Salvage reirradiation for local prostate cancer recurrence after radiation therapy. For who? When? How?

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Réirradiation de rattrapage pour les cancers de prostate après irradiation première. Pour qui ? Quand ? Comment ?

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Conflict of interest statement

The authors have no conflict of interest to declare.

Abstract

Purpose: Literature review reporting results of salvage brachytherapy and stereotactic body radiotherapy for prostate recurrence only after radiotherapy for prostate cancer.

Materials and methods: A total of 38 studies (including at least 15 patients per study) were analysed: 19 using low-dose-rate brachytherapy, nine high-dose-rate brachytherapy and ten stereotactic body radiotherapy. Only five studies were prospective. The median numbers of patients were 30 for low-dose-rate brachytherapy, 34 for high-dose-rate brachytherapy, and 30 for stereotactic body radiotherapy. The median follow-up were 47 months for low-dose-rate brachytherapy, 36 months for high-dose-rate brachytherapy and 21 months for stereotactic body radiotherapy.

Results: Late genitourinary toxicity rates ranged, for grade 2: from 4 to 42% for low-dose-rate brachytherapy, from 7 to 54 % for high dose-rate brachytherapy and from 3 to 20% for stereotactic body radiotherapy, and for grade 3 or above: from 0 to 24% for low dose-rate brachytherapy, from 0 to 13% for high dose-rate brachytherapy and from 0 to 3% for grade 3 or above (except 12% in one study) for stereotactic body radiotherapy. Late gastrointestinal toxicity rates ranged, for grade 2: from 0 to 6% for low dose-rate brachytherapy, from 0 to 14 % for high dose-rate brachytherapy and from 0 to 11% for stereotactic body radiotherapy, and for grade 3 or above: from 0 to 6% for low dose-rate brachytherapy, and from 0 to 1% for high dose-rate brachytherapy and stereotactic body radiotherapy. The 5-year biochemical disease-free survival rates ranged from 20 to 77% for low dose-rate brachytherapy and from 51 to 68% for high dose-rate brachytherapy. The 2 and 3-year disease-free survival rates ranged from 40 to 82% for stereotactic body radiotherapy. Prognostic factors of biochemical recurrence have been identified.

Conclusion: Despite a lack of prospective data, salvage reirradiation for prostate cancer recurrence can be proposed to highly selected patients and tumours. Prospective comparative studies are needed.

Keywords

prostate cancer, localized recurrence, salvage reirradiation

Résumé

Objectif de l'étude: Il s'agit d'une revue de la littérature rapportant les résultats de la curiethérapie et de la réirradiation en conditions stéréotaxiques dans le cadre de récidive prostatique exclusive après radiothérapie de cancer de prostate.

Matériels et méthodes: 38 études ont été analysées (incluant au moins 15 patients par étude): 19 utilisant une curiethérapie de bas débit de dose, neuf une curiethérapie de haut débit de dose et dix une radiothérapie en conditions stéréotaxiques. Cinq études étaient prospectives. Le nombre médian de patients était de 30 pour la curiethérapie de bas débit de dose, 34 pour la curiethérapie de haut débit de

dose et 30 pour la radiothérapie en conditions stéréotaxiques. Le suivi médian des études était respectivement de 47, 36 et 21 mois.

Résultats: Les taux de toxicité tardive urinaire de grade 2 variaient de 4 à 42% pour la curiethérapie de bas débit de dose, de 7 à 54% pour la curiethérapie de haut débit de dose, et de 3 à 20% pour la radiothérapie en conditions stéréotaxiques ; de grade 3 respectivement de 0 à 24%, de 0 à 13% et de 0 à 3% (sauf 12% dans une étude). Les taux de toxicité tardive digestive de grade 2 variaient respectivement de 0 à 6%, de 0 à 14%, et de 0 à 11% ; ceux de grade 3 de 0 à 6% pour la curiethérapie de bas débit de dose, et de 0 à 1% pour la curiethérapie de haut débit de dose et la radiothérapie en conditions stéréotaxiques. Les taux de survie sans progression biochimique à 5 ans étaient de 20 à 77% pour la curiethérapie de bas débit de dose et de 51 à 68% pour la curiethérapie de haut débit de dose. À 2 et 3 ans, ils variaient de 40 à 82% pour radiothérapie en conditions stéréotaxiques. Des facteurs pronostiques de rechute biochimique ont été identifiés.

Conclusion: Malgré un manque de données prospectives, une réirradiation de rattrapage d'un cancer de prostate peut être proposée chez des patients hautement sélectionnés. Des études comparatives prospectives sont nécessaires.

Mots clés

Cancer de prostate, rechute locale, réirradiation

1. Introduction

Despite a treatment by external beam radiation therapy or brachytherapy in a curative intent for localized prostate cancer, 5-year biochemical relapse rates reach 10 to 15% for low risk cancer, 20 to 25% for intermediate risk cancer and 30 to 40 % for high risk cancer [1,2]. In this group of patients with biochemical recurrence, 20 to 40% of patients experiment prostate recurrence only [3], as confirmed by recent imaging modalities such as multiparametric MRI, choline-PET/CT and PSMA-PET/CT [4]. Historically, the treatment of these locally recurrent patients was a simple surveillance or intermittent or continuous androgen deprivation. Androgen deprivation has the two main drawbacks of being a palliative treatment and of decreasing quality of life, in addition of the cost of the treatment [5]. Salvage local treatments are another attractive treatment option offering a curative treatment, or at least delaying the use of androgen deprivation and preventing local disease progression [76]. Thanks to the advances of technology, several salvage treatments have been developed and improved. Salvage radical prostatectomy is the first historical salvage treatment, proposed by experiment surgical teams. The rates of 5-year biochemical disease-free survival range from 47% to 82% [6]. The main risk of salvage surgery is however incontinence, concerning around 50% of patients [6]. Cryotherapy and high-intensity focused ultrasound lead to 5-year biochemical disease-free survival ranging from 50% to 70%, depending on patient selection [7–11]. Corresponding incontinence rates range from 20 to

30%, even if the use of modern technology have strongly decreased urinary toxicity [7–11]. As in other tumour localization, reirradiation is another possible option. The first experience of external beam radiation therapy was disappointing. Indeed, external beam radiation therapy with conventional fractionation has been quickly abandoned since the reirradiation modality was both highly toxic and not efficient [12]. Brachytherapy and more recently stereotactic body radiation therapy are other rising highly conformal reirradiation modalities. Indeed, their first advantage is to limit the volume of irradiated organs at risk. Both techniques use also different radiation schedules than the first irradiation which led to the treatment failure, corresponding to a dose escalation for brachytherapy or benefiting theoretically of the low α/β ratio of prostate cancer when using severe hypofractionated stereotactic body radiotherapy [13]. Recently, Philippou et al. carried out a meta-analysis from 63 studies (25 on salvage radical prostatectomy, eight on salvage high-intensity focused ultrasound, 16 on salvage cryotherapy and 14 on salvage brachytherapy) to determine whether there was a difference in oncologic and toxicity functional outcomes of salvage modalities in the postradiation setting [14]. There were no differences between salvage radical prostatectomy and other non-surgical techniques. However, salvage radical prostatectomy seems to be associated with more rates of urinary incontinence.

This literature review reports results of salvage brachytherapy and salvage stereotactic body radiotherapy for local recurrence after radiotherapy for prostate cancer. Only studies comprising at least 15 patients have been selected in the review.

