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Salvage Radical Prostatectomy after External Beam Radiation Therapy: A Systematic Review of Current Approaches

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Key Words

External beam radiation therapy · Oncologic outcome · Prostate cancer recurrence · Radiation therapy · Salvage prostatectomy

Abstract

Background: Radical external beam radiotherapy (EBRT) is a standard treatment for prostate cancer patients. Despite this, the rate of intraprostatic relapses after primary EBRT is still not negligible. There is no consensus on the most appropriate management of these patients after EBRT failure. For these patients, local salvage therapy such as radical prostatectomy, cryotherapy, and brachytherapy may be indicated. ***Objective:*** The objectives of this review were to analyze the eligibility criteria for careful selection of appropriate patients and to evaluate the oncological results and complications for each method. ***Methods:*** A review of the literature was performed to identify studies of local salvage therapy for patients who had failed primary EBRT for localized prostate cancer. ***Results:*** Most studies demonstrated that local salvage therapy after EBRT may provide long-term local control in appropriately selected patients, although toxicity is often significant. ***Conclusions:*** Our results suggest that for localized prostate cancer recurrence after EBRT, the selection of a local treatment modality should be made on a patient-by-patient basis. An improvement in selection criteria and an integrated definition of biochemical failure for all salvage methods are required to determine which provides the best oncological outcome and least comorbidity.

Introduction

Biochemical recurrence (BCR) rates after primary external beam radiation therapy (EBRT) for prostate cancer have been reported to reach 63%. In 20–30% of the cases, these are local recurrences, which means patients could

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still benefit from local salvage therapy [1, 2]. Nevertheless, only a small portion of these cases (0.9–2%) are actually managed with salvage radical prostatectomy (SRP), whereas most end up receiving castration therapy, regardless of the relapse being local or metastatic [1, 3].

Careful patient selection is important to guide the decision-making process in the management of patients with local recurrence after EBRT failure. SRP, defined as a radical prostatectomy procedure performed for local failure after primary EBRT, has been refined over the past decade. Increasing surgical experience has resulted in a decrease in the rate of surgical complications. In addition, biochemical outcomes reported in recent series suggest a superiority of SRP over other salvage treatment modalities, such as cryotherapy, high-intensity focused ultrasound, or brachytherapy [4].

The aim of the present study is to provide a systematic evidence-based analysis of the current literature on SRP in patients with radiation-recurrent prostate cancer.

Literature Search and Study Selection

A systematic review of the literature was performed in July 2014 using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/). Identification and selection of the studies was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria (www.prisma-statement.org) using the search term: 'salvage radical prostatectomy'. Only studies specifically looking at the outcomes of SRP after failure of EBRT were considered for the present analysis. The level of evidence was reported as described by the Oxford Center for Evidence-Based Medicine (www.cebm.net). Data related to the following topics were specifically analyzed: definition of BCR after EBRT and identification of local recurrence.

Definition of Recurrence after EBRT

All of the reported series on SRP consider as a definition criterion for BCR three or more consecutive increases of prostate-specific antigen (PSA) after nadir, occurring at least 6 months after the nadir (previous ASTRO definition). More recent series have adopted the Phoenix 'nadir + 2' definition (most recent ASTRO definition) [5]. This last criterion was conceived with the aim of ruling out patients with fluctuating PSA (approx. 25% of all EBRT-treated patients), thus preventing overtreatment [6]. However, two factors may potentially delay relapse diagnosis when adopting this 'updated' definition: the lack of an ideal (or, at least, desired) PSA nadir value, and the need to obtain a 'nadir + 2 ng/ml' level to consider the PSA elevation as BCR.

According to Zelefski et al. [7], the ideal nadir should be <0.5 ng/ml, as patients developing metastatic progression were found to have higher nadir values (mean of 2.2) than those with local relapse only (mean of 1.1). The nadir value after EBRT strongly correlates with different time points; thus, it should not be considered a value by itself but only a 'time-dependent variable'. According to this group of investigators, 'evaluation should be performed to rule out persistent local and systemic disease for patients with PSA nadir levels >1.5 ng/ml at 2 years', i.e. even without having reached the nadir +2 level.

