing the number of treatment fractions (and dose) seems a logical solution. From a radiobiological perspective, fractionation can be beneficent regarding hypoxia and redistribution of cells to other cell cycle phases [30]. In a primary treatment setting, an RCT compared whole-gland HDR brachytherapy with a single dose of 1x19 Gy with a 2-fraction arm of 13.5 Gy. Five-year's bDFS and local failure rate were in favour of the 2-fraction arm: 95% versus 73.5% and 3% versus 29%, respectively [31]. In the salvage setting, fractionated HDR

Table 3a
Univariable Cox regression analysis for local recurrence.

Risk factor	HR	95% CI		*p*-value
		lower	upper	
Time primary-salvage (months)	0.99	0.99	1.00	0.00*
PSADT pre-treatment	0.97	0.95	1.00	0.03*
cT pre-HDR	2.05	1.25	3.37	0.01*
cN pre-HDR	0.86	0.21	3.57	0.83
GTV size	1.09	1.04	1.15	0.00*
CTV size	1.06	1.02	1.10	0.00*
D90 CTV	0.96	0.87	1.06	0.40
D95 CTV	0.96	0.87	1.07	0.50
PSA nadir post-HDR	1.12	1.01	1.25	0.04*

HR: hazard ratio. 95% CI: 95% confidence interval. PSADT: PSA doubling time. cT: clinical T-stage. cN: clinical N-stage. GTV: gross tumour volume. CTV: clinical target volume. D90 CTV: percentage of the CTV receiving 90% of prescribed dose. D95 CTV: percentage of the CTV receiving 95% of prescribed dose.

Table 3b
Univariable Cox regression analysis for in-field recurrence.

Risk factor	HR	95% CI		*p*-value
		lower	upper	
Time primary-salvage (months)	0.99	0.98	1.00	0.01*
PSADT pre-HDR	0.96	0.92	1.00	0.04*
cT pre-HDR	1.45	0.72	2.92	0.29
cN pre-HDR	1.10	0.15	8.29	0.93
GTV size	1.09	1.03	1.17	0.01*
CTV size	1.06	1.02	1.11	0.01*
D90 CTV	0.94	0.82	1.08	0.40
D95 CTV	0.96	0.83	1.12	0.59
PSA nadir post-HDR	1.08	0.91	1.28	0.37

HR: hazard ratio. 95% CI: 95% confidence interval. PSADT: PSA doubling time. cT: clinical T-stage. cN: clinical N-stage. GTV: gross tumour volume. CTV: clinical target volume. D90 CTV: percentage of the CTV receiving 90% of prescribed dose. D95 CTV: percentage of the CTV receiving 95% of prescribed dose.

brachytherapy has been described in various (non-randomised) studies, yielding moderate to good results [11,13,32]. Brachytherapy has the advantage of obtaining a very high dose within the GTV, a dose modulation that is not achievable with EBRT. However, fractionated focal salvage HDR brachytherapy is more burdensome for patients and can be logistically challenging. Fractionated MR-guided adaptive stereotactic external beam radiotherapy can overcome these barriers, but as of yet little data are available for locally recurrent prostate cancer. A recent paper described 1-year results of MR-guided EBRT in 37 patients, with acceptable toxicity and a 12-month bRFS of 65% [33].

In conclusion, after focal salvage HDR brachytherapy with a dose of 1x19 Gy for local prostate cancer recurrence, subsequent recurrences are mostly local and in-field. Knowledge on recurrence characteristics following local salvage in prostate cancer can guide treatment strategies to further improve local control for these patients and postpone or prevent subsequent systemic treatments.

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Declarations of interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109495.

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