2. Diagnostic of local recurrence of prostate cancer after radiotherapy

Excluding metastases when proposing salvage therapies is crucial. Bone scintigraphy can be used to exclude bone metastases with a high sensibility (greater than 80%) when serum concentration of prostate specific antigen (PSA) is greater than 10 ng/mL [15–17]. Nodal recurrences can be searched by computed tomography (CT) with a poor sensitivity (40%) and a specificity around 80%, or by magnetic resonance imaging (MRI) with similarly sensitivity and specificity rates [18]. (^{11}C)-choline PET/CT has shown a sensibility of 90% if serum concentration of PSA is greater than 2ng/mL after radiotherapy [19]. A recent meta-analysis enhanced a detection rate of radiolabelled choline PET/CT of 80% when serum concentration of PSA is greater than 2ng/mL [20]. However, this detection rate dropped to 20% when serum concentration of PSA is less than 1 ng/mL. Both (^{68}Ga) -prostate specific membrane antigen (68Ga-PSMA) and (^{18}F)-fluciclovine have been shown to be more accurate in the detection of recurrent disease as compared with radiolabelled choline PET/CT [20]. Indeed, the overall percentage of positive (^{68}Ga)-PSMA PET among patients was 76% for patients with biochemical recurrence and increased with pre-PET PSA [21]. For the serum concentration of PSA categories of 0 to 0.2 ng/ml, 0.2 to 1 ng/ml, 1 to 2 ng/ml, and above 2 ng/ml, the percentages of positive scan were 42%, 58%, 76%, and 95%, respectively. The sensitivity and specificity rates were 80% and 97% [21].

A mixed post-prostatectomy and non-prostatectomy cohort demonstrated a (^{18}F)-fluciclovine detection rate of 37,5% at a serum concentration of PSA of less than 1 ng/ml, 78% between 1 and 2 ng/ml and 92% at more than 2 ng/ml [22].

In addition of excluding distant recurrence, imaging is also justified for local recurrence visualization and targeting. Indeed, in the past, salvages therapies were based on poor spatial information such as rectal examination, endorectal echography and biopsy in the vast majority of cases. Currently, multiparametric MRI allow the visualization of recurrent nodule(s) in pre-irradiated prostate [23–28]. Multiparametric MRI associating standard T2-weighted and advanced functional MRI techniques such as diffusion-weighted imaging and dynamic contrast-enhanced imaging, offers a high level of sensibility 94% and specificity 75% after a first course of radiation [29]. Moreover, voxel-wise tumour probability tool derived from multiparametric MRI have been proposed for target definition in focal salvage treatment [30].

In total, the French association of urology (Afu) recommend the use of a choline PET, and of an MRI if negative, for any suspicion of local recurrence after radiotherapy, if the patient has a good performance status and is eligible to a salvage treatment [17]. The European Association of Urology (EAU) guidelines recommend PSMA PET/CT (if available) or fluciclovine or choline-PET-CT, and multiparametric MRI to localize abnormal areas and guide biopsies in patients eligible for curative salvage treatment [16].

The diagnosis of recurrence after radiotherapy implies in any cases positive prostate biopsy. The Gleason score after irradiation is however often artificially modified. Moreover, the diagnosis of recurrence can be difficult since a recurrence can be interpreted like a radiation effect and a delayed tumour regression can be interpreted like a false positive [31–34]. In total, EAU guidelines recommend performing biopsies 18-24 months after primary radiation if a salvage treatment is considered, and multiparametric MRI can be used for biopsy targeting [16]. Afu guidelines recommend also histology proof before considering any salvage treatment, and biopsies have to be performed at least 2 years after the primary radiation. Biopsies can be targeted or random [17].

3. Salvage prostate brachytherapy as reirradiation modality

A total of 28 studies comprising at least 15 patients report results of salvage brachytherapy, either using low dose-rate brachytherapy in 19 studies (Tables 1 and 2), or pulsed-dose rate brachytherapy in one study (Table 3) or high dose rate brachytherapy in eight studies (Table 3). The first prostate irradiation modality was external beam radiation therapy in the vast majority of cases (90%), with total dose ranging from 52 Gy to 81 Gy. The median time between the two schedules of radiation was 67.5 months (range: 4-287 months), and the median serum concentration of PSA at relapse was 4.5 ng/ml. When reported, the percentage of Gleason Score more than 7 was 30%. Most of the tumour at

recurrence was intraprostatic, with a proportion of T3 stage ranging however from 0 to 52% depending on the studies. The pathological diagnostic of recurrence was confirmed in all the series except two studies [35,36], more often performed after at least 2 years after the first irradiation.

The first experience of low-dose-rate salvage brachytherapy have been published in the 1990s, with half of the studies reporting more than 30 patients, up to a maximum of 98 patients (Tables 1 and 2). Only two studies were prospective, comprising 25 and 92 patients [37,38]. Low-dose-rate salvage brachytherapy was based on the use of ^{125}I in the vast majority of cases (85%) delivering a dose ranging from 100 to 160 Gy, or less frequently with ^{103}Pd (53%) delivering a dose ranging from 90 to 144 Gy or even ^{198}Au in two studies published in 1990's [39,40]. The target volume was the whole gland in the majority of cases (74%). Androgen deprivation was combined with low-dose-rate salvage brachytherapy in 60% of study, with various duration. The median follow-up of the low-dose-rate salvage brachytherapy studies was 47 months, ranging from 23 to 108 months. 5-year biochemical disease-free survival rates ranged from 20 to 77%. The distant metastatic recurrence rates ranged from 3 to 27%. Most studies did not report acute toxicity. Late genitourinary toxicity rates ranged from 4 to 42% for grade 2 and from 0 to 24% for grade 3 or above, most being haematuria, stenosis, fistula and incontinence. Late gastrointestinal toxicity rates ranged from 0 to 6% for grade 2 and from 0 to 6% for grade 3 or above most being rectal bleeding, fistula complicating of definite digestive stoma. In the prospective study published in 2019 and reporting 92 patients with a follow-up of 54 months, grade 3 late genitourinary and gastrointestinal toxicity rate was 14%, including 4% of urinary incontinence, 4 % of retention and 1% fistula [38].

Most of the studies on high dose-rate salvage brachytherapy have been published after 2013, including a number of patients ranging from 15 to 115 (Table 3). Two studies were prospective, including 15 and 42 patients [41,42]. Salvage brachytherapy was delivered to the whole gland in 62% of the series. The doses ranged from 19 Gy in one fraction to 36 Gy in six fractions. Androgen deprivation was combined with high dose-rate salvage brachytherapy in 88% of studies. The median follow-up of these studies was 36 months, ranging from 10 to 60 months. In the three studies reporting results at 5 years, biochemical disease-free survival rates were 51%, 68% and 67% [41,43,44]. The distant metastatic recurrence rates ranged from 0 to 19%. Acute genitourinary toxicity was low, with no reported grade 3 or above in the five most recent studies. Acute gastrointestinal toxicity was very low, with a maximum of 4% of grade 2 and no grade 3 or above. Late genitourinary toxicity rates ranged from 7 to 54 % for grade 2, and from 0 to 13% for grade 3 or above. Late gastrointestinal toxicity rates ranged from 0% to 14% for grade 2, and from 0 to 1% for grade 3 or above. In the prospective study comprising 42 patients, with a follow-up of 36 months, the 5 year biochemical disease-free survival and metastasis rates were 68% and 19%, respectively [41]. Late genitourinary grade 2 and 3 toxicity rates were 48% and 2%, respectively. Late gastrointestinal grade 2 and 3 toxicity rates were 14% and 0%, respectively.

One study, comparing retrospectively low dose-rate- and high dose-rate salvage brachytherapy (respectively n=37 and n=61), did not find statistical difference in 3-year biochemical disease-free survival and in late toxicity rates [45]. However, there was a higher peak in urinary symptoms in patients receiving high dose-rate salvage brachytherapy but most patients in both groups returned to baseline 24 to 36 months after treatment.