In contrast, an increase in PSA of +2 greater than the nadir may potentially delay the diagnosis of disease failure, resulting in detrimental outcomes mostly in patients with local recurrence or persistence, as these patients can meanwhile develop metastatic progression. According to Stephenson et al. [8], this EBRT failure definition can delay the diagnosis by up to 5 years, thus minimizing the likelihood of a local salvage approach.

Hence, BCR after primary EBRT requires a more precise definition to improve the balance between the potential effects of delaying the detection of failure and the risk of overtreatment. Additional criteria, such as the timing [7, 9] and pattern [10] of the PSA decrease after RT, may be more useful for characterizing and understanding the failure phenomenon.

The scenario is more complicated in the case of high-risk patients who have received EBRT with androgen deprivation therapy (ADT) [11]. These patients will more easily obtain very low nadir levels (close to 0 presumably due to ADT), but they might have higher metastatic risk. Three scenarios should be expected for these cases: (1) At 9–12 months after EBRT, ADT is stopped, and a low PSA kinetic BCR occurs; these patients have a higher probability of only local recurrence/persistence of the disease [12]. Thus, waiting until the PSA elevation reaches 2 ng/ml could be truly detrimental for any local salvage therapy. (2) After ADT suspension, a high PSA kinetic BCR occurs, indicating metastatic disease progression of a subclinical, yet micrometastatic, disease at presentation. (3) PSA elevation occurs during ADT, indicating a shift toward androgen independence, which is associated with a poor prognosis [13].

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Identification of Local Recurrence

Once a BCR is recorded, criteria are necessary to identify potential candidates for local salvage therapy, where a local (vs. systemic) recurrence is most likely.

PSA kinetics can be useful for recognizing local recurrence or persistence of disease. A short PSA doubling time (<3 months) indicates a rapidly growing tumor, with a higher risk of clinical progression to metastatic disease [11]. A longer PSA doubling time (>6–10 months) is associated with a higher likelihood of local failure [14].

Local failure should be ideally proven by means of a biopsy, despite the reported false-positive (up to 60%) and false-negative (up to 20%) rates [15]. In the series by Vance et al. [16] the 2-year post-RT prostate biopsy was atypical or positive in 26% of cases, and it was statistically correlated with PSA level, demonstrating that post-RT prostate biopsy can be useful in identifying patients who are suitable for aggressive salvage therapy.

In contrast, Kaplan et al. [17] showed in their series of patients who underwent radical cystoprostatectomy at a median time of 60 months from EBRT that histological evidence of prostate cancer was present in 50% of patients with no BCR at the time of surgery. Although the biological significance of the presence of active prostate cancer cells in this selected population is uncertain, the study highlights the limitations of PSA in monitoring prostate cancer disease activity following definitive RT.

In other series, Gleason score-indefinable rates were present in 18–25% of cases [18, 19]; current pathology guidelines discourage the use of Gleason scoring in specimens obtained from previously treated patients (ADT, as well as RT), as the induced histological changes could determine an apparently more clustered gland pattern. Markers of cell proliferation (such as Ki-67) could provide a more objective and reliable pathologic evaluation of post-RT prostate biopsies [15, 20].

Imaging workups are ordered to exclude metastatic progression and often also to guide biopsy. New encouraging data have been obtained with dynamic contrast-enhanced MRI [21] and diffusion MRI imaging [22–24]. Moreover, for patients with PSA levels >2.5 ng/ml, ^{11}C-choline PET has been reported to have a sensitivity of 89% and a positive predictive value of 72% [25, 26]. Similarly, the sensitivity and specificity of ^{18}F-choline PET in detecting bone metastases from prostate cancer were reported to be 79 and 97%, respectively [27, 28]. Nevertheless, no consensus exists yet regarding the panel of imaging modalities to be performed to distinguish local from systemic recurrence.

