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TOPIC PAPER

Is it worth to perform salvage radical prostatectomy for radio-recurrent prostate cancer? A literature review

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Abstract

Purpose Salvage radical prostatectomy (sRP) represents a curative option for prostate cancer (PCa) biochemical recurrence (BCR) after radiation therapy (RT). In this review, we aimed to outline the contemporary results and use of sRP.

Methods A web search was performed on the Ovid platform using Embase and Medline databases from January 2010 using pre-defined search terms. Web search was implemented by manual search. Oncological and functional outcomes and complications were summarized using standard classification systems, when feasible.

Results sRP is currently underused, being chosen for radio-recurrent PCa treatment in around 1% of the cases. Surgery is complex due to radiation-induced tissue changes making posterior planes and apex dissection particularly challenging. Patient selection is paramount to maximize the oncological benefit. Most series report a BCR-free survival > 60%, mainly at the end of a short- to intermediate-term follow-up. Five-year progression-free survival is nearly 50% and 5-year cancer-specific survival rates are around 90%. Major peri-operative complications, anastomotic leaks and strictures, still more frequent than in a primary RP setting, have been steering towards more acceptable rates in recent years, when compared to historical series. Continence rates are widely variable, often in between 39 and 60%. Potency remains difficult to recover.

Conclusions sRP represents a curative option with promising short- to medium-term oncological results and acceptable side effects, in high-volume institutions. In appropriately selected patients, the procedure should not be underused due to the fear of poor functional outcomes and/or complications. Prospective studies are needed to assess the long-term outcomes and to further refine patient selection criteria.

Keywords Prostate cancer · Recurrence · Radiotherapy · Radical prostatectomy · Salvage treatment

Introduction

Biochemical recurrence (BCR) rates after primary radiation therapy (RT) for prostate cancer (PCa) have been reported to range between 22 and 69%, depending on the series [1, 2]. If we think that PCa is the most common cancer diagnosed worldwide among men [3], that the majority of diagnosed PCas are suitable for a localized and curative therapy [4] and that 20–38% of them undergo primary RT [5–8], BCR after RT is a common event.

Salvage radical prostatectomy (sRP) is a therapeutic option for PCa recurring after a primary non-surgical treatment. Many alternative options are available for the management of these patients, including watchful waiting, androgen deprivation therapy (ADT), salvage cryotherapy or HIFU, salvage interstitial radiation therapy and re-irradiation, all with different and often unclear oncological results in the

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mid and long terms, leading to an unstandardized approach. However, only 2–3% of patients will receive a local salvage therapy, while the vast majority of them will be managed with observation or palliative ADT alone [9].

sRP was first described in 1985 by Mador et al. [10]. The authors reported about seven patients, three of whom underwent cystoprostatectomy with urinary diversion. The operating times averaged 4.9 h and mean blood transfusion was 5.3 units, while two patients experienced a rectal injury. From this first experience, the outcomes of sRP have improved considerably, both from the surgical and the oncological standpoints. Following these leads, it has been increasingly used in uro-oncological tertiary referral centers. In 2011, a multi-institutional study enrolled 404 patients from seven institutions covering a period from 1985 to 2009 and encompassing open and minimally invasive approaches. Rectal injuries were present in 0–19%, while incontinence in 21–100%. As for the oncological results, 37% patients were BCR free while 75% were metastasis free at 10-year follow-up [11]. Despite some advancements, complications were still considerable and functional results still poor. However, since then, several reports evaluating contemporary surgeries were published suggesting improved functional results and decreasing complications. Whether sRP is worth performing remains an open question crossing the mind of the uro-oncologists when faced with potential surgical candidates.

Our aim was to provide, through a comprehensive literature review, an evidence-based answer to this question, focusing on the most controversial aspects and summarizing the risk–benefit ratio of sRP according to the most relevant series in the contemporary literature.

Evidence acquisition

A web search was performed on 1 August 2018 through the Ovid platform using Embase and Medline databases. The search strategy included the following terms and Boolean operators: "prostate cancer" AND "salvage'' AND "(prostatectomy OR therapy OR treatment)''. Two authors (G. C. and G. M.) screened all the retrieved records to identify full texts of interest. Discrepancies were solved by a third author (P. G.). Web search was implemented by manual search, based on the references of included records and senior authors' consultation. We a priori excluded full texts published before 2010, reporting outcomes for < 10 patients and non-English language records. Most relevant series were selected based on senior authors' consultation.

Primary outcomes were oncological and functional outcomes (including complications) of sRP after radiation therapy. sRP use, patient selection tools and crucial surgical steps were also summarized and discussed.

As for oncological outcomes, we considered the proportion of BCR-free patients at the end of the follow-up and, when reported, 3-year and 5-year BCR-free survival and cancer-specific survival (CSS). To allow a rough comparison among series, BCR-free survival was plotted against follow-up duration (Fig. 1), and the mean proportion of BCR patients per year was calculated (by dividing the final proportion of BCR patients by the median follow-up duration).

Continence, when possible, was classified according to the number of pads/day (continent: no pad use; severely incontinent: ≥ 3 pads/day). Erectile function was divided into patients with preserved erections (spontaneous or with the use of PDE-5 inhibitors) versus others. Peri- and postprocedural complications were graded according to the Clavien–Dindo classification.