4. Salvage prostate stereotactic body reirradiation

A total of ten studies reported results of salvage stereotactic body radiotherapy, including a number of patients ranging from 19 to 100, with only three studies comprising more than 50 patients (Table 4). Only one study comprising 29 patients was prospective [46]. External beam radiation therapy was the primary radiation in the vast majority of cases (90%). It must also be pointed out that 60% of studies comprised also patients who underwent a primary radical prostatectomy before the first radiation (with percentage of patients ranging from 10 to 69%). In all the series except two [47,48], local recurrence was biopsy-confirmed with a minimum delay of 2 years after the first irradiation. Median time between the primary radiation and salvage stereotactic body radiotherapy was 90 months. Median value of serum concentration of PSA at relapse was 3.35 ng/ml. The target volume was very variable, corresponding to the whole gland, a subpart of the gland only or the recurrent macroscopic disease after prostatectomy, depending on the studies. Planning target volume margins varied from 0 to 7 mm in all directions, except in posterior direction with a 5 mm maximum margin in all cases. The dose schedules varied from 25 Gy in five fractions to 36 Gy in six fractions every other day. Dose-constraints in the schedule of 36 Gy in six fractions are reported Table 5. For prostate tracking, patients had fiducial markers implanted into the target. Figure 1 shows an example of stereotatic reirradiation with CyberKnife®. Concomitant/adjuvant androgen deprivation was combined with stereotactic body radiotherapy in most of the studies, with a frequency varying from 0% to 61% of the patients. The median follow-up of the studies was 21 months, ranging from 12 to 29. At an evaluation time ranging from 12 to 36 months, biochemical disease-free survival rates ranged from 40 to 83%, metastasis rates 7 to 27%, and local relapse from 0 to 25%. Acute genitourinary toxicity rates ranged from 0 to 13% for grade 2, and for 0 to 7% for grade 3. Acute gastrointestinal toxicity rates ranged from 0 to 11% for grade 2 with no grade 3 or above. Late genitourinary toxicity rates ranged from 3 to 20% for grade 2, and from 0 to 3% for grade 3 or above, except 12% in one study reporting target volume corresponding to both the prostate and the seminal vesicles for 61% of patients [49]. One study reported cystoprostatectomy after salvage stereotactic body radiotherapy in one patient, because of major haematuria [46]. Late gastrointestinal toxicity rates ranged from 0 to 11% for grade 2, and from 0% to 1% for grade 3 or above.

The French and European Institute of Oncology (Milan) experience of salvage stereotactic body radiotherapy reported very recently by Pasquier et al including a serie of 100 patients [50]. This series

comprises the updated data of some patients that were included in previous report [51,52]. Androgen deprivation therapy was combined with salvage stereotactic body radiotherapy in 34% of patients. With a median follow-up of 29 months, the 3-year biochemical disease-free survival, local relapse and metastasis rates were 55%, 10% and 7%, respectively. Three-year late genitourinary toxicity rates were 20% for grade 2 and 1% for grade 3. Three-year late gastrointestinal toxicity rates were 1% for grade 2, without any grade 3.

5. Prognostics factors after salvage reirradiation and selection of patients for salvage treatments

Oncological findings depend strongly on the selection of the patients and of the tumours at recurrence. Indeed, Tables 1, 3 and 4 show that recurrence characteristics varied widely among the studies, whatever was the chosen salvage treatment. Several prognostic factors have been identified. After salvage brachytherapy or stereotactic body radiotherapy, high primary Gleason score, high initial disease stage or D'Amico risk group, high initial serum concentration of PSA nadir, high presalvage serum concentration of PSA, delayed the salvage treatment, high post-treatment serum concentration of PSA nadir, long time to achieve salvage nadir, serum concentration of PSA doubling time at salvage less than 12 months and short time between the two irradiations, low salvage stereotactic body radiotherapy dose and use of androgen deprivation at salvage have been associated with poor outcome [36,40,44,45,48–50,53–58].

Patients selection appears therefore crucial to optimize the efficiency/toxicity ratio of salvage reirradiation. Table 6 presents the recommendations for salvage reirradiation from four instances: the Delphi consensus of the European group of brachytherapy–European Society of Therapeutic Radiation Oncology (Gec-ESTRO) based on the opinion of 18 experts analysed in 38 digital questionnaires, the EAU, the AFU and the Australian and New Zealand Radiation Oncology Genito-Urinary group (FROGG) [16,17,59,60]. Overall the expert societies are very cautious to propose salvage reirradiation in both highly selected patients (who are of good performance status with minimal comorbidities and sufficient life expectancy greater than 10 years) and highly selected recurrence (with biopsy-confirmed and isolated local prostate recurrence). Local salvage treatment option as well as observation, immediate or differed androgen deprivation should also be discussed with the patients. Such local recurrences are to be considered for clinical trials.

6. Conclusions

A total of 38 studies report results of salvage reirradiation for prostate recurrence. Salvage brachytherapy is the most explored reirradiation modality, concentrating 75% of the publication and with more follow-up than salvage stereotactic body radiotherapy. Salvage stereotactic body radiotherapy should not be considered for routine practice and has to be administered with caution in competent centres; inclusion in clinical trials is recommended. Only five studies are prospective and

not comparative. With a lot of cautious, salvage low dose-rate brachytherapy may provide slightly more severe toxicity than salvage high dose-rate brachytherapy and stereotactic body radiotherapy. Biochemical disease-free survival rates appear not very different between reirradiation modalities and depend strongly on both patient selection and on the association with androgen deprivation. Several issues still need to be addressed, such as target definition based on multimodal imaging and biopsy, dose distribution optimization, choice of the dose-constrains in organs at risk and indication/duration of androgen deprivation in combination with reirradiation.

At present, no authoritative recommendations can be concluded because of the absence of randomized data with standardized definitions and protocols. Overall, there is therefore a need for prospective study evaluating and comparing both oncological findings and quality of life between the various treatment options. The results of two French studies exploring reirradiation for prostate cancer are expected, Capricur using brachytherapy and Getug 31 (Stereo-Re-Pro) using salvage stereotactic body radiotherapy.

Author contributions

Conception and design of study: RDC; drafting of the manuscript: MB, GC, DP, XP, AD, KG, LB, JC. All authors approved the final version of the manuscript.

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Figure legend

Figure 1. Dose distribution and beams of salvage focal stereotactic body reirradiation with CyberKnife® for prostate cancer. A 70-year-old patient presented an isolated right lateral prostate relapse shown in MRI and choline-PET/CT, confirmed by biopsy, 6 years after the primary external beam radiation therapy (75 Gy). The total dose was 36 Gy in 6 fractions every other day. A total of 116 beams were used.