Salvage Radical Prostatectomy

Outcomes

Twenty-seven single-center or multicenter retrospective case series (level of evidence: 4) were reported on the use of SRP for radiorecurrent prostate cancer (table 1). In two series, the outcomes of SRP have been compared to those of other forms of salvage therapy (cryotherapy and brachytherapy).

The careful evaluation of SRP prognostic factors is of paramount importance for the appropriate selection of patients. Many retrospective studies and two high-quality literature reviews [29, 30] have highlighted the main prognostic factors, which have emerged from retrospective univariate or multivariate analyses. As Chade et al. [30] have shown, the strongest prognostic factor was pre-SRP PSA, which was shown to often predict progression-free, cancer-specific or overall survival; evaluation of pre-SRP PSA should be followed by prostate biopsy Gleason scoring (although the data should be considered very carefully because of the objective difficulties in correctly and reproducibly scoring post-RT prostate needle specimens, as previously shown). Further prognostic factors, such as pre-RT clinical stage, percentage of positive cores at biopsy and PSA doubling time >12 months, have been reported to predict SRP clinical outcomes in fewer series.

Type of Surgery

The surgical salvage approach is not limited to SRP; pelvic exenteration [31], cystoprostatectomy [32–38], or prostatectomy with permanent cystostomy [39] can also be considered. The frequency of these demolition procedures was clearly decreased in the last published surgical salvage series because of the migration of the patients in the initial early stages as a result of an early diagnosis of disease relapse.

The median follow-up ranged from 12.5 to 120 months. The definition of BCR after SRP varies depending on the institution, but may be PSA >0.12 [39], >0.2 [6, 37, 40–46], or >0.4 ng/ml [32, 47, 48]. The reported BCR-free survival probability ranges between 28 and 93%. Because the BCR-free survival definition depends on the PSA nadir, it is also a time-dependent variable, and by plotting the reported BCR-free rates with the follow-up lengths of different series, a decreasing tendency can be observed (Spearman's rank correlation, 2-sided p = 0.05), which is clearly more significant (R^2 = 58.5 vs. 15.7%, respectively) if only series with >40 patients are considered (fig. 1) [8, 19, 37, 41–43, 45].

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Table 1. Oncological outcomes and complication rates of SRP series reported in the literature

Reference (first author)	Year	Patients, n	Follow-up, months	OCD, %	BCR, %	CSS, %	PSM, %	Involved LN, %	BL, l	Rectal injury, %	Anastomotic stenosis, %	Incontinence, %
Neerhut [58]	1988	16	20	25	88				0.9	19	25	25
Link [57]	1991	14	18	30.8	57		43		1	0	9	55
Zincke [59]	1992	32	44		82				1.219	6	19	27
Ahlering [60]	1992	11	53.5		71	71				0	0	64
Stein [35]	1992	13		38.5					1.1	7.7	15	64
Pontes [36]	1993	35	12–120	30	28	79	70	12		9	11	46
Brenner [61]	1995	10	30	30	30		40					
Rogers [47]	1995	40	39.3	22	47	95	37	5	0.91	15	28	58
Lerner [37]	1995	79	50	39	53	72				6	12	39
Gheiler [32]	1998	30	36.1	39.5	47	87	13	16	1.1	3.3	16.7	50
Garzotto [62]	1998	29	63.6	28	69		31		1.16	6.9	22	67
Cheng [55]	1998	86	70			64		16				
Amling [40]	1999	108		39	43	70	36	18		6	21	51
Stephenson [8]	2004	100	60	50	66		10	7	1	1	30	32
Bianco [41]	2005	100	60	35	55	73	21	9				
Ward [38]	2005	138	84	39		77				10	22	44
Heidenreich [42]	2006	25	12.5		93	100	8	8				
Darras [63]	2006	11	83	81	55	91	0	0				
Sanderson [48]	2006	51		25	47		36	28				30
Boris [64][1]	2009	11	20		73		27	18	0.113	9	9	20
Seabra [43]	2009	42	18	74	79	100		0	0.3	4.8	50	72
Leonardo [44]	2009	32	35	53	75		34	0	0.55	0	12	79
Paparel [45]	2009	146	45	44	54		16	13				
Eandi [46][1]	2010	18	18	50	67		28	5.5	0.15	17	17	67
Heidenreich [49]	2010	55	23	73	87		11	20	0.36	2	11	19
Chade [19]	2011	404	55	55	37	83	25	16				
Zugor [53][1]	2014	13			46		0		0.13	0	0	46

