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Oncological outcomes of salvage radical prostatectomy for recurrent prostate cancer in the contemporary era: A multicenter retrospective study

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Abstract

Background: Salvage radical prostatectomy (sRP) historically yields poor functional outcomes and high complication rates. However, recent reports on robotic sRP show improved results.

Our objectives were to evaluate sRP oncological outcomes and predictors of positive margins and biochemical recurrence (BCR).

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Methods: We retrospectively collected data of sRP for recurrent prostate cancer after local nonsurgical treatment at 18 tertiary referral centers in United States, Australia and Europe, from 2000 to 2016. SM and BCR were evaluated in a univariate and multivariable analysis. Overall and cancer-specific survival were also assessed.

Results: We included 414 cases, 63.5% of them performed after radiotherapy. Before sRP the majority of patients had biopsy Gleason score (GS) ≤7 (55.5%) and imaging negative or with prostatic bed involvement only (93.3%). Final pathology showed aggressive histology in 39.7% (GS ≥9 27.6%), with 52.9% having ≥pT3 disease and 16% pN+. SM was positive in 29.7%. Five years BCR-Free, cancer-specific survival and OS were 56.7%, 97.7% and 92.1%, respectively. On multivariable analysis pathological T (pT3a odds ratio [OR] 2.939, 95% confidence interval [CI] 1.469−5.879; ≥pT3b OR 2.428−95% CI 1.333−4.423) and N stage (pN1 OR 2.871, 95% CI 1.503−5.897) were independent predictors of positive margins. Pathological T stage ≥T3b (OR 2.348 95% CI 1.338−4.117) and GS (up to OR 7.183, 95% CI 1.906−27.068 for GS >8) were independent predictors for BCR. Limitations include the retrospective nature of the study and limited follow-up.

Conclusions: In a contemporary series, sRP showed promising oncological control in the medium term despite aggressive pathological features. BCR risk increased in case of locally advanced disease and higher GS. Future studies are needed to confirm our findings. © 2020 Published by Elsevier Inc.

Keywords: Prostate cancer; Recurrence; Salvage radical prostatectomy; Open; Robotic

1. Introduction

More than 1 in 4 men with newly diagnosed prostate cancer (CaP) currently undergo nonsurgical treatments with curative aims [1]. Of these patients, 1 to 2 in 3 will have biochemical recurrence (BCR) within 10 years [2−4]. Also, recurrences after nonsurgical treatment will likely increase with the expansion of whole-gland and of focal ablative strategies, which are attracting the interest of the Urological community [5].

Despite approximately half of recurrences are localized to the prostate, 90% of men will indiscriminately undergo androgen deprivation therapy (ADT) [6] experiencing ADT-related comorbidities and losing the chance of being cured.

However, this trend largely relies on historical series of salvage radical prostatectomy (sRP) yielding high complication rates and poor functional outcomes.

Recently, our group and others reported significant improvements in functional outcomes and decrease in overall complications following sRP [7−9]. Namely, when sRP is performed in high-volume centers, major complications are now recorded in approximately 1 in 10 cases while 1 in 4 men experiences newly onset severe incontinence. Nonetheless, results remain worse compared to a non-salvage setting and potential side effects need to be justified by oncological results.

While functional benefits of technical and technological improvements in the salvage setting are now well-acknowledged, no large series has documented whether oncological control may also have improved compared to the past. The largest study to date included 404 men treated as far back as 1985, showing approximately 1 in 2 patients experiencing BCR at 5 years [10]. Older studies reported a wide variety of BCR rates ranging from 18% up to 70% [11].

More recent studies showed overall BCR rates ranging from approximately 30% at 1 year to 50% at 5 years from sRP. However, the majority of these series derive from single institutions and have a limited follow-up [12].

Thus, we performed a multicenter study to verify whether medium-term oncological outcomes mirror those of previous series in a large contemporary retrospective series of sRP.

2. Materials and methods

2.1. Data collection

We retrospectively collected data of $n = 629$ men undergoing sRP for recurrent CaP at 18 tertiary referral centers until October 2016. Data quality review was carried out independently by 2 physicians (G.M. and P.A.). Internal Review Board approval for the present study and for retrospective data collection was obtained according to each institution's policy, when required. In case of uncertainty or missing information, centers were recontacted for data revision. Recurrent CaP was defined according to the Phoenix criteria − nadir + 2 ng/ml PSA rise. We excluded procedures performed before the year 2000, laparoscopic procedures, cases with less than 6 months follow-up, unclear outcomes with no revision performed and castration resistant CaP (CRPC) before sRP (Fig. 1). Patients' follow-up was performed with periodical visits and PSA according to institutional protocols.