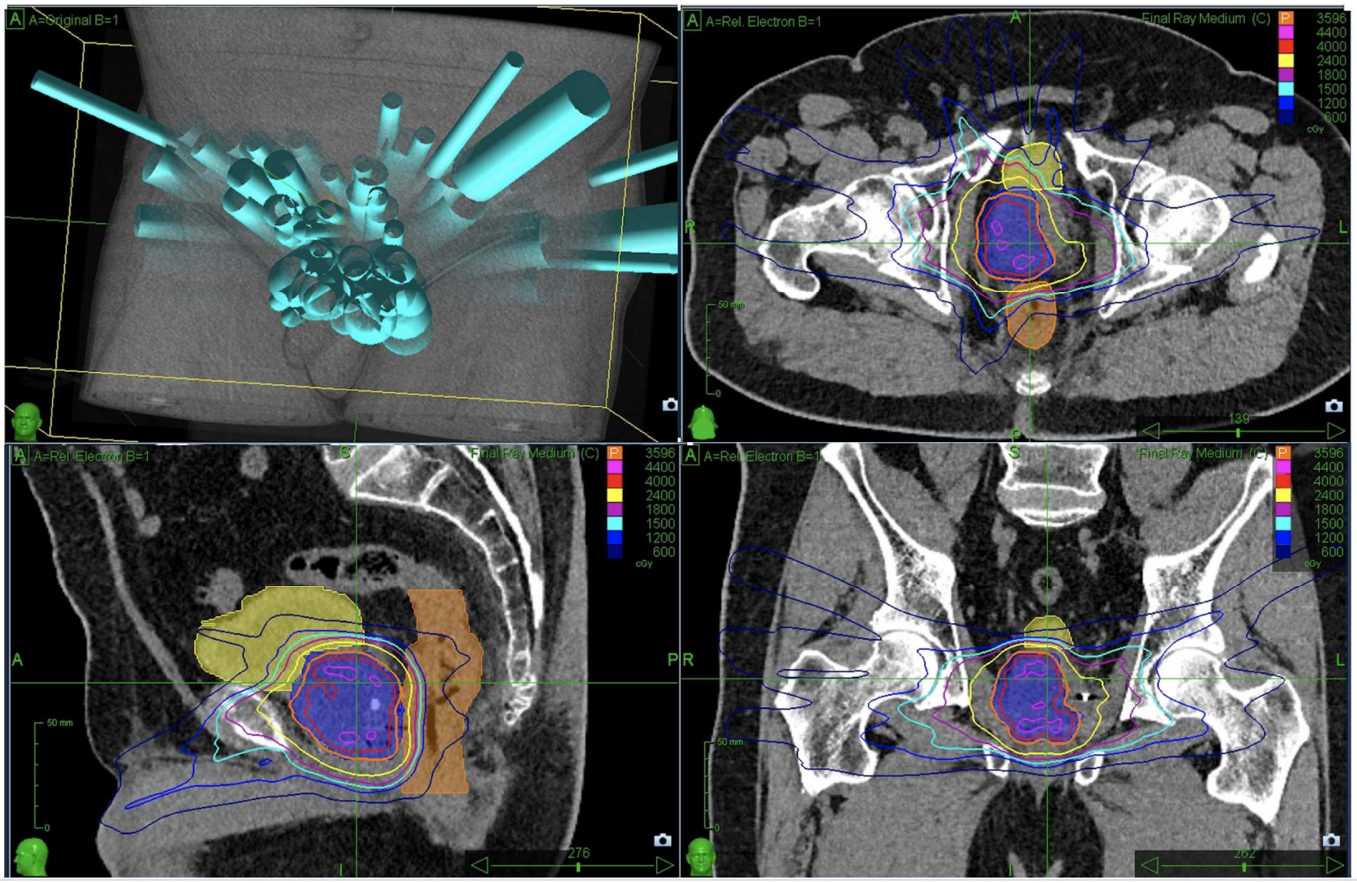
A=Original B=1
A=Rel. Electron B=1
Final Ray Medium (C)
3596
4400
4000
2400
1800
1500
1200
600
cGy
50 mm
0
139
276
262

Table 1. Salvage prostate low-dose rate brachytherapy: primary radiotherapy, recurrence and salvage treatment.

Reference	Number of patients	Primary radiotherapy (%)	Primary dose (Gy)	Time between two radiotherapy in months	[PSA] at salvage [range] (ng/ml)	Tumour stage Gleason score at relapse	Type of brachytherapy	Source	Volume	Salvage dose
Loening and Turner (1993)[39]	31	external beam radiation therapy (100%)	6000 rads	48 [12-156]	NR	NR	low dose-rate	^{198}Au	Whole gland	100-200 Gy
Butler et al. (1997)[40]	30	external beam radiation therapy / brachytherapy (NR)	NR	NR	11 [0,12-51]	Well differentiated: 0% Poorly differentiated:16% Unknow: 33%	low dose-rate	^{198}Au	Whole gland	20 Gy with 20 seeds
Beyer (1999)[61]	17	external beam radiation therapy (100%)	63 Gy	54 [23-146]	2,2 [0,3-27]	NR	low dose-rate	^{125}I (88%) ^{103}Pd (12%)	Whole gland	120Gy 90 Gy
Grado et al. (1999)[57]	49	external beam radiation therapy (94%) ^{125}I (6%)	66 Gy NR	42 [22-185]	5,6 [1,5-79]	Gleason score ≤6: 45% Gleason score ≥7: 55%	low dose-rate	^{125}I (24%) ^{103}Pd (76%) + external beam radiation therapy 8%	Whole gland	160 Gy 120 Gy +45 Gy
Koutrouvelis at al. (2003)[62]	31	^{103}Pd (84%) ^{125}I (6%)	120 Gy 144 Gy	30 [12-87]	<10 [97%]	T2a : 30% ; T2b-T3 : 35% ; T3b : 5% Gleason score 6 : 54% ; Gleason score 7: 36%; Gleason score ≥8: 22%	low dose-rate	^{125}I (77%) ^{103}Pd (23%)	Whole gland + seminal vesicles if involved	100-144 Gy 100-120 Gy
Wong et al. (2006)[63]	17	external beam radiation therapy (100%)	68 Gy	72 [30-115]	4,7 [1,2-12]	T1 : 53% ; T2a : 41% ; T2c : 6% ; Gleason score 6 : 29% ; Gleason score 7 : 41% ; Gleason score ≥8 : 30%	low dose-rate	^{103}Pd (47%) ^{125}I (53%)	Whole gland	119 Gy 133 Gy
Nguyen et al. (2007)* [37]	25	external beam radiation therapy (52%) brachytherapy (48%)	66-70 137 Gy	62 [30-154]	5,5 [1,4-12]	NR	low dose-rate	^{125}I	Partial gland (MRI guided)	137 Gy
Aaronson et al. (2009)[64]	24	external beam radiation therapy (96%) With high dose-rate brachytherapy (4%)	72 Gy NR	49 [26-109]	3,4 [0,3-10]	Re-staged <T3	low dose-rate	^{125}I (80%) ^{103}Pd (20%)	Whole gland with boost	108 Gy 144 Gy
Burri et al. (2010)[54]	37	external beam radiation therapy (86%) low dose-rate brachytherapy (11%)	68 Gy 47-113 Gy	62 [26-171]	5,6 [1,7-35]	Gleason score 6: 19%; Gleason score 7: 46%; Gleason score ≥8: 32%; NR: 3%	low dose-rate	^{103}Pd (97%) ^{125}I	Whole gland	110 Gy 135 Gy
Moman et al. (2010)[53]	31	external beam radiation therapy (65%) low dose-rate brachytherapy (35%)	66 Gy NR	60 [+/- 34]	11,4 [+/-7,6]	Gleason score 6: 16%; Gleason score 7: 55%; Gleason score ≥8: 13%; NR: 16%	low dose-rate	^{125}I	Whole gland	145 Gy
Hsu et al. (2013)[65]	15	^{125}I (100%)	144 Gy	69 [28-132]	3,5 [0,9-5,6]	T1c : 80% ; T2a : 20% ; Gleason score 6: 67%; Gleason score 7: 13%; Gleason score ≥8: 13%; NR: 7%	low dose-rate	^{125}I ^{103}Pd	Partial gland (MRI-guided)	144 Gy 125 Gy
Henriquez et al. (2014)[55]	56	external beam radiation therapy (82%) ^{125}I (8%)	72 Gy 145 Gy	93% > 24 months	3,7 [1,1-30]	Gleason score 6: 16%; Gleason score 7: 25%; Gleason score ≥8: 14%; NR: 45%	low dose-rate (66%) high dose-rate (34%)	^{125}I ^{192}I	Whole gland	145 Gy 50,5 Gy
Peters et al. (2014)[66]	20	external beam radiation therapy (65%) ^{125}I (35%)	70-76 Gy 145 Gy	79 [42-144]	4,7 [0,3-14]	Gleason score 6: 35%; Gleason score 7: 30%; NR: 35%	low dose-rate	^{125}I	Partial gland	≥144 Gy
Vargas et al. (2014)[56]	69	external beam radiation therapy (100%)	68,4 Gy	90 [27-240]	10,6 [NR] with only 2,8% >20	T1: 45%; T2: 51%; T3: 4,2%; Gleason score 6: 32%; Gleason score 7: 41%; Gleason score ≥8: 27%; Perineuronal invasion: 8,5%	low dose-rate	^{103}Pd	NR	100 Gy
Rose et al. (2015)[67]	18	external beam radiation therapy (100%)	70,5 Gy	94 [42-204]	4,3 [1,8-8,2]	Gleason score 6: 17%; Gleason score 7: 22%; Gleason score ≥8: 61%	low dose-rate	^{125}I	Whole gland (83%) Partial gland	130-144 Gy 140 Gy
Lacy et al. (2016)[68]	21	brachytherapy (100%) external beam radiation therapy (14%)	NR	45 [4-287]	6,3 [1-19]	NR	low dose-rate	^{125}I	Partial gland	108-144 Gy