Evidence synthesis

sRP in the contemporary era: an underused procedure

BCR after RT is a challenging finding for uro-oncologists. Currently, there is no consensus on the most appropriate management after RT failure. Grossfeld et al., using a PCa national registry, examined the chance to receive a second treatment after BCR [12]. Overall, 2336 patients were primarily treated either with RP (1744) or with RT (592), and 590 of them received a second treatment due to BCR (391 and 199 in RP and RT group, respectively). While the secondary treatment after RP was almost equally distributed between RT (52%) and ADT (47%), the vast majority of patients who received primary RT was treated with ADT (92%). Actually, sRP was performed only in four patients (2%). A more recent analysis of the CaPSURE registry from 2000 to 2010 for recurrent PCa, despite describing a trend towards an increased use of local salvage therapy, confirmed

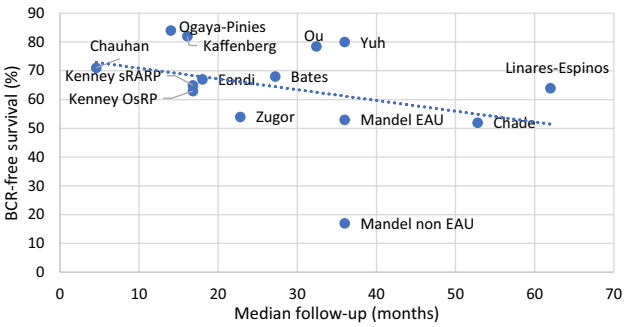

Fig. 1 BCR-free survival of the included studies is plotted against median follow-up duration ($r^2 = 0.12$; $p = 0.26$). *sRARP* salvage robot subgroup-assisted radical prostatectomy subgroup; *OsRP* open radical prostatectomy subgroup; *EAU* EAU guidelines-compliant subgroup; *non EAU* non-EAU guidelines-compliant subgroup

a marked underuse of sRP. Indeed, out of 366 BCR patients who received either brachytherapy (BT) or EBRT as primary treatment, only three underwent sRP [13].

This happens despite the lack of evidence for efficacy of ADT in this setting, being this therapy unable to cure patients who often present local recurrence manageable with curative local therapy and causing significant morbidity that leads to a decreased quality of life [14].

The reasons behind the underuse of sRP in patients experiencing BCR after primary RT include both technical challenges (see "Open and robotic surgical steps: a challenging procedure") and patient- and disease-related issues, generally being performed on men with higher Gleason score and tumor stage compared to those undergoing a primary RP [15]. However, as discussed below, several recent studies have demonstrated improved functional outcomes with lower morbidity rates, and, when an appropriate patient selection is performed, high degree of short- to medium-term oncological control, claiming sRP in patients experiencing BCR after RT should not be precluded upfront.

Open and robotic surgical steps: a challenging procedure

RT induces a broad spectrum of short- to long-term changes in the prostate and surrounding tissues [16], from neo-angiogenesis to necrosis. As a consequence tissues are more frail, adhesions more frequent and healing becomes less effective, altering surgical planes and anatomical landmarks compared to a non-irradiated pelvis [17–20].

Both open and minimally invasive sRP have been described and surgical steps are rather the same of standard RP, even if technical difficulties may arise during some crucial steps of the procedure [21]. During endopelvic fascia dissection, vessel injury and consequent bleeding are more frequent than in a standard RP. Therefore, special attention must be paid to haemostasis and to the suture of dorsal venous complex [21, 22]. Posterior planes are usually difficult to identify because of fibrosis and accurate blunt dissection is crucial to avoid rectal injury [22]. In some cases, sharp dissection might be required, avoiding the use of thermal energy. A multi-phase check of the rectal wall, requiring full bowel preparation, has been strongly suggested by some groups. First, a digital rectal exploration (DRE) under the vision of robotic camera can be performed. Next, filling the pelvic cavity with saline and the rectum with air, signs of leakage can be ascertained. Finally, inspection and transillumination using a sigmoidoscope may be useful to detect thinning of rectal wall [22, 23]. Apex isolation is another delicate step and requires the preparation of a long urethral stump, to improve continence. Some authors report a higher surgical complexity after BT than after EBRT [15, 24, 25]. Bonet et al. have pointed out that blunt neurovascular bundle dissection, when feasible, is paramount if a nerve-sparing approach is attempted [21].

The rectal wall injury is probably the most feared complication. The rate of this event dropped from 20 to 30% in the first series, to less than 10% over the last years. An increased surgical experience and, according to some authors, the detailed and magnified vision given by laparoscopic and robotic cameras are possibly important elements favoring such a decrease [26]. The anastomotic leak represents another frequent complication, detected in up to 33% of cases in some series [19, 23]. Poor vascularization of bladder neck and urethral stump as a result of RT can delay the healing process of the anastomosis. Recently, Ogaya-Pinies et al. reported the use of a scaffold (UB-ECM) that can be sutured to the Denonvilliers' fascia to wrap the posterior aspect of the vesicourethral anastomosis, reducing the risk of urinary leakage from 35 to 6% after robotic sRP [27]. Other series report rates of anastomotic leakage under 20% also with the standard technique, stressing the existence of a learning curve [28]. Following these leads, a radiological check of the anastomosis is strongly suggested before catheter removal. Besides, to minimize bladder neck stricture risk, a wide bladder neck excision is recommended, leading also to safer cancer control [17, 29].

Considering the most significant series, it is worth noting that surgeries are usually performed by urologists with a strong background in standard procedures [17, 22, 29]. This is definitely a key factor to maximize procedural outcomes.

Oncological outcomes: sRP cures

The vast majority of sRP series are retrospective and non-controlled [11, 19, 20, 23, 30–38], with cancer features and treatment characteristics not being homogenous across the studies. Moreover, follow-up duration is often limited (Table 1).

Median patient age varies between 62 and 68 years, confirming the tendency to perform sRP on relatively young patients. Median PSA before sRP varies greatly, from 3.7 ng/ml [23] to 15.7 ng/ml [34]; these data witness a heterogenous spectrum of indications concerning this procedure, sometimes beyond the guideline recommendations. Median time to BCR after primary treatment or to sRP is over 36.5 months and below 68, with the exceptions of Linares-Espinos and Chauhan studies (28 and 24 months, respectively) [35, 38].