2.2. Categorization of the variables

Continence was recorded at baseline, 6 and 12 months considering the number of pads used/day being categorized as full continence (no pads), terminal dribbling, mild (1 pad/day), moderate (2 pads/day) and severe incontinence (≥3 pads/day), as previously detailed [9,12−15]. Final continence evaluation was performed using the 12 months results (6 months data were used in case of missing 12 months evaluation). Complications were graded using the Clavien-Dindo classification and adhering to the EAU guidelines on reporting complications, considering as major

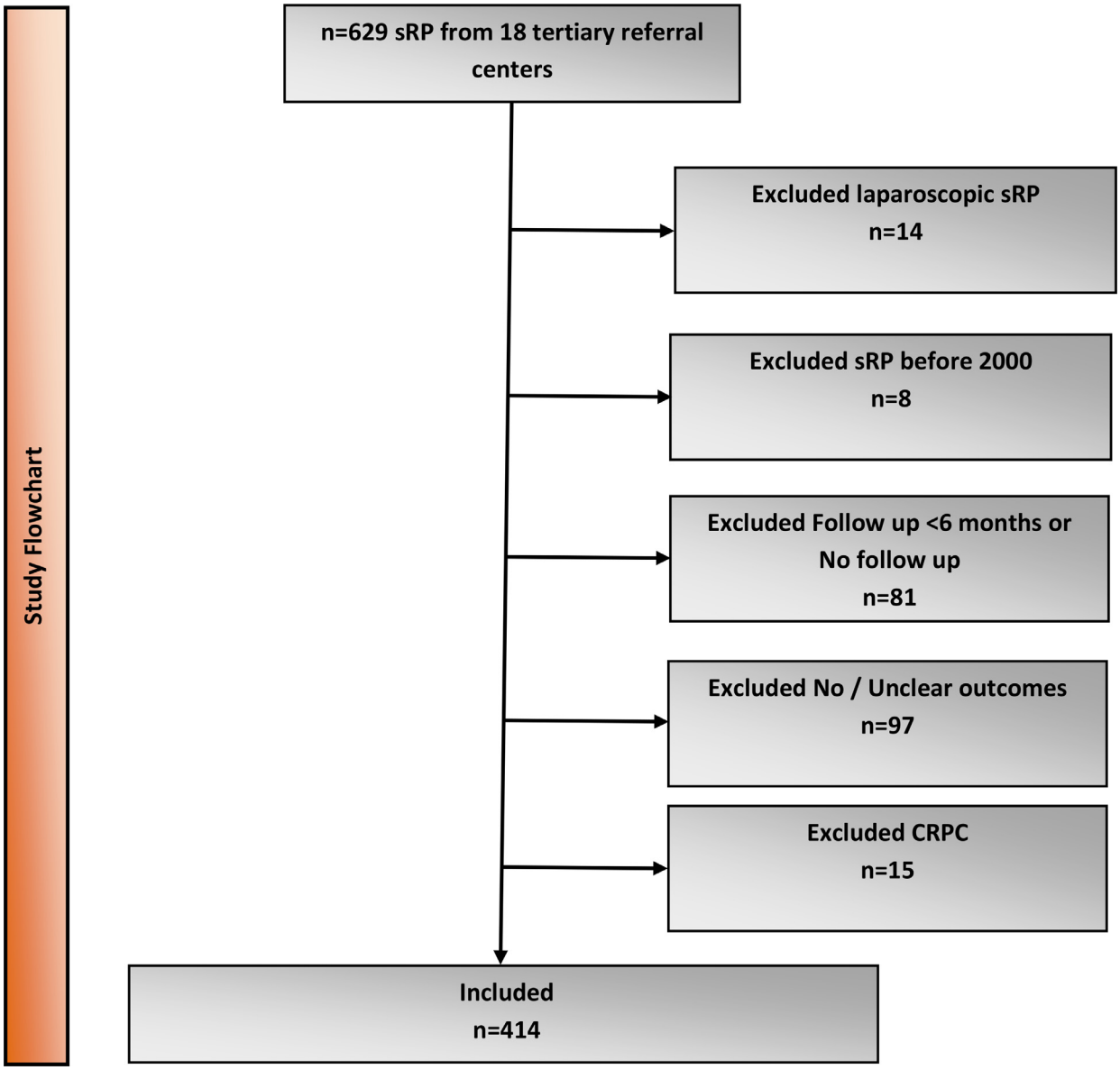

Fig. 1. Study flowchart with excluded procedures and reason for exclusion.