Barbara et al. (2017)[35]	19	external beam radiation therapy (100%)	74 Gy	84 [12-187]	3,4 [2,7-6,8]	NR	low dose-rate	^{125}I	Whole gland	130 Gy
Kollmeier et al. (2017)[45]	98	external beam radiation therapy (88%) brachytherapy (10%) brachytherapy + external beam radiation therapy (2 %)	81 Gy NR	72 [12-172]	3,8 [0-59]	Gleason score 6: 5%; Gleason score 7: 56%; Gleason score ≥8: 39%	low dose-rate (n=37) high dose-rate (n=61)	^{103}Pd 35% ^{125}I 3% ^{192}I 62%	Whole gland Except one boost (high dose-rate)	125 Gy 144 Gy 32 Gy, 4 fractions
Crook et al. (2019)*[38]	92	external beam radiation therapy (100%)	74 Gy	85 [60-119]	4,1 [0,4-9,7]	NR	low dose-rate	^{125}I (92%) ^{103}Pd	Whole gland	140 Gy 120 Gy

* Prospective study
NR: Not reported

Table 2. Salvage prostate low-dose rate brachytherapy: follow-up, toxicity and oncological results.

References	Follow-up [range], months	Acute genitourinary/gastrointestinal toxicity rates	Late genitourinary/gastrointestinal toxicity rates	Sexual toxicity rate	biochemical disease-free survival	Clinical control local relapse, metastasis relapse, disease-free survival, cancer specific survival	Overall survival
Loening and Turner (1993)[39]	23 [6-82]	NR	NR	NR	NR	local relapse 3% metastasis relapse 9,6%	67% (5 year) 2 cancer deaths
Butler et al. (1997)[40]	49 [12-55]	genitourinary : grade 1 30%, grade 2 3%, no grade 3 or above gastrointestinal : grade 1 10%, grade 2 3%, no grade 3 or above	genitourinary: grade 2 30%, no grade 3 or above gastrointestinal: grade 2 3%, no grade 3 or above	NR	83% at follow-up	local relapse 20%, locoregional relapse 3% metastasis relapse 27%	NR
Beyer (1999)[61]	62 [15-77]	NR	genitourinary 24% incontinence (5 year) gastrointestinal : 0	NR	53% (5 year)	NR	93% (5 year)
Grado et al. (1999)[57]	64 [26-97]	Timing NR: genitourinary: 14% transurethral resection prostate with 6% urinary incontinence after, 4% haematuria, 6% dysuria gastrointestinal: 4% rectal ulcers, 2% colostomy		2% decrease activity	48% (3 year) 34% (5 year)	local relapse 2% disease-free survival 79% (5 year)	75% (3 year) 56% (5 year)
Koutrouvelis at al. (2003) [62]	30 [12-84]	NR	genitourinary/gastrointestinal: grade 2/3 13% (NR), grade 4 6% (3% colostomy)	NR	87% at follow-up	metastasis relapse 3%	NR
Wong et al. (2006)[69]	44 [13-77]	NR	NR	NR	75% (4 year)	At 4 year: local relapse 0% metastasis relapse 5%, disease-free survival 94%	83% (4 year)
Nguyen et al. (2007)*[37]	47 [14-75]	NR	genitourinary/gastrointestinal: grade 3/4 30% with 8% rectal bleeding, 4% urethral stricture, 4% abscess, 13% fistula with require colostomy and urostomy	NR	70% (4 year)	NR	NR
Aaronson et al. (2009)[64]	30 [13-65]	NR	genitourinary: grade 2: 4% urethral stricture, 21% haematuria, 4% urinary incontinence, grade 3 4% haematochezia, no grade 4 gastrointestinal: grade 3 4% haemorrhage, no grade 4	NR	88% (2,5 year)	cancer specific survival 96% (2,5 year)	NR
Burri et al. (2010)[54]	86 [2-156]	NR	genitourinary: grade 2: 24% obstructive symptoms, 6% urinary incontinence grade 3 8% (obstruction and haematuria), grade 4 3% fistula gastrointestinal : grade 2 5% diarrhea	NR	65% (5 year) 54% (10 year)	At 10 year: local relapse 24%, metastasis relapse 21% cancer specific survival 96%	94% (5 year) 74% (10 year)
Moman et al. (2010)[53]	108 [+/-48]	genitourinary: grade 1 29%, grade 2 58%, grade 3 3% gastrointestinal : grade 1 45%, grade 2 10%, no grade 3 or above	genitourinary: grade 2 39%, grade 3 19% (fistula, urethral stricture) gastrointestinal: grade 2 3%, grade 3 6% (fistula), no grade 4	NR	51% (1 year) 20% (5 year)	metastasis relapse 26% (5 year), 46% (10 year)	72% (5 year) 39% (10 year)
Hsu et al. (2013)[65]	23 [8-88]	NR	genitourinary: grade 2 33% (requiring medication or catheterization), no grade 3 or above gastrointestinal: no above grade 1	grade 1 13%, grade 2 67%, grade 3 13%	71% (3 year)	local relapse 13% disease-free survival 63% (3 year)	NR
Henriquez et al. (2014)[55]	48 [25-109]	NR	genitourinary: grade 3 24% (spams, obstruction, stricture), no grade 4 gastrointestinal: grade 3 2% rectal bleeding, grade 4 2,7% colostomy for fistula	NR	77% (5 year)	NR	70% (5 year)
Peters et al. (2014)[66]	36 [10-45]	NR	genitourinary: grade 3 5% ureteral stricture gastrointestinal: no grade 3 or above	NR	60% (3 year)	metastasis relapse 15%	NR
Vargas et al. (2014)[56]	60 [7-164]	NR	genitourinary: grade 2 4% (retention), grade 3 8,7% (hematuria), no grade 4 gastrointestinal: grade 2 5,7% (rectal bleeding), no grade 3 or above	NR	prostate cancer castration resistant 22%, prostate cancer non castration resistant 74%	metastasis relapse 10% (5 year)	64% (5 year) With 52% of cancer deaths
Rose et al. (2015)[67]	31,5 [12-104]	genitourinary: 33% urinary catheter gastrointestinal: grade 1/2 44% (frequency, urgency, pain, rectal bleeding), no grade 3 or above	genitourinary: grade 1/2 urinary incontinence 33%, grade 2 22% urethral stricture grade 3 11% (abscess and necrosis after transurethral resection prostate) gastrointestinal: grade 3 5% (proctitis, ulcer)	NR	78% (at follow-up)	locoregional relapse and metastasis relapse 5%	NR
Lacy et al. (2016)[68]	49 [10-149]	NR	genitourinary : grade 1 9,6% urinary incontinence. grade 3 4,8 % bladder obstruction, 4,8% fistula, 4,8% leimyosarcoma gastrointestinal : NR	Decrease in 45%	52% (5 year)	NR	NR
Barbara et al. (2017)[35]	24 [6-45]	genitourinary: « common » and transitory haematuria (NR) gastrointestinal: grade 2 5,3%	genitourinary: grade 1 21%, grade 2 42%, grade 3 10.5% (haematuria) gastrointestinal: grade 4 5,3% (fistula/uretero and colostomy)	NR	85% (3 year)	NR	NR
Kollmeier et al. (2017)[45]	31 [2-97]	genitourinary: grade 2 58%, no grade 3 or above gastrointestinal: grade 2 1%, no grade 3 or above	genitourinary: grade 2 37% (urinary incontinence, hematuria), grade 3 9% (ureteral stricture, hematuria, fistula, urinary incontinence, abscess) gastrointestinal: grade 2 3%, grade 3 2% (rectal bleeding)	NR	60% (3 year)	metastasis relapse 22% cancer specific survival 92%	88% (at follow-up) 3 deaths of non-cancer