BCR definition after RT varies across studies, reflecting both the temporal evolution in the guidelines and the differences among examined series: in some cases, BCR is defined documenting three consecutive increases in PSA [19, 33]; elsewhere, the Phoenix Consensus definition (PSA nadir + 2 ng/ml) [39] is adopted [20, 31, 34, 35]; others report no BCR definition based on PSA kinetics.

Table 1 Pathology characteristics and oncological outcomes of main recent studies on salvage radical prostatectomy for radio-recurrent prostate cancer

Author (Ref.)	Study features							Pre-sRP biopsy GS (%)				Clinical staging (%)			LAD (%)
	Year	Study type	Accrual years	First treatment	Time to sRP [months] (range)	*N*	Follow-up [months] (range)	6	7	≥ 8	NA	T1–2	T3–4	NA	
Eandi et al. [19]	2010	R	2004–2008	RT *n* = 8 BT *n* = 8 PBT *n* = 2	NA	18	18 (4.5–40.0)	22	28	33	17	0	0	100	100
Chade et al. [11]	2011	R	1985–2009	BT = 796 RT = 263 Unknown = 52 ET + BT = 13	41 (27–58)	404	52.8 (NA)	24	30	20	17	65	18	17	86
Chauhan et al. [38]	2011	R	NA	RT *n* = 5 BT *n* = 5 RT + BT *n* = 3 PBT *n* = 2	24 (13.25–34.75)	15	4.6 (3–9.75)	7	73	20	0	100	0	0	80
Kaffenberger et al. [30]	2013	R	2006–2011	RT *n* = 11 RT + BT *n* = 6 BT *n* = 13 Others *n* = 4	48.5 (28.9–70.8)	34	16.1 (8.4–31.8)	38	24	35	0	64	6	0	56
Yuh et al. [20]	2014	P	2004–2012	RT *n* = 18 BT *n* = 22 RT + BT *n* = 1 PBT *n* = 6 Others *n* = 4	68 (40–96)	51	36 (NA)	NA	NA	NA	NA	0	0	100	84
Zugor et al. [33]	2014	R	2006–2011	RT = 7; BT = 6	48.9 (12–108)	13	22.8 (4–51)	46	15	38	0	5	0	8	100
Mandel et al. [34]	2015	R	2007–2012	–	56 (NA)	55	36 (NA)								–
	EAU			RT = 13 BT = 16 HIFU = 3		32	–	63	38	0	0	100	0	0	88
	Non-EAU			RT = 14 BT = 8 HIFU = 1		23	–	13	30	57	0	85.7	14.3	0	83
Bates et al. [23]	2015	R	2008–2014	RT *n* = 28 BT *n* = 14 IMRT *n* = 3 Others *n* = 6	NA	53	27.2 ± 17.7	26	43	30	0	83	17	0	NA
Kenney et al. [31]	2016	R	2007–2011	–	NA	39	16.8 (NA)	0	0	0	0				100
	Robotic			RT *n* = 13 BT ± RT *n* = 8	NA	20	–	0	20	35	45	75	15	10	
	Open			RT *n* = 11 BT ± RT *n* = 8	NA	19	–	0	42	37	21	84	16	0	

Table 1 (continued)

Author (Ref.)	Study features							Pre-sRP biopsy GS (%)				Clinical staging (%)			LAD (%)
	Year	Study type	Accrual years	First treatment	Time to sRP [months] (range)	*N*	Follow-up [months] (range)	6	7	≥ 8	NA	T1–2	T3–4	NA	
Linares-Espinos et al. [35]	2016	R	2001–2015	RT = 7 BT = 3 HIFU = Cryo = 12	28 (16–46)	28	62 (43–110)	36	50	4	0	68	0	32	29
	RT sub-group						–	NA	NA	NA	NA	NA	NA	NA	–
Pokala et al. [36]	2016	Reg[a]	1998–2010	RT = 364	NA	364	NA	NA	NA	NA	NA	NA	NA	NA	78.6
Ou et al. [37]	2017	P	2005–2016	RT = 11 Cyberknife = 2 HIFU = 1	36.5 (13–103)	14	32.4 (NA)	35.7	42.9	21.4	0	71.4	28.6	0	100
Ogaya-Pinies et al. [27]	2018	R	2001–2016	RT *n* = 37 BT *n* = 14 RT + BT *n* = 13 Cyberknife *n* = 3 PBT *n* = 1 Others *n* = 28	81.5 (18.25–335.5)	96	14 (5–24)	NA	NA	NA	NA	0	0	100	89

Author (Ref.)	SRP features	LAD (%)	Pathology (%)										Oncological		
	Technique		T2	ECE	SVI	T4	GS 6	GS 7	GS 8	Not graded	PSM	N1	BCR-free survival (%)	% BCR per year of FU	5-Year BCR free
Eandi et al. [19]	sRARP-tp	100	50	22	28	0	0	44	22	33	28	0	67	22	NA
Chade et al. [11]	NA	86	53	45	30	0	14	37	24	25	45	16	52	11	0.48
Chauhan et al. [38]	sRARP-tp	80	20	80	20	0	0	60	40	0	13	7	71.4	73	NA
Kaffenberger et al. [30]	sRARP-tp	56	53	38	35	3	9	50	26	0	26	0	82	13	NA
Yuh et al. [20]	sRARP-tp	84	49	51	27	0	8	53	22	18	31	6	80	7	NA
Zugor et al. [33]	sRARP-tp	100	54	46	38	0	15	31	54	0	0	0	54	24	NA
Mandel et al. [34]		–													0.49
	OsRP	88	59	41	28	NA	19	69	13	0	22	13	53	16	0.74
	OsRP	83	39	48	57	NA	4	57	39	0	35	35	17	28	0.12