complications those with a Clavien grade ≥3 [16]. Preoperative comorbidity status was recorded using the ASA score, the Charlson Comorbidity Index and the ECOG Performance Status. Persistent CaP was defined as PSA never being undetectable following sRP; BCR was defined as a previously undetectable post-sRP PSA persistently rising and reaching >0.2 ng/ml (one or more evaluations). CRPC was defined as 3 consecutive rises in PSA 1 week apart resulting in 2 50% increases over the nadir, and a PSA >2 ng/ml despite castrate serum testosterone.

2.3. Study outcomes

Primary outcome was to assess oncological results of sRP including positive surgical margin (PSM), BCR, Cancer-specific survival (CSS) and overall survival (OS).

Secondary outcomes included (1) identification of predictors for PSM and BCR; (2) evaluation of functional outcomes and complications; (3) evaluation of pre-sRP biopsy Gleason Score (GS) concordance with the final sRP specimen.

2.4. Statistical analysis

Comparisons were made using (1) *T*- or Wilcoxon-Mann-Whitney test according to type of distribution – continuous variables; (2) Chi-square or Fisher exact test as appropriate – categorical variables. Surgical margins and BCR were evaluated in multivariable analysis. Clinically meaningful variables or variables with 0.2 statistical significance level were entered in a multivariable logistic regression model as independent factors. Level of statistical

significance was set at 0.05. Statistical analysis was conducted using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina).

3. Results

3.1. Primary treatment features

We included 414 cases undergoing sRP after external beam radiotherapy (64.5%), brachytherapy (25.7%) or other primary treatments (13.6%). Baseline features at primary treatment are displayed in **Supplementary Material 1**, with only a minor proportion of men yielding aggressive CaP (GS >7 10.3%) or having extra-prostatic disease (>cT2 11.5%). sRP was performed in $n = 32$ (7.7%) patients from 2000 to 2005 and $n = 272$ (65.7%) from 2010 to 2016.

3.2. Pre- and intraoperative features, complications and continence

Ninety-six percent had a biopsy proven recurrence ($n = 396$) before surgery whilst a minority ($n = 18$) underwent sRP due to positive imaging and biochemical recurrence according to the Phoenix criteria without confirmatory biopsy. Before sRP the majority of patients had an ASA score ≤2 (66.0%), biopsy GS ≤7 (55.5%) and CaP recurrence either negative or localized to the prostate at preoperative imaging (93.3%). Median age and PSA was 66 years (IQR 62−70) and 4.2 ng/ml (IQR 2.5−7.3), respectively.

Nerve sparing was rarely performed (14.6%) while 84.3% underwent extended or standard lymphadenectomy in the majority of the cases (84.4%) (Table 1).

Complications occurred in 41.5% with median hospital stay being 4.5 (IQR 2−7) days. Detailed complications are described in **Supplementary Material 3**.

Following the procedure 54.1% of men were fully continent whilst 26.9% severely (≥3pads/day) incontinent.

3.3. Pathological results

Final pathology showed ISUP ≥4 in 39.7% (ISUP 5 27.6%), with 52.9% having extraprostatic disease and 16% pathologically positive nodes. Surgical margins were positive in 29.7% (Table 2). Overall, 23.9% ($n = 82$) had GS upgrading from pre-sRP biopsy to sRP including 7.8% ($n = 23$) from GS ≤7 to GS ≥8 (**Supplementary Material 1**). Concordance was 64.7% ($n = 222$, K = 0.488).

3.4. Oncological Outcomes

At a median follow-up of 36 (IQR 20.4−60.5) months 59.8% ($n = 229$) of men did not experience BCR, 9.4% ($n = 39$) had disease persistence after sRP and 30.9% ($n = 115$) had BCR (median time of BCR being 12 (IQR 5.75−30) months from surgery). During follow-up

Table 1
Salvage radical prostatectomy technical features, intraoperative features and postoperative continence and complications. ; Others= treatments other than the ones listed.