			No difference between low- and high dose-rate				
Crook et al. (2019)*[38]	54 [4-97]	genitourinary/gastrointestinal: grade 3 14% (rectal bleed, rectal pain, ureteral stricture, urinary incontinence). No grade 4	Primary endpoint = late toxicity genitourinary/gastrointestinal : grade 3 : 14% (1% fistula, 4% urinary incontinence, 4% retention, 3% cystitis, 1% proctitis)	NR	NR	NR	NR

*Prospective study

Table 3. Salvage prostate high-dose rate brachytherapy

Reference	Number of patients	Primary radiotherapy	Primary dose	Time between 2 radiotherapies, [range] (months)	[PSA] at salvage [range], (ng/ml)	Tumour stage, Gleason score at relapse	Type of brachytherapy	Source	Volume	Salvage dose	follow-up [range] (months)	Acute genitourinary/gastrointestinal toxicity rate	Late genitourinary/gastrointestinal toxicity rate	Sexual toxicity rate	biochemical disease-free survival rate	Clinical control :local relapse, metastasis relapse, cancer specific survival	overall survival %
Lahmer et al. (2013)[70]	18	external beam radiation therapy (89%) low-dose rate ^{125}I (5%) external beam radiation therapy + brachytherapy (5%)	69 Gy 200 Gy 36 + 150 Gy	64,5 [27-271]	4,46 [0,54-46]	Gleason score 6: 5,5% Gleason score 7: NA Gleason score ≥8 : 28%	Pulse-dose rate	^{192}I for all	Whole gland	60 Gy in 2 sessions	21 [8-77]	Timing NR : genitourinary: grade 2 11% (cystitis, urinary incontinence), grade 3 17% (retention, urinary incontinence) gastrointestinal : none above grade 1		NR	57% (3 year)	metastasis relapse 22%	89% (3 year)
Lee et al. (2007)[71]	21	external beam radiation therapy (86%) brachytherapy (9%) Protons (5%)	72 Gy NR NR	64 [24-125]	5,9 [1,4-9,5]	T1 : 9,5% T2 : 48% T3a : 19% T3b : 24% Gleason score 7 : 47% Gleason score ≥8 : 47%	high-dose rate		Whole gland with or without seminal vesicles	36 Gy in 6 fractions	19 [6-84]	genitourinary: grade 1/2 86% (frequency, dysuria), grade 3 14% (haematuria), no grade 4 gastrointestinal: grade 1/2 14%, no grade 3 or above	genitourinary: grade 3 4%, no grade 4 gastrointestinal: no grade 3 or above	grade 1/2 18% grade 3 9%	89% (2 year)	metastasis relapse 10%	NR
Lyczek et al. (2009)[36]	115	external beam radiation therapy (62%) brachytherapy (23%) external beam radiation therapy + high-dose rate (6%)	52 (30-76) Gy 30 Gy NR	49,5 [20-220]	NR	NR	high-dose rate		NR	30 Gy in 3 fractions	NR, at least 60 months	genitourinary: grade 1 11%, grade 2 18%, grade 3 2,6% (frequency, urgency, nocturia) gastrointestinal: grade 2 1%	genitourinary: grade 2 7%, grade 3 2,6%, grade 4 3,5%. Grade and timing NR: 5% haematuria, 1,5% fistula, 1,7% permanent catheter, 3,4% urinary incontinence gastrointestinal: grade 2 1,7%, grade 3 0,9%	NR	46% (if [PSA] ≤6 ng/ml) 18% (If [PSA] >6 ng/ml)	NR	86% ([PSA] ≤6) 48% ([PSA] >6)
Chen et al. (2013)[43]	52	external beam radiation therapy (81%) brachytherapy (19%)	NR	NR	9,3 [1,2-58]	T1 : 17% T2 : 31% T3 : 52% Gleason score 6 : 4% Gleason score 7 : 44% Gleason score ≥8 : 52%	high-dose rate		Whole gland	36 Gy in 6 fractions	60 [6-155]	genitourinary: grade 2 36%, grade 3 2%, no grade 4 gastrointestinal : no grade 2 or above	genitourinary: grade 2 54%, grade 3 2% gastrointestinal: grade 2 4%, none above grade 2	Acute : grade 2 19% Late : grade 2 29%, grade 3 6%	51% (5 year)	NR	92% (5 year)
Kukielka et al. (2014)[72]	25	external beam radiation therapy (100%)	74 Gy	68 [19-139]	2,8 [1-25]	T1: 28% T2: 64% T3: 20% Gleason score 6: 20% Gleason score 7: 40% Gleason score ≥8: 20%	high-dose rate + intraninterstitial hyperthermia		Whole gland	30 Gy in 3 fractions with interstitial hyperthermia 41-43°C for 60 minutes	13 [4-48]	genitourinary: grade 1 56% haematuria, 40% cystitis, grade 2 32% nocturia, 40% retention, 4% urinary incontinence, 8% haematuria, no grade 3 or above gastrointestinal: grade 2 4% rectal bleeding	genitourinary (>3 months): grade 1 55%, grade 2 18% (nocturia, obstruction), no grade 3 or above gastrointestinal : 0	NR	74% (2 year)	local relapse 4% metastasis relapse 8%	NR