PSM = Positive surgical margin. [1] Only robotic series.

BCR-free rates are also correlated with the organ-confined disease (OCD) rates of the series (R^2 = 14.2%); the significance of the correlation improves (R^2 = 85.8%) if series with only >40 patients are considered (excluding the series by Chade et al. [19], which was too heterogeneous and multicentric and extended over a rather long [25 years] period) (fig. 2) [8, 37, 41, 43, 45, 47, 49]. The series published before 1995 had fewer patients than those published after 1998 (mean 27.8 vs. 62.7, not considering the series by Chade et al. [19] for the previously mentioned reasons; t test: p = 0.047), and the rate of OCD was clearly higher, thus confirming the migration of patients toward lower stages (30.75 vs. 47%; t test p = 0.02).

The positive surgical margin rate decreased from an average of 47.5% before 1995 to an average of 20.8% after 1995 (Student's t test: p = 0.002). Even if a longer follow-up is associated with worse biochemical control, early diagnosis of recurrence (by determining higher OCD with lower positive surgical margin rates) will allow for higher BCR-free rates. In fact, the reported cancer-specific survival (CSS) has ranged from 70 to 83% at 10 years (table 1).

The Role of Lymph Node Dissection

Lymph node dissection (LND) associated with SRP was reported in only few series (table 1), and it was not standardized, which precludes both the assessment of its possible impact on CSS and any comparison among series.

In a completely different setting, Winter et al. [50] were the first to demonstrate, in a small series of 6 patients, the role of ^{11}C-choline PET/CT-guided secondary lymph node surgery in patients with PSA failure and single lymph node recurrence after radical retropubic prostatectomy, showing a complete permanent PSA remission without adjuvant therapy in 3 patients (median follow-up: 24 months, range: 21–35).