Baseline features	Median (IQ range)/*n* (%)
Age (y)	66 (62−70)
PSA (ng/ml)	4.2 (2.5−7.3)
ASA score	
1	105 (26.7)
2	155 (39.3)
3	132 (33.5)
4	2 (0.5)
Imaging	
Negative	85 (35.6)
Prostate	138 (57.7)
Lymph nodes pelvis	4 (1.67)
Lymph nodes retroeritoneum	0
Prostate + lymph nodes pelvis	11 (4.6)
Prostate + retroperitoneum nodes	1 (0.4)
Biopsy	
not performed	18 (4.3)
yes	396 (95.6)
Biopsy Gleason Score	
6	67 (16.9)
7	153 (38.6)
8	73(18.4)
>8	67 (16.9)
Undetermined^	36 (9.1)
Time from 1st treatment to sRP (ys)	5.2 (2.9−7.5)
Time from BCR to sRP (ys)	0.5 (0.5−1)
Technical features	
Technique	
Open	216 (52.2)
Robotic	198 (47.8)
Nerve sparing	
No	297 (85.3)
Monolateral	7 (2.0)
Bilateral	44 (12.6)
Lymphadenectomy	
Yes	349 (84.3)
No	65 (15.7)
Lymphadenectomy template	
Limited (obturator only)	93 (35.9)
Standard (external iliac + obturator)	123 (47.5)
Extended (at least external, internal, obturator, presacral)	42 (16.2)
Including retroperitoneum	1 (0.3)
Intraoperative features	
Operating time (min)	186.5 (149−240)
Estimated blood loss (ml)	300 (150−600)
Transfusions[a]	14 (4.4)
Hospital Stay (d)	4.5 (2−7)
Complications and post-sRP continence	
Complications[b]	
≥1	144 (41.5)
≥1 Major	65 (18.7)
Continence	
Full continence	85 (28.2)
Terminal dribbling (no pads)	78 (25.9)
Mild incontinence (1 pad/day)	32 (20.6)
Moderate incontinence (2 pads/day)	25 (8.3)
Severe incontinence (≥3 pads/day)	81 (26.9)

[a] Patients receiving transfusions.
[b] Number of patients experiencing at least one complication (major complications defined as Clavien >2).

Table 2
^=PCa confirmed on the biopsy specimen but without possibility of attributing a Gleason Score

Pathological results	median (IQR)
pT stage	
0	5 (1.2)
2	189 (45.9)
3a	71 (17.2)
3b	145 (35.2)
4	2 (0.5)
pGleason score	
6	32 (8.4)
7	198 (52.0)
8	46 (12.1)
>8	105 (27.6)
pISUP	
1	32 (8.4)
2	96 (25.3)
3	101 (26.57)
4	46 (12.1)
5	105 (27.6)
pN	
x	65 (16.0)
0	276 (68.0)
1	65 (16.0)
Nodes removed	11 (7−17)
Nodes positive[a]	2 (1−4)
Surgical margins	
Negative	291 (70.3)
Positive	122 (29.7)
Focally	48 (53.9)
Diffusely	41 (46.06)

[a] Calculated on patients having positive nodes.

$n = 31$ men developed CRPC and $n = 25$ died, 9 of them due to CaP.

Five-year BCR, CSS and OS were 56.7%, 97.7%, and 92.1%, respectively (Fig. 2).

3.5. Multivariable analysis

Uni- and multivariable analysis for surgical margins and BCR are detailed in Table 3. Pathological T (pT3a odds ratio [OR] 2.939, 95% confidence interval [CI] 1.469 −5.879; ≥pT3b OR 2.428, 95% CI 1.333−4.423) and N stage (pN1 OR 2.871, 95% CI 1.503−5.897) were predictors for PSMs.

Pathological T stage ≥T3b (OR 2.348, 95% CI 1.338 −4.117) and GS (up to OR 7.183, 95% CI 1.906−27.068 for GS >8) were predictors for experiencing BCR. Interestingly, PSMs was not associated with an increased risk of BCR. PSA, year of surgery, sRP approach, previous treatment and time from BCR or first treatment to sRP were not associated with an increased probability of experiencing PSMs and/or BCR.