Table 1 (continued)

Author (Ref.)	SRP features	LAD (%)	Pathology (%)										Oncological		
	Technique		T2	ECE	SVI	T4	GS 6	GS 7	GS 8	Not graded	PSM	N1	BCR-free survival (%)	% BCR per year of FU	5-Year BCR free
Bates et al. [23]	sRARP-tp	NA	51	45	28	0	2	49	36	13	19	NA	68	14	NA
Kenney et al. [31]		100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–
	sRARP-tp		30	70	NA	NA	0	30	45	25	15	15	65	25	NA
	OsRP		47	53	NA	NA	0	37	47	16	16	11	63	26	–
Linares-Espinos et al. [35]	12 laparoscopic sRP 16 sRARP-ep or tp	29	50	50	21	4	18	71	11	0	14	0	64	7	NA
		–	0	100	43	14	0	71	29	0	29	0	NA	NA	NA
Pokala et al. [36]	NA	78.6	48.9	24.7	NA	26.4	57.7[b]		41.2	1.1	NA	11	NA	NA	NA
Ou et al. [37]	s-RARP	100	57.1	42.9		0	NA	NA	NA	NA	21.4	14.3	78.5	29.1	NA
Ogaya-Pinies et al. [27]	sRARP-tp or ep	89	50	48	23	0	4	55	30	10	17	8	84	14	NA

P prospective, *R* retrospective, *PBT* proton beam therapy, *RT* radiotherapy, *BT* brachytherapy, *sORP* salvage open radical prostatectomy, *sRARP* salvage robotic-assisted radical prostatectomy, *TP* transperitoneal, *EP* extraperitoneal, *GS* Gleason score, *LAD* lymphadenectomy, *BCR* biochemical relapse, *PSM* positive surgical margins, *N1* positive lymph nodes, *FU* follow-up

[a]This registry-based study may include patients already described in other series

[b]Sum of GS 6 and GS 7

Clinical local staging before sRP is inconsistently assessed and reported among series, the majority of authors reporting clinically organ-confined disease in roughly four out of five patients. Local recurrence is always documented by a positive prostate biopsy.

Total Gleason scores after sRP are unevenly distributed across series. Excluding the cases in which grading is not expressed, a score sum of 7 is the most frequently observed (8 out of 11 studies). The proportion of Gleason scores equal or greater than 8 is widely variable, ranging from 11% [35] to 54% [33]. It is to be considered that, after RT, it is difficult to correctly evaluate Gleason score, and most pathologists in their reports define a "Gleason-like" score.

At final pathology, organ-confined disease is found in around half of the patients, except for the robotic subgroup presented by Kenney and for the study by Chauhan (where pT2 disease occurs in 30% and 20% of patients, respectively) [31, 38]. Seminal vesicle invasion (SVI) rate is surprisingly high, being present in about one out of three patients. Positive surgical margin (PSM) rate varies from 13% [38] to 45% [11] and PSM are frequently located near the apex of the prostate [30, 32]. Lymphadenectomy is not systematically performed by all surgeons during sRP, some of them preferring a risk-based approach. At final pathology, positive nodes are encountered in between 6 and 16% of the cases, apart from the remarkable 35% nodal involvement reported by Mandel et al. in a high-risk subgroup.

Median follow-up duration varies from 4.6 to 62 months. At the end of follow-up, BCR-free survival was over 50% in all series, except in a high-risk subgroup [34]. As highlighted by Zargar [18], longer follow-up periods show a non-statistically significant trend toward a diminished BCR-free survival (plotted in Fig. 1). Yuh and Bates report, respectively, 57% and 67% 3-year BCR-free survival [20, 23], while Mandel and Chade 5-year BCR-free survival rates are 48.7% and 48% [11, 34]. Metastasis-free survival after 5 years is 69% in Mandel and 83% in Chade. Yuh, Chade and Mandel report 5-year CSS of 100, 92 and 88.7%, respectively [11, 20, 34]. According to a wide registry-based study, overall survival (OS) at 10 years was 77.5% and at 20 years was 37.3%; CSS was 88.6% at 10 years and 72.7% at 20 years [36].

According to EAU guidelines, patients with a life expectancy greater than 10 years may be evaluated for sRP in case of organ-confined PCa $\leq$ T2b, Gleason score ≤ 7 and a pre-operative PSA < 10 ng/ml. Subjects meeting EAU criteria show a significant oncological advantage: in Mandel et al., the difference between EAU and non-EAU compliant subgroup is statistically and clinically significant (5-year BCR-free survival of 73.9% vs 11.6%) [34].

Functional outcomes and complications: not as bad as previously thought

Due to radiation-induced changes, sRP has been historically related to poor functional outcomes and high risk of intra- and post-operative complications. A systematic review including studies from 1988 to 2011 reported relatively long operating time and significant blood loss, with four series yielding more than 1L mean blood loss. Similarly, less than one out of ten men had a valid erectile function and up to 70–100% were incontinent post-operatively. Complications were frequent, with up to one on three experiencing high-grade (Clavien ≥ 3) complications; amongst these anastomotic strictures and rectal injuries occurred in 7–41% and 0–19% of the patients, respectively [17].

However, recent studies, mainly reporting outcomes of robotic sRP, show promising improvements compared to what was previously thought (Table 2) [18–20, 23, 30–32, 37, 38].

Mean operating time is now rarely longer than 3 h even when performing lymph node dissection and nerve-sparing procedures, with reduced blood loss and almost no transfusion needs. Hospital stay is usually 1–3 days. Intra-operative complications are also infrequent with sporadic cases of small accidental enterotomies, ureteric and rectal injuries, mainly being managed intra-operatively [19, 20, 30, 31]. In two recent large robotic series, no intra-operative complications were reported [23, 32, 38].