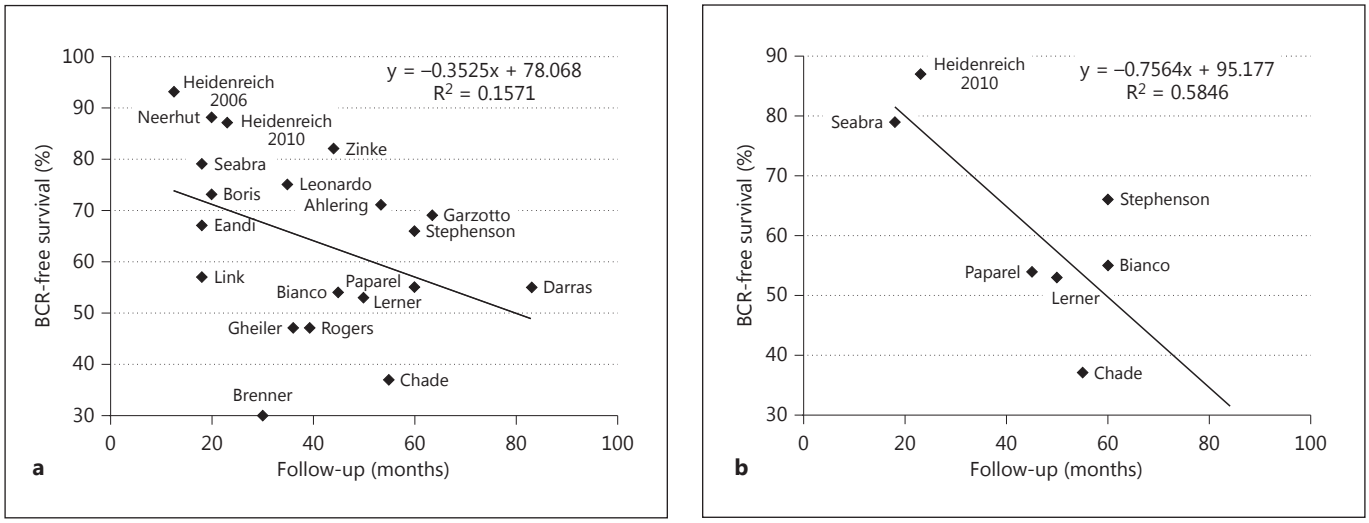

Fig. 1. BCR-free survival rates plotted with the mean follow-up (**a**) and only in series with >40 patients (**b**).

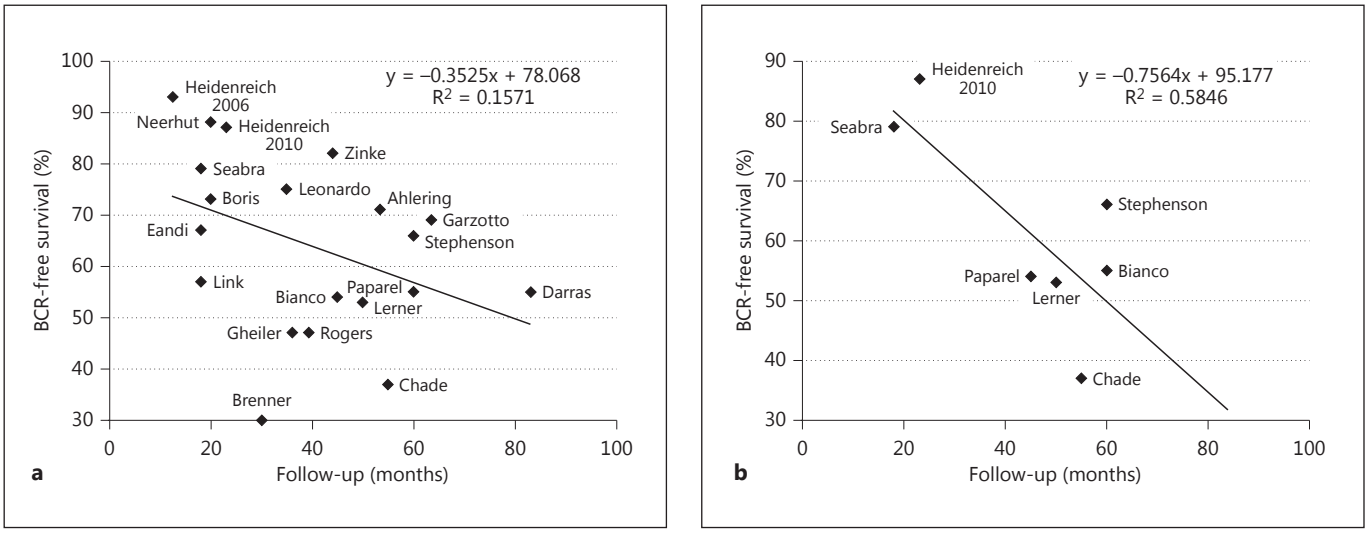

Fig. 2. BCR-free survival rates plotted with the mean OCD% (**a**) and only in series with >40 patients (**b**).

After 1 year, Rigatti et al. [51] showed that 24 out of 28 patients (85.7%) who received no adjuvant ADT after salvage LND had verified BCR after a mean follow-up of 38.9 months (median: 14.9), corresponding to a 5-year BCR-free survival rate of 19% (in only the 'responder' subgroup).