4. Discussion

In the current study, we report medium-term oncological results of the largest series of sRP. Also, our work focused on surgeries performed after 2000 better to reflect sRP results in the contemporary era. We believe several findings are of relevance.

First, sRP often has to face aggressive PCa recurrence. Furthermore, disease is significantly underestimated by current pre-sRP assessment strategies. Final histopathology results, when compared with preoperative evaluation, confirm recent findings by other single-center series of sRP after external beam radiotherapy or other primary treatments [9,12].

Recurrences are frequently high grade, with 27 % having a GS ≥9 compared to 90% having a GS of ≤7 at initial CaP diagnosis. Although disease undergrading may have occurred in some cases, this discrepancy is likely largely related to first-line treatment induced changes and selection of resistant CaP clones, altering CaP natural history towards adverse features. GS upgrading from pre-sRP biopsy should also be kept in mind as it occurs in a significant proportion of cases. Extraprostatic involvement is present in more than half, and despite preoperative imaging being negative or indicating organ confined recurrence in the vast majority, more than 1 in 10 men harbors positive nodes. Although some recent studies questioned the ability of mpMRI in local staging of CaP recurrences after nonsurgical treatment [17], modern imaging techniques, including PSMA-PET, and their impact on treatment selection and, eventually, outcomes, will indeed require further evaluation.

Second, PSM rate is acceptable, lying close to the upper PSM limit of recent single-center reports [7,12] but still comparable to a first-line treatment scenario [18]. This is true especially when considering the high rate of locally advanced disease, which, as confirmed in multivariable analysis, together with lymph node involvement is an independent predictor of PSM.

Third, oncological outcomes are promising in the medium term and a significant proportion of men remain free of disease at 5 years following sRP. BCR rate is high as only 56.7% of patients are free of PSA recurrence at 5 years. However, it seems to have mildly improved when compared to reports by others. In particular, the largest cohort to date found 5-year BCR free survival being lower [10]. Recent evidence detailed better results on a short follow-up, but, when reporting five-year outcomes, acknowledged BCR in at least 1 in 2 men [12]. On the contrary, at 5 years, CSS remains high, with CaP related deaths being a rare event. In line with BCR, also CSS seems improved if compared with older reports [10].

Fourth, we confirmed the findings of a separate analysis from the current cohort, which focused on functional outcomes and complications [13]. sRP is a complex procedure, morbidity being considerable and higher compared to a first-line setting. Nonetheless, there is a remarkable