Post-operative complications also seem reduced compared to older series. Nonetheless, up to one out of three men [20] may still experience high-grade complications (Clavien ≥ 3) and up to three out of four patients [31] experience at least one complication. Anastomotic leak occurs in 15.0 [30] to 42.1% [31], mainly resolving with prolonged urinary drainage, leading to a mean 10–15 days of catheterization time [18–20, 23, 32]. Anastomotic strictures also vary significantly, ranging from 0% [23] to 55% [40]; as strictures may occur several months after surgery, this aspect indeed warrants further investigation as the majority of the series have a mean follow-up shorter than 2 years.

Continence varies widely, with 15 [31]–76.9% [23] being continent at last follow-up. Nonetheless, four to six out of ten men do not use pads at all in the majority of the studies. On the contrary, erectile function is poorly preserved with generally less than one on five maintaining spontaneous or PDE-5 inhibitor-assisted erections. It is to be considered that a large proportion of patients is already impotent due to previous RT; furthermore, the performance of a nerve-sparing procedure can be questioned when dealing with a salvage surgery addressing a PCa already in progression after a previous radical treatment.

Two studies compared salvage to primary RARP. In the single-institutional matched-pair analysis by Bates and

Table 2 Functional outcomes and complications of main recent studies on salvage radical prostatectomy for radio-recurrent prostate cancer

Authors (Ref.)	Study features						SRP Features									
	Year	Study type	Accrual years	First treatment	Time to sRP (months)	*N*	Technique	PSA (ng/ml)	Age (years)	LAD	NS	Operating time (min)	EBL (ml)	Transfusions	HS (days)	Cath time (days)
Eandi et al. [19]	2010	R	2004–2008	RT $n=18$	NA	18	sRARP-tp	6.8 (NA)	NA	Y	NA	2.6′ (1.7–3.7 h)	150′ (50–350)	0	2 (1–5)	14 (8–61)
Chauhan et al. [38]	2011	R	NA	RT = 5	24 (13.25–34.75)	15	sRARP-tp	6.9 (4.75–9.6)	62 (55.5–65)	Y	$n=2$ partial	138 (95–159)	75 (50–100)	0 (0)	1 (1–1.75)	10.8 (7–19)
				BT = 5												
				PBT = 2												
				RT + BT = 3												
Kaffenberg et al. [30]	2013	R	2006–2011	RT $n=11$	48.5′ (28.9–70.8)	34	sRARP-tp	3.86 (2.41–5.07)	66.5′ (57.9–69.9)	Y	NA	176′ (159–191)	88.0% < 250	0	1 in 94%	NA
				RT + BT $n=6$												
				BT $n=13$												
				Others $n=4$												
Prasad et al. [40]	2013	R	2002–2007	RT or BT or IMRT	NA			NA	> 65	NA	NA	NA	NA	NA	NA	NA
					55.8 (29.6–87.4)	99	OsRP		NA					17.5 (17)	7 (NA)	
						18,218	ORP		NA					14.4 (2626)	3 (NA)	
														$p=0.6$	$p<0.01$	
Yuh et al. [20]	2014	P	2004–2012	RT $n=18$	68′ (40–96)	51	sRARP-tp	5.27′ (3.2–7.4)	68′ (63–71)	Y	NA	179′ (144–222)	175′ (100–250)	0	2′ (1–2)	15′ (NA)
				BT $n=22$												
				RT + BT $n=1$												
				PBT $n=6$												
				Others $n=4$												
Bates et al. [23]	2015	R	2008–2014	RT $n=28$		53	sRARP-tp	3.7′ ± 3.2	67.0′ ± 6.9	Y	$n=44$ partial	130.0′ ± 17.0	100′ ± 52.1	0	1.0′ ± 4.4	10.0′ ± 6.9
				BT $n=14$							$n=4$ full					
				IMRT $n=3$												
				Others $n=6$												
						53	RARP-tp	4.7′ ± 2.1	66.0 ± 6.4		$n=35$ partial	121.7′ ± 18.7	100′ ± 67.1	0	1.1′ ± 0.3	5.0 ± 0.9
											$n=18$ full					
								$p=0.306$				$p=0.022$	$p>0.05$		$p>0.05$	$p<0.001$

Table 2 (continued)

Authors (Ref.)	Study features						SRP Features									
	Year	Study type	Accrual years	First treatment	Time to sRP (months)	*N*	Technique	PSA (ng/ml)	Age (years)	LAD	NS	Operating time (min)	EBL (ml)	Transfusions	HS (days)	Cath time (days)
Kenney et al. [31]	2016	R	2007–2011		NA	39	sRP	NA		Y	NA	NA	NA	NA	NA	NA
				RT $n=13$		20	sRARP-tp	2.97″ ± 2.4				303.3″ ± 73.1	381.3″ ± 303.4		3.2″ ± 1.6	
				BT ± RT $n=8$												
				RT $n=11$		19	OsRP	4.51″ ± 3.1				291.5″ ± 60.1	865.0″ ± 616.4		3.6″ ± 2.3	
				BT ± RT $n=8$				$p=0.094$				$p=0.855$	$p=0.001$		$p=0.838$	
Ou et al. [37]	2017	P	2005–2016	RT = 11	36.5 (13–103)	14	sRARP	6.69 (0.56–25)	67.8 (51–84)	Y	$n=3$ full	134.9 (105–170)	99.6 (30–160)	NA	NA	NA
				Cyberknife = 2												
				HIFU = 1												
Ogaya-Pinies et al.[c] [27]	2018	R	2001–2016	RT $n=37$	81.5′ (18.25–335.5)	96	sRARP-tp or ep	4.0′ (2.61–6.30)	65.75′ (61.29–71.10)	Y	$n=71$ partial	125′ (119–138)	100′ (100–200)	1	1′ (1–2)	12′ (10–28)
				BT $n=14$							$n=14$ full					
				RT + BT $n=13$												
				Cyberknife $n=3$												
				PBT $n=1$												
				Others $n=28$												
Chade et al.[b] [17]	2012	Syst Rev	before 1988	RT and/or BT	18′–84′	1096 compl	sRP	NA	NA	Y	NA	120′–480′	75″–1850″	0–43%	NA	NA
						1190 funct outcomes	(OsRP-sRARP-laparoscopic sRP)									
Zargar et al.[b] [18]	2017	Syst Rev	2002–2014	RT and/or BT or PBT or others	55.1″ (NA)	197	sRARP	NA	62.7″ (NA)	Y	$n=64$ (on 128)	178.8″ (NA)	153″ (NA)	NA	2.3 (NA)	11.7 (NA)