Consequently, performing LND during SRP in LN-choline-PET-negative patients might have only a small impact on disease control.

Surgical Complications

Intraoperative complications and functional results have been quite stable over time, showing a slight (but not statistically relevant) improvement. The only relevant association was found by plotting the rectal injury rate and the blood loss (BL) against the OCD rate in different published series, and the results showed, as expected, that locally advanced disease exposes the patient to higher intraoperative risk, at least with regard to rectal injury (R^2 = 19%) and BL (R^2 = 54%).

Table 2. Minimally invasive SRP series: oncologic outcomes and complication rates

Reference (first author)	Technique	Year	Cases, n	Clavien >2 complication rate, %	Incontinence rate, %
Vallancien [52]	laparoscopic	2003	84	0	29
Stolzenburg [65]	laparoscopic	2007	9	11	22
Nunez-Mora [66]	laparoscopic	2009	9	11	33
Kaouk [67]	robotic	2008	7	0	25
Boris [64]	robotic	2009	11	9	20
Eandi [46]	robotic	2010	18	17	67
Strope [68]	robotic	2010	6	33	100
Chauhan [69]	robotic	2011	15	6	29
Zugor [53]	robotic	2014	13	15	54

Table 3. ED and SRP: literature overview

Reference (first author)	Cases, n	Pre-SRP ED, %	Post-SRP ED, %
Link [57]	75	57	100
Stephenson [8]	1,288	–	72
Masterson [70]	372	53	79
Leonardo [44]	120	91	91
Darras [63]	72	–	100
Gotto [71]	54	67	92
Heidenreich [49]	403	73	93
Vallancien [52]	84	72	100
Stolzenburg [65]	9	67	100
Nunez-Mora [66]	9	80	100
Boris [64]	11	10	80
Eandi [46]	18	56	100
Strope [68]	6	50	100
Chauhan [69]	15	33	100
Zugor [53]	13	38	77

Table 4. Clinical outcome of main salvage cryotherapy and high-intensity focused ultrasound (**a**) and recently published SBT series (**b**)

a Salvage cryo and high-intensity focused ultrasound series

Reference (first author)	Follow-up, months	n	BCR-FS, %	Rectal fistula, %	Incontinence	Potency
Pisters [56]	17	150	42	1	44	
Pisters [72]	21.6	279	58.9	1.2	89.8	
Pisters [73]	66	56	21			
Perrotte [74]	16.7	150			28	15.2
Spiess [75]	41	797	34			
Williams [76]	90	187	39			
Chin [77]	43	106	97	3.3	8.5	
Miller [78]	16.8	33	33	0	4	
De la Taille [79]	21.9	43	60			
Han [80]	20	18	72	0	7	
Donnelly [81]	20	46	72	2.2	6.5	55.6
Ismail [82]	33.5	100	59	1	13	42.9
Bahn [83]	82.3	59	59	3.4	4.3	
Eisenberg [84]	18	15	50		6.7	
Ng [85]	39	187	56		37	
Philippou [98]	24	19	58			
Murat [86][1]	36	167	55.7	3	49.5	
Uchida [87][1]	24	22	52	4.5	18.2	
Mallick [96]	12	50	54			
Gelet [97]	40	106	40			

b Recently published SBT series

Reference (first author)	Year	n	Follow-up, months	BCR-FS, %	Grade 3–4 toxicity, %
Beyer [88]	1999	17	62	53	
Grado [89]	1999	49	64	34	16
Wong [90]	2006	17	44	75	47
Allen [91]	2007	12	45	63	0
Nguyen [92]	2007	25	47	70	30
Lee [93]	2008	21	36	38	0
Aaronson [94]	2009	24	30	88	4
Burri [95]	2010	37	86	54	11
Shimbo [99]	2012	15	33	66	7

BCR-FS = BCR-free survival. [1] High-intensity focused ultrasound series.