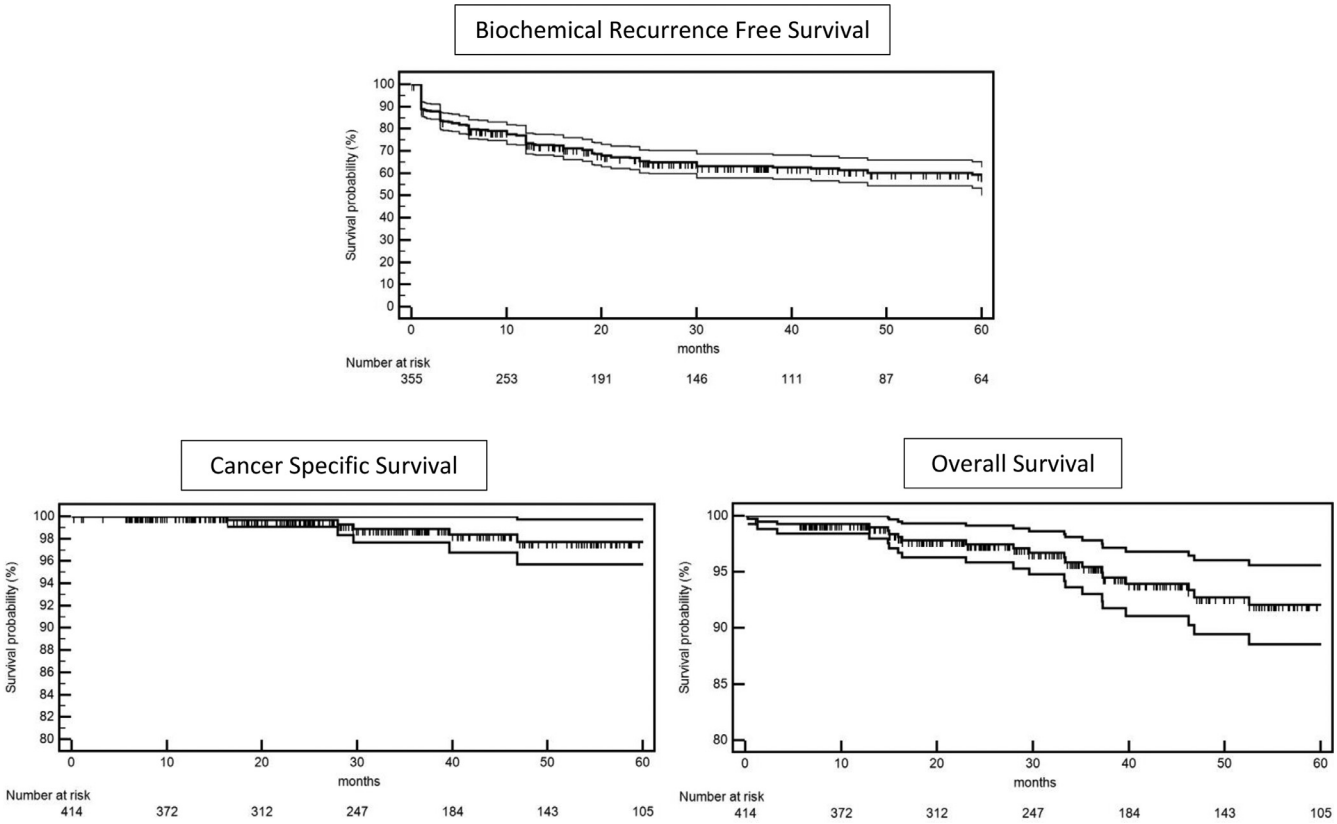

Fig. 2. Kaplan-Meyer curves indicating biochemical recurrence-free, cancer specific and overall survival (95% CI). Exact time to BCR was not available for $n = 59$ patients.

improvement when considering historical series reporting the majority of men with postoperative incontinence and up to 1 in 3 experiencing severe complications [11].

Not surprisingly, considering the relatively young age of the patients and the combination of an almost 100% CSS together with a relatively limited morbidity, OS at 5 years from surgery is high.

Series of ADT alone following radio-recurrent disease show one on four men developing metastases and/or dying for non−cancer-related causes at 5 years and CSS being similar or slightly inferior compared the present series [19].

Overall, data from our cohort may not be mature enough to define the entity of survival benefits of sRP over ADT alone as BCR does not always reflect survival accurately. Furthermore, OS in ADT series is inferior but hardly comparable with sRP given the differences in baseline features, including age and morbidity, which are often higher in cohorts undergoing ADT [19]. Also, we did not assess progression-free survival which constitutes an important surrogate end-point to mirror longer term oncological outcomes [20].

Nonetheless, given the promising oncological results of sRP, we believe it should not be a priori precluded and it should be offered in well-selected patients after appropriate counselling concerning complications and risk of recurrence.

Fifth, we investigated independent predictors for experiencing BCR with the aim of identifying cases which are less likely to benefit from surgery.

On the one hand, not surprisingly, a more advanced pathological stage and aggressive GS were confirmed as independent predictors for experiencing recurrence.

On the other hand, other factors, which are commonly associated with disease recurrence in a primary setting, were not relevant in the current analysis. As for PSM, focal positivity, which has been shown not to correlate with recurrence risk, was present in a significant proportion of men. Although we noted a protective trend in case of negative margins, the number of cases being only focally positivity may partly explain the absence of statistical significance. [21]. Concerning PSA, possible explanations lie in some patients undergoing neoadjuvant ADT and others having poorly differentiated tumors, thus expressing PSA values which do not truly reflect disease aggressiveness [22]. Also, due to selection bias, only a minority ($n = 14$) of men who underwent surgery had PSA values >20 ng/ml. Probably, within a limited range that coincides with candidates for curative sRP, differences in PSA may have a limited impact on recurrence risk [23].