Authors (Ref.)	Complications							Continence		Erectile function	
	Follow-up (months)	Intra-op compl	All	Clavien ≥ 3	Anastomotic leak	Rectal inj	An stricture	Rectourethral fistula	Pre-sRP	Post-sRP	Pre-sRP	Post-sRP
Eandi et al. [19]	NA	$n=1$ enterotomy	NA	NA	33.3 (6)	0	NA	0	NA	33.3 (6)	44.4 (8)	0 (0)

Table 2 (continued)

Authors (Ref.)	Complications								Continence		Erectile function	
	Follow-up (months)	Intra-op compl	All	Clavien ≥ 3	Anastomotic leak	Rectal inj	An stricture	Rec-tourethral fistula	Pre-sRP	Post-sRP	Pre-sRP	Post-sRP
		Managed intra-op								7″ (3–18) months $n=7>2$ pads/day		
Chauhan et al. [38]	4.6 (3–9.75)	$n=0$	20 (3)	7 (1)	7 (1)	0	7 (1)	0	NA	71.4 (10)	33.3 (5)	0 (0)
Kaffenberg et al. [30]	16.1′ (8.4–31.8)	$n=1$ rectal laceration	35.0 (12)	3.0 (1)	15.0 (5)	1	9.0 (3)	0	33	39.0 (12)	21.0 (7)	14.7 (5) PDE-5
		Requiring temporary colostomy								$n=11>3$ pads/day	29.0 (10) drugs	
Prasad et al. [40]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	2.0 ± 1.9		60.1 (60)				55.4 (55)					
	4.3 ± 2.0		22.7 (4135)				11.7 (2131)					
	$p=$NA		$p<0.01$				$p<0.01$					
Yuh et al. [20]	36 (NA)	$n=1$ small enterotomy	47.0 (24)	35.0 (18)	18.0 (9)	0	16.0 (8)	2.0 (1)	84.0	45.0 (23)	28.0 (13)	5.8 (3) PDE-5
		$n=1$ ureteric injury										5.8 (3) PGE
		All managed intra-op										
Bates et al. [23]	26.0′ ± 17.7	0	1.9 (1)	0	34.0 (18)	0	0	0	8.0′ ± 7.5	76.9 (34)	15.0′ ± 8.7	31.5 (14)
									AUA score	At 3′ ± 8.2 months	SHIM score	75.0 (3) of fNS at 4.4′ ± 8.0 months
	25.0′ ± 6.9	0	0	0	5.7 (3)	0	0	0	9.0′ ± 7.3	96.2 (51)	14.0′ ± 8.8	49.4 (26)
												at 1.8′ ± 6.4mo
									AUA score	At 1.9 ± 3.0 mo	SHIM score	55.6 (10) of fNS
	$p>0.05$			$p>0.05$	$p<0.01$				$p=0.472$	$p<0.01$	$p=0.536$	$p=0.016$ overall
												$p=0.616$ for fNS

Table 2 (continued)

Authors (Ref.)	Complications								Continence		Erectile function	
	Follow-up (months)	Intra-op compl	All	Clavien ≥ 3	Anastomotic leak	Rectal inj	An stricture	Rec-tourethral fistula	Pre-sRP	Post-sRP	Pre-sRP	Post-sRP
Kenney et al. [31]	16.8 (NA)	$n=3$	74.3 (29)	23.0 (9)	41.0 (16)	2	25.6 (10)	0	NA	10.2 (4)	NA	NA
	–	$n=1$ enter-otomy Managed intra-op	70.0 (14)	30.0 (6)	40.0 (8)	0	25.0 (5)	0		5.0 (1)		
	–	$n=2$ rectal injury	78.5 (15)	15.7 (3)	42.1 (8)	2	26.3 (5)	0		15.0 (3)		
		Management NA	$p=0.785$	$p=0.501$	$p=0.848$		$p=0.999$			$p>0.05$		
Ou et al. [37]	32.4	$n=1$ bladder tear Managed intra-op	28.5 (4)	0 (0)	0 (0)	0	14.3 (2)	0	NA	71.4 (10)	NA	66.7 (2) of fNS
Ogaya-Pinies et al.[c] [27]	14 (5–24)	$n=0$	26.0 (25)	4.1 (4)	14.6 (14)	0	NA	0	100.0 (96)	57.3 (55) 16.7 (16) > 2pads/dy	32.3 (31)	17.7 (17) ± PDE-5
Chade et al.[b] [17]	5′–120′	NA	67–91%	0–33%	NA	0–19%	0–41%	NA	NA	0–100%	9–90%	0–28%
Zargar et al.[b] [18]	18.7″ (NA)	NA	NA	16.3 (31)	NA	2	8.4 (16)	NA	NA	60.4 (119)	NA	26.0 (30)[a]