Yamada et al. (2014)*[41]	42	external beam radiation therapy (100%)	81 Gy	78 [NR]	3,54 [NR]	Gleason score 6: 7% Gleason score: 7 60% Gleason score ≥8: 33%	high-dose rate		Whole gland	32 Gy in 4 fractions	36 [6-66]	genitourinary: grade 1 38%, grade 2 40% gastrointestinal: NR	genitourinary: grade 1 38%, grade 2 48% (7% resolved grade 3 urethral stricture), grade 3 2% urinary incontinence, no grade 4 gastrointestinal: grade 1 43%, grade 2 14% (rectal bleeding), no grade 3 or above	NR	68% (5 year)	metastasis relapse 19% cancer specific survival 90%	79% (5 year)
Wojcieszek et al. (2016)[44]	83	external beam radiation therapy (61%) external beam radiation therapy + brachytherapy (39%)	74 Gy NR	67 [22-124]	3,1 [0,06-20]	Gleason score 6: 19% Gleason score 7: 27 % Gleason score ≥8: 7% NA: 47%	high-dose rate		Whole gland	30 Gy in 3 fractions	41 [11-76]	genitourinary: grade 1 52%, grade 2 35%, no grade 3 or above gastrointestinal : none above grade 1	genitourinary: grade 1 33%, grade 2 39%, grade 3 13% (retention with urostomy or intervention) gastrointestinal: none above grade 1	NR	76% (3 year) 67% (5 year)	metastasis relapse 14% (5 year)	93% (3 year) 86% (5 year)
Maenhout et al. (2017)[73]	17	external beam radiation therapy (47%) low-dose rate ^{125}I (53%)	70-77 Gy 145 (Gy)	96 [30-228]	4,8 [0,9-6,8]	NR	high-dose rate		Focal (guided by MRI + PET/CT)	19 Gy in 1 fraction	10 [3-40]	genitourinary: grade 2 13%, no grade 3 or above gastrointestinal: none above grade 1	genitourinary: grade 2 37% (1 year), grade 3 1/5 patients (urethral stricture) (2 year) gastrointestinal: none above grade 1	At 3 months : grade 2 53%, grade 3 27% 2 year : grade 3 3/5 patients	92% (1 year)	metastasis relapse 5%	NR
Murgic et al. (2018)*[42]	15	external beam radiation therapy (100%)	70-78 Gy	91 [12-146]	4,1 [1,3-9,3]	Gleason score 6: 7% Gleason score 7: 53 % Gleason score ≥8: 40%	high-dose rate		Focal or MRI positive quadrant	27 Gy in 2 fractions	36 [23-52]	genitourinary: grade 2 93%, no grade 3 or above gastrointestinal: none above grade 1	genitourinary: grade 1 20%, grade 2 46%, grade 3 6% (haematuria) gastrointestinal: grade 2 13%, no grade 3 or above	NR	87% (2 year) 61% (3 year)	local relapse 21% metastasis relapse 0%	NR

* Prospective study

[PSA]: prostate specific antigen serum concentration; NR: Not reported; PET: positrons emission tomography: CT: computed tomography; MRI: magnetic resonance imaging

Table 4. Salvage prostate stereotactic body reirradiation

Reference	Number of patients	Primary radical prostatectomy rates	Primary radiotherapy	Primary dose (Gy)	Time between 2 radiotherapy [range]	[PSA] at salvage [range] (ng/ml)	Tumour stage, Gleason score at salvage	Type of treatment	Target volume, clinical target volume	planning target volume, mm (posterior)	Salvage dose (Gy)	follow-up [range] (months)	Acute genitourinary toxicity rates	Acute gastrointestinal toxicity rates	Late genitourinary toxicity rates	Late gastrointestinal toxicity rates	biochemical disease-free survival rates	Clinical control (local relapse, metastasis relapse)	Overall survival rates
Jereczek-fossa et al. (2012) [74]	19 local relapse (prostate: 15, anastomosis: 4)/ 38	41	external beam radiation therapy (100%)	NR	66 (24-180)	prostate (recurrence): 3,51 [1,7-23] anastomosis (recurrence): 6,6 [0,47-11]	NR	Stereotactic radiotherapy (linear accelerator or CyberKnife)	gross tumour volume + 1-2 mm	NR	prostate (recurrence): 30 Gy in 4,5 fractions anastomosis (recurrence): 30 Gy in 5 fractions	prostate (recurrence): 9,5 [3-29] anastomosis (recurrence): 23 [4-31]	prostate (recurrence): grade 2 13%, grade 3 7% [haematuria, urinary incontinence], no grade 4 anastomosis (recurrence): grade 2 25%, no grade 3 or above	None above grade 1	prostate (recurrence): grade 2 7%, grade 3 7% (haematuria, urinary incontinence) anastomosis (recurrence): 0%	prostate (recurrence): 0 anastomosis (recurrence): grade 2 25%	At follow-up prostate (recurrence): 66% anastomosis (recurrence): 50%	local relapse: 7% (prostate) and 50% (anastomosis) Metastasis relapse: 27% (prostate) and 25% (anastomosis)	100% at follow-up
Fuller et al.*(2015) [46]	29	0	external beam radiation therapy (97%)	74 (65-81)	88 [32-200]	3 [0,1-49]	Median T: T1c Gleason score ≥7: 79%	Stereotactic radiotherapy (CyberKnife)	whole gland	clinical target volume=planning target volume	34 Gy in 5 fractions	24 [3-60]	grade 2 0% grade 3 3% No grade 4	None above grade 1	grade 2 10% grade 3 3% (obstruction) grade 4 3% cystoprostatectomy for haematuria	none above grade 1	82% (2 year)	local relapse 0% Disease-free survival 100% (2 year)	NR
			low dose-rate ^{125}I brachytherapy (3%)	NR															
Zerini et al. (2015) [51]	32	69	external beam radiation therapy (100%)	74	115 [33-182]	3,1 [0,7-52]	NR	3D-radiotherapy (3%) Stereotactic radiotherapy (41%) Intensity-modulated radiotherapy (47%) CyberKnife (6%)	whole gland or nodule or prostate bed	+ 5-7 mm (3-5)	25 Gy in 5 fractions	21 [2-53]	grade 1 19% grade 2 6% no grade 3 or above	grade 2 3%, no grade 3 or above	grade 1 19%, grade 2 3%, no grade 3 or above	grade 1 16%. none above grade 1	41% (at follow-up)	local relapse 12% locoregional relapse 3% Metastasis relapse 22% Disease-free survival 53%	88% (2 death by prostate disease)
Janoray et al. (2016) [47]	21	52	external beam radiation therapy (100%)	71 (45-76)	111[33-1892]	3,2 [0,4-24]	NR	Stereotactic radiotherapy (CyberKnife)	gross tumour volume (MRI / PET) + 1-2 mm	Post primary radical prostatectomy: + 3 mm (+1) No primary radical prostatectomy: + 5 mm (+3)	36,25 Gy in 5 fractions	12 [2,5-46]	grade 1 14% (dysuria, nocturia) grade 2 4% (pollakiuria) no grade 3 or above	none above grade 1	grade 1 4% (dysuria), none above grade 1	0	83% (1 year)	local relapse 4,7% Metastasis relapse 9%	NR
Leroy et al. (2017) [52]	23	0	external beam radiation therapy (83%)	76	65 [28-150]	2,5 [0-12]	43% ≥T3	Stereotactic radiotherapy (CyberKnife)	whole gland 83%, hemiprostate 4%, focal (MRI) 13%	+ 2 mm	36 Gy in 6 fractions	22 [6-40]	genitourinary/gastrointestinal acute and late (NR): none above grade 1 if focal treatment grade 2 39%: 4% dysuria, 17% cystitis, 9% urethral stenosis, 9% proctitis grade 3 13%: 9% cystitis no grade 4				54% (2 year)	At 20 months: local relapse 22%, locoregional relapse 4%, metastasis relapse 13%	100% (2 year)
			brachytherapy (17%)	NR															