The lower reported rates of BL in the last series were caused by the presence in the review of two series of robotic SRP [46, 52, 53]. The average rates of reported rectal injury, anastomotic stricture, and incontinence were 6.8, 18.3, and 47.8%, respectively.

The introduction of minimally invasive approaches (laparoscopy and robotic laparoscopy), themselves having evolved from SRP, has resulted in some advantages (table 2), at least with regard to the rates of overall and serious complications (Clavien >2).

Thus, although difficult and challenging, SRP has been shown to present no relevant technical difficulties in high-volume centers. Moreover, it is also a 'land of conquest' for minimally invasive approaches, e.g. robotic SRP [53, 54].

Early diagnosis and appropriate selection of patients will improve oncologic results and decrease the intraoperative complication rate (BL and rectal injuries, which clearly depend on the disease stage). Concerning sexual

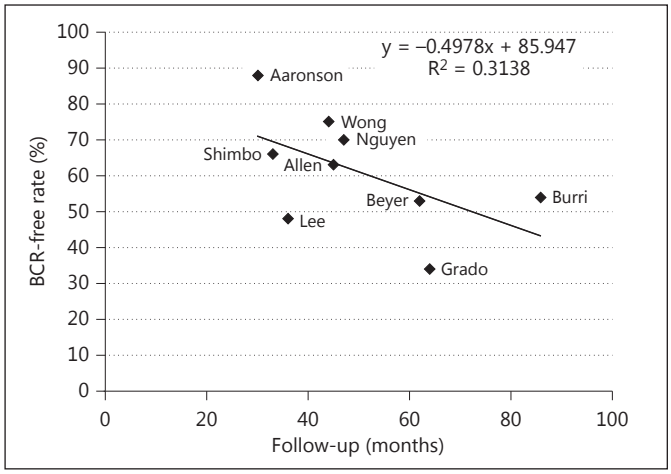

Fig. 3. BCR-free survival decay after SBT.

function, erectile dysfunction (ED) is often present before SRP (table 3), and even in patients with residual sexual function after RT, it should not be a problem in this setting (i.e. post-RT failure). However, the most common salvage approach proposed in these cases is ADT, which is well known to induce ED. The CAPSURE data, which were recently analyzed and published by Agarwal et al. [1], showed that 93.5% of patients presenting with post-RT failure (including a relevant number with only local relapse) received and accepted castration therapy, despite the adverse effect of ED.

Comparison with Other Local Salvage Modalities

Incontinence rates after SRP remain high (table 1), but this disadvantage must be weighed against the greatest and most durable obtainable biochemical control available and CSS; other apparently attractive salvage approaches, such as cryotherapy or high-intensity focused ultrasound are not free of (often serious) complications (table 4).

Salvage brachytherapy (SBT) offers a realistic alternative to SRP (table 4). Plotting of the BCR-free rates with the lengths of the follow-ups of the different SBT series revealed the same time-dependent tendency. The BCR-FS decay was slightly faster than that observed for the surgical series ($\alpha = 0.49$ vs. -0.35) (fig. 3).

The superiority of SRP may be attributed not so much to a desirable positive effect of the associated LND on micrometastases (as previously shown, the data are insufficient to defend this theory), but rather to the peculiar pattern of tumor recurrence after RT [18], i.e. in the periurethral zone, which is generally spared during these approaches to minimize side effects [100].

Conclusions

SRP seems to offer durable oncologic outcomes while potentially avoiding systemic noncurative therapy. However, rather high rates of incontinence and ED are associated with the procedure. The main issue continues to be the early detection of post-RT failure, which could facilitate further improvement in long-term oncologic results. This reinforces the need for proper patient counseling and selection. Robot-assisted prostatectomy has been largely described over the last years, with some potential advantages that are related to the three-dimensional magnification vision and the more precise dissection. Promising new imaging tools could improve patient selection, thus avoiding the surgical morbidity associated with this type of challenging procedure.

Disclosure Statement

The authors state that there are no conflicts of interest regarding the publications of this article.

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