P prospective, *R* retrospective, Syst *Rev* systematic review, *PBT* proton beam therapy, *RT* radiotherapy, *BT* brachytherapy, ′ median (range or IQ range), ″ mean, *sORP* salvage open radical prostatectomy, *sRARP* salvage robotic-assisted radical prostatectomy, *TP* transperitoneal, *EP* extraperitoneal, *LAD* lymphadenectomy, *EBL* estimated blood loss, *HS* hospital stay, *post-operative complications* reporting according to the number of patients experiencing complications and not according to the absolute number of complications, *NS* nerve sparing, *compl* data on surgical complications, *funct outcomes* data on functional outcomes

[a]Calculated on the number of those who underwent a nerve sparing procedures

[b]Include some of the other studies showed in the table

[c]Include cases from Bates et al.; Chade et al. = results are reported as range of median values

colleagues, sRARP yielded rare complications, low blood loss as well as short operating time and hospital stay, all being comparable to primary RARP [23]. However, anastomotic leak and catheterization time, continence and erectile function were better for primary RARP. Interestingly, when analyzing only those undergoing full nerve sparing, no differences were found. On the contrary, an analysis of the SEER registry showed remarkable differences for all the included variables except for blood transfusions, including three times higher complication rates and five times higher anastomotic strictures [40]. Indeed, surgeon's experience may at least in part justify these marked differences [23].

To conclude, despite recent improvements supporting its use to cure recurrent PCa, sRP after primary RT remains associated with poorer functional outcomes and increased complication risk compared to first-line RP. Patients should thus be adequately counselled about increased risks of post-operative incontinence, impotence and intra-operative complications, reflecting the high surgical complexity of the salvage setting.

Future directions

Patient selection is key to attaining good functional and oncological outcomes. It is acknowledged that an early surgery after BCR is associated with better results. According to Chade et al., the most favorable group of patients for a sRP lies below a PSA cut-off of 4 ng/ml [11]. Hence, there is a need to anticipate as much as possible the diagnosis of a local recurrence to boost the chances of cure. In this context, current BCR definitions are probably not adequate to timely detect a pure local recurrence [17]. New imaging techniques for re-staging purposes might become of great help to reach this goal in the near future. Multiparametric MRI and MRI-guided biopsies are already widespread to refine local staging and to plan the surgical approach both in primary and salvage RP [41]. Ménard et al. have shown a sensitivity ranging from 0.65 to 0.82 for MRI-guided biopsies after RT [42]. PET/CT using 11C-choline or 68 Ga-PSMA is increasingly used in a post-RP setting to guide salvage EBRT or lymphadenectomy [43]. Sathianathen et al., in a meta-analysis including recurrent PCa after any primary treatment, have observed a sensitivity of 80.9% and a specificity of 84.1% for 11C-choline PET/CT; unfortunately, the authors were not able to stratify on the basis of PSA levels, due to insufficient data [44]. In a recent prospective study, 68 Ga-PSMA PET/CT has shown high clinical yield in a post-RP BCR setting, identifying recurrent PCa in 76% of men at a median PSA of 1.0 ng/ml (80% of the foci being invisible using CT or MRI) [45]. These promising results need to be confirmed in radio-recurrent PCa and the benefits of their application to sRP are to be balanced against possible drawbacks, such as the non-negligible false-positive rate, the current questionable quality of evidence and the absence of a gold-standard to precisely measure their accuracy.

Moreover, to lower peri-operative and long-term complications of the procedure, high-volume uro-oncological centers seem to be the ideal setting for sRP. A review by Wilt et al. has described statistically significant lower surgery-related mortality and morbidity in centers performing at least 43 primary RP per year [46]. Surgical volume, considering both the center and the surgeon, has shown a proportional relation to cancer control and urinary function, too [47]. It is reasonable to apply the same criteria for sRP, which bears a higher surgical complexity per se.

Surgical volume impacts also on the direct costs of open and robotic procedures, as it has been described by a large retrospective series and implemented into clinical guidelines [48, 49]. A deeper understanding of the elements at the base of this effect, and their widespread adoption, will be paramount to design a health-care system able to offer a safer and sustainable curative procedure to an increasing number of patients [47].

Discussion

The vast majority of PCa patients who develop recurrent disease after EBRT or BT are treated with palliative ADT [13]. sRP represents instead a curative option which can be offered to highly selected patients in experienced centers [50]. At present, registry analysis reveals a surprising under-use: around 1% of the patients recurring after BT or EBRT undergo salvage surgery, while nearly one out of three patients experiencing BCR after RP receives salvage RT [13].

If sRP has historically been considered a challenging procedure, yielding an important burden of peri-operative and long-term complications, data extrapolated from recent series, published after 2010, suggest a promising and improved benefit–risk ratio. The surgical pitfalls of the salvage procedure are better described and acknowledged than in the past, allowing improvements both in the open and in the robotic techniques to prevent and/or manage complications. Most reports agree on the importance of a careful hemostasis during endopelvic fascia incision and of a slow blunt dissection of posterior planes. The rectal wall check may take an advantage of gas inflation and transillumination using a sigmoidoscope. Apical preparation is another delicate step, being frequently the location of a positive margin [22, 23, 25].

Major peri-operative complications, incontinence rates, anastomotic leaks and strictures, though still more frequent than in a primary RP setting, are steering towards more acceptable values [23]. For instance, rectal injuries attained

20% of the cases in older series [17], while nowadays their frequency can be estimated between 0 and 10% [31].