Mbeutcha et al. (2017) [75]	18	0	low dose-rate brachytherapy (83%) external beam radiation therapy (17%)	NR	49[37-70]	4,5 [3-5]	Gleason score 6: 11%, Gleason score 7: 11%, Gleason score ≥8: 17%	Stereotactic radiotherapy (CyberKnife)	gross tumour volume (MRI / PET) + 1 mm	+ 1 mm	35 Gy in 5 fractions	14,5 [7-23]	grade 2 11% no grade 3 or above NE 50%	grade 2 11% no grade 3 or above NE 50%	At 1 year: 1 patient with grade 4 septic shock after prostate necrosis At follow-up: grade 2 17% no grade 3 or above. NE 28%	At follow-up: grade 2 11%, no grade 3 or above. NE 28%	56% (at follow-up)	local relapse 17%	NR
Loi et al. (2018) [48]	50	44	external beam radiation therapy (100%)	74	76 [9-205]	2,6 [1-30]	NR	Stereotactic radiotherapy (CyberKnife)	gross tumour volume (MRI / PET) + 2 mm	+ 3 mm (+ 1)	30 Gy in 5 fractions	21 [6,1-49]	grade 2: 2% (dysuria), G3 2%(haematuria)	grade 1:8% proctitis, no ≥G2	grade 12 6% grade 3 2%	grade 2 4% no grade 3 or above	80% (1 year), 60%(at follow-up)	Metastasis relapse 8% (1 year)	1 death non-cancer related
Miszczyk et al. (2018) [49]	38	10	external beam radiation therapy (90%) high dose-rate brachytherapy (2%) external beam radiation therapy+brachytherapy (8%)	45 (primary radical prostatectomy), 78 (no primary radical prostatectomy) NR	101 [22-179]	4,3 [0,44-66]	Gleason score 6: 13% Gleason score 7: 16% Gleason score ≥8: 16% NA: 24%	Stereotactic radiotherapy (CyberKnife)	whole gland + 1 cm of seminal vesicles (61%), Focal (gross tumour volume + 5 mm) (2,6%) With boost (8%)	whole gland: + 5 mm (+3) Focal: clinical target volume=planning target volume	36,25 Gy in 5,5 to 10 Gy/fractions For 63%: 7,25 Gy / 5 fractions	14 [1,6-46]	grade 1: 18%, grade 2: 7,4%, grade 3: 3,7%. No grade 4	none above grade 1	At 1 year (24 patients): grade 2 4,8% At 2 year (9 patients): grade 3 12,5%	At 1 year: grade 1 9,5%, grade 2 4,8% At 2 year: grade 1 11%	68,4% (16,5 months)	local relapse 13% Metastasis relapse 13%	NR
Jereczek-Fossa et al. (2019) [58]	64	30	3D-radiotherapy (86%)	70 Gy	99 [23-208]	3,89 [0,17-52]	Median of Gleason score: 7 (6-9)	IMradiotherapy (78%) SBradiotherapy (22%)	whole gland (63%) Focal (6%) Boost (1%) Prostate bed 30%	+ 5 mm (+3)	30 Gy in 5 fractions	26 [3-82]	grade 1: 20%, grade 2: 5%, grade 3: 1,5%. No urinary incontinence	grade 1 8%, grade 2 2%. no grade 3 or above	grade 1 28%, grade 2 9%, grade 3 1,5% (reduction of bladder capacity), no urinary incontinence	NR	40% (2 year)	At 2 year: Disease-free survival 53%, local relapse 25%, locoregional relapse 12%, metastasis relapse 12%, cancer specific survival 95%	92% (2 year): 3 died for prostate cancer
			Intensity-modulated radiotherapy (6%)	66 Gy															
			low dose-rate brachytherapy (6%)	145 Gy															
			3D+brachytherapy (1%)	NR															
Pasquier et al. (2019) [50]	100	0	external beam radiation therapy (80%)	74 (66-80)	90 [24-216]	4,3 [2-38]	Gleason score 6: 14%, Gleason score 7: 52%, Gleason score ≥8: 34%, NA: 26%	CyberKnife (81%) Intensity-modulated radiotherapy (19%)	Focal (32%): gross tumour volume (MRI / PET) + 2-5 mm Half gland (18%) whole gland (49%) seminal vesicles only (1%)	+ 1-2 mm	36 (25-36,25) Gy in 6 (5-6) fractions	29,3 [4-91]	grade 2 8% grade 3 1%	none above grade 1	At 3 year: grade 2+ 20,8% (cystitis / micturition pain 10%, retention 1%, haematuria 2%, urinary incontinence 3%), grade 3 1% (cystitis and fistula, and neuritis)	At 3 year: grade 2+ 1%	73% (2 year) 55% (3 year)	local relapse 10% with 4% inside planning target volume Metastasis relapse 7%	96% (2 year) 94% (4 year)
			brachytherapy (17%)	NR															
			external beam radiation therapy+brachytherapy (3%)	NR															

*: prospective study

NA : Not available; NR: Not reported; NE : not evaluated; [PSA] : prostate specific antigen serum concentration; MRI; magnetic resonance imaging; PET: positron emission tomography; CT: computed tomography

Table 5. Dose volume constrains for prostate stereotactic body radiotherapy in case of reirradiation with CyberKnife®

Organs at risk	Dose–volume constraints		
	Dose	Volume	maximal dose
Rectum wall	27 Gy	2 cm^3	
	12 Gy	20%	
Bladder wall	27 Gy	5 cm^3	
	12 Gy	15%	
Urethra + 3 mm	24 Gy	< 30 %	39 Gy
	36	1 cm^3	

Total dose of 36 Gy delivered in six fractions every other day, according to the Oscar-Lambret cancer centre (Lille, France) and used in the Groupe d'étude des tumeurs urogénitales-Association française d'urologie (Gétug-Afu) 31 phase I/II trial

Table 6. Recommendations for prostate salvage reirradiation depending on the expert societies

Expert societies	Recommendations of salvage reirradiation
Gec-ESTRO [59]	Considering brachytherapy: (% of agreement) - ECOG/WHO performance score of 0 or 1 (89%) - ≤T3b both at primary and at time of relapse (81%) - Gleason score at primary treatment ≤ 8 (95%) - Maximum of International Prostate Score Symptom (IPSS) from 8 to 15 (88%) - 12-24 biopsy should be performed at relapse (83%)
Afu [17]	Considering brachytherapy: high- or low dose-rate brachytherapy possible, keeping in mind the few and retrospective data. The potential toxicity (genitourinary particularly) must be discussed with the patient. There is no consensus for the modalities of implantation and constraints of organs at risk
EAU [16]	Considering reirradiation and salvage treatment: Although there is no role for salvage external beam radiotherapy following local recurrence after previous definitive radiotherapy, in carefully selected patients with a good performance score, primary localized prostate cancer and histologically proven local recurrence, high- or low dose-rate brachytherapy remain effective treatment options with an acceptable toxicity profile Do not offer high-intensity focused ultrasound, cryosurgical ablation or salvage brachytherapy to patients with proven local recurrence since it is still experimental Salvage radical prostatectomy should only be performed in experienced centres
FROGG [60]	Salvage therapy for local relapse post-radiotherapy should only be considered in men with biopsy-confirmed, isolated local prostate recurrence who are of good performance status with minimal comorbidities and a life expectancy greater than 10 years. Suitable treatment options include observation, immediate or deferred androgen deprivation, or local salvage therapy (including radical prostatectomy, brachytherapy, stereotactic body radiotherapy, high-intensity focused ultrasound, cryotherapy). Suitable patients should be considered for clinical trials

GEC: Groupe européen de curiethérapie (European group of brachytherapy); ESTRO: European Society of Therapeutic Radiation Oncology; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; Afu: Association française d'urologie (French association of urology); EAU: European Association of Urology; FROGG: Faculty of Radiation Oncology Genito-urinary Group