Anyway, a non-negligible morbidity is still associated with the procedure, as witnessed by Clavien–Dindo ≥ 3 complications rates, ranging from 0 to 35%. Anastomotic strictures rates vary broadly across series: given the late onset of this complication, longer follow-up periods will allow to clarify this aspect. Continence rates are also quite variable from one study to another (5–76.9%), partly due to diverse definitions and baseline patient characteristics, partly because this outcome is probably dependent on surgeon experience, as shown in primary RP setting [46]. Nevertheless, many series report no pad use in between 39 and 60.4% of patients at the last follow-up. Potency outcomes must be interpreted considering also the prevalence of a pre-existing dysfunction (15–44%). Overall, around one out of five patients is potent after sRP in most series. When planning a nerve-sparing procedure in a salvage setting, the functional benefits should be carefully balanced against the risks of jeopardizing the oncological control.

Despite not reaching results of first-line RP, it seems that morbidity and functional outcomes of the procedure have improved during the years. This may be explained by several underlying reasons. First, RT techniques for PCa treatment have evolved over the years, allowing to administer higher doses with comparable or diminished toxicity; for instance, intensity-modulated radiation therapy (IMRT) can reduce rectal irradiation [51]. More focused dose distributions could possibly better preserve local anatomy, making the surgical approach easier and allowing a less traumatic dissection.

Second, almost all reports refer to high-volume centers, where sRP is performed by highly experienced surgeons, thus ensuring the attainment of satisfactory results and a better management of complications [17, 18]. A recent single-institutional study aiming to describe the primary RP learning curve has documented a statistically significant drop in PSM and BCR hazard ratios after 100 cases of RARP [52]. An adequate hospital volume can spare up to 30% of perioperative deaths and the surgeon's experience can influence long-term cancer control and comorbidity [46]. Even if no data specifically addressing the impact of surgical volumes on sRP outcomes are available, the lesson learnt for primary RP probably applies to the salvage setting, too.

Finally, the onset of minimally invasive surgery has surely played a role in improving the outcomes in terms of blood loss, hospital stay, surgical complications and catheterization time. The robotic approach, with its magnified three-dimensional vision and improved precision of movements, enables careful hemostatic control and precise antegrade dissection, which can represent an advantage especially considering radiation-induced changes [18, 23]. How much the recent improvements of sRP are attributable to the robotic approach, however, remains to be demonstrated. To date, only one small study compared the open and robotic techniques in the sRP setting, finding no relevant differences [31]. It has to be considered, though, that the vast majority of recent reports describe only robotic sRP series, showing that robotic surgery has gained a clear role in salvage surgery, at least in terms of surgeon preference [53]. We are currently undertaking a large multi-center study including open or robotic sRP performed after 2000 [54, 55]. Results will help to clarify possible advantages, if any, of the robotic technique, current outcomes of sRP and its contemporary role in the management of radio-recurrent PCa.

As for oncological outcomes, most series report a high rate of Gleason score of 8 and around 50% of extracapsular extension, at final pathology. This confirms that radio-recurrent PCa is a biologically aggressive and possibly life-threatening disease [23]. An interesting propensity score matched analysis has pointed out that candidates treated with sRP are affected by significantly higher risk disease if compared to patients undergoing primary RP: this finding is confirmed by the reports included in our review [23].

PSM rates are variable and can reach 45% in some multicenter series. According to Heidenreich et al., previous brachytherapy, a low tumor burden at pre-sRP biopsy and a slow PSA doubling time are associated with organ-confined disease and negative surgical margins [29]. The importance of achieving R0 resection is underlined by Chade et al., who describe a trend towards an augmented risk of death from PCa for PSM (HR 1.8, $p = 0.068$) [11].

Although follow-up duration is often insufficient to draw definitive conclusions, the vast majority of the included studies report a BCR-free survival greater than 60% at the end of follow-up; noticeably, longer follow-ups show a trend towards lower progression-free survivals (PFS). Intermediate-period outcomes seem encouraging: nearly half of the patients are free from biochemical relapse 5 years after surgery and 5-year CSS rates are around 90% [11, 34].

Since the rationale of sRP is to treat localized recurrent disease, patient selection is of paramount importance. ASTRO and Phoenix definitions of BCR lead to a late identification of potential sRP candidates, as witnessed by the long interval between primary and salvage treatments in the reported series [56]. New imaging modalities, especially PET/CT using 68 Ga-PSMA, are likely to become fundamental instruments to identify sRP candidates. A biopsy-confirmed pelvic recurrence, the absence of radiological evidence of metastases and a low-risk profile for systemic disease, as stated by guidelines, are widely applied criteria for identifying patients who might draw the greatest potential benefit from sRP [50]. Mandel et al. have clearly shown that sRP patients fulfilling EAU criteria have a statistically significant higher BCR-free survival and show trends towards a better metastasis free and CSS [34].

The type and quality of published evidence limit the strength of the conclusions of the present review. No evidence from prospective, controlled trials is available. Moreover, all the series included report only on surrogate or short-term endpoint (such as PSM rates and 5-year CSS) which might actually have a limited impact on the natural history of the disease. In addition to potential selection and information biases intrinsic of retrospective studies, the inability to stratify patients on the basis of primary treatment, the heterogeneity of baseline characteristics (eminently in terms of PSA and histological grading), the short follow-up periods, and the use of diverse disease and outcome definitions across the included series hinder the robustness and generalizability of the results. However, all the recently published series witness a renewed interest in sRP and confirm its role as a potential curative option for a wide number of patients.

Conclusions

SRP is an underused complex procedure historically linked to high morbidity. Although results are inferior compared to a primary setting, when performed in high-volume referral centers, salvage surgery has acceptable oncological and functional outcomes and morbidity. Hence, sRP should not be precluded in appropriately selected radio-recurrent patients. Large prospective studies with longer follow-up are warranted to confirm the improvements of sRP in terms of oncological and functional outcomes, especially in the robotic setting. The improvement of imaging techniques would be welcomed to refine the criteria for patient selection, possibly providing a direct benefit on surgical outcomes.

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Compliance with ethical standards

Conflict of interest The author(s) declares that they have no competing interests.

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