Recently, PSA doubling time was confirmed of utmost importance to evaluate biological behavior of recurrences [24] and its role may be more relevant than PSA alone in

Table 3
Univariable and multivariable analysis of variables possibly influencing positive surgical margins and biochemical recurrence. Others= treatments other than radiotherapy and brachytherapy

	Surgical margins					Biochemical recurrence				
	Univariable ($n = 413$)			Multivariable		Univariable ($n = 383$)			Multivariable	
	Negative ($n = 291$) - 70.3%	Positive ($n = 122$) - 29.7%	*P*	OR	95% CI	No ($n = 229$) - 59.8%	Yes ($n = 154$) - 40.2%	*P*	OR	95% CI
Original treatment			0.33					0.9514		
RT	180 (43.8)	85 (20.6)				148 (38.6)	98 (25.6)			
BT	80 (19.5)	26 (6.3)				59 (15.4)	42 (11.0)			
Others	29 (7.1)	11 (2.7)				20 (5.2)	14 (3.6)			
sRP technique			0.16					0.421		
Open	158 (38.3)	57 (13.8)		0.668	(0.378−1.179)	130 (33.9)	81 (21.1)			
Robot	133 (32.2)	65 (15.7)		1.00		99 (25.85)	73 (19.0)			
Lymphadenectomy			0.74					0.2509		
Yes	247 (59.8)	102 (24.7)				43 (11.23)	22 (5.7)			
No	44 (10.6)	20 (4.8)				186 (48.6)	132 (34.5)			
Age at sRP	66 (61.7−69.9)	66 (61.7−70.4)	0.5822			66 (61−70)	66 (62−70)	0.7661		
PSA	4 (2.5−6.9)	4.6 (2.7−9)	0.07	1,015	(0.984−1.047)	3.8 (2.3−6.8)	5.3 (2.6−9)	0.065	1,026	(0.990−1.063)
ASA score			0.52					0.3228		
1	67 (17.0)	37 (9.4)				68 (18.7)	37 (10.2)			
2	108 (27.5)	47 (11.9)				82 (22.6)	61 (16.8)			
3	95 (24.)	37 (9.4)				63 (17.4)	50 (13.8)			
4	2 (0.5)	0				2 (0.55)	0			
pT stage			**<0.0001**					**<0.0001**		
≤pT2	164 (39.8)	30 (7.3)		1.00		136 (35.6)	46 (12.0)		1.00	
pT3a	42 (10.2)	29 (7.0)		**2,939**	**(1.469−5.879)**	36 (9.4)	27 (7.1)		1,267	(0.637−2.522)
≥pT3b	85 (20.6)	62 (15.0)		**2,428**	**(1.333−4.423)**	57 (14.9)	80 (20.9)		**2,348**	**(1.338−4.117)**
pN stage			**0.0001**					**0.0004**		
x	44 (10.9)	20 (4.9)				43 (11.5)	22 (5.9)			
0	209 (51.6)	67 (16.5)		1.00		160 (42.7)	89 (23.7)		1.00	
1	32 (7.9)	33 (8.1)		**2,871**	**(1.503−5.879)**	23 (6.1)	38 (10.1)		1,397	(0.724−2.699)
Gleason Score			**0.0057**					**<0.0001**		
6	28 (6.8)	4 (1.0)	33	1.00		27 (7.0)	3 (0.78)		1.00	
7	141 (34.1)	57 (13.8)		2,518	(0.695−9.121)	121 (31.6)	67 (17.5)		**3,766**	**(1.070−13.255)**
8	35 (8.5)	11 (2.7)		1,399	(0.329−5.945)	21 (5.5)	17 (4.4)		**5,509**	**(1.372−22.126)**
>8	61 (14.7)	44(10.6)		2,711	(0.700−10.500)	36 (9.4)	60 (15.7)		**7,183**	**(1.906−27.068)**
Surgical margins								**<0.0001**		
Negative	-	-				177 (46.3)	88 (23.0)		0.606	(0.364−1.010)
Positive	-	-				52 (13.6)	65 (17.0)		1.00	
sRP year		-	0.6					0.4586		
2000-2005	21 (5.0)	11 (2.7)		1.00		17 (44.4)	14 (3.6)			
2006-2010	107 (25.8)	40 (9.7)		0.897	(0.302−2.668)	83 (21.7)	60 (15.6)			
≥2011	160 (38.6)	74 (17.9)		0.669	(0.219−2.048)	129 (33.7)	80 (20.9)			
Time from BCR to sRP (mo)	5 (3−87)	6 (2−15)	0.6			5 (3−9)	7 (4-13)	0.174		
Time from Ist to sRPtreatment (ys)	4.9 (2.7−7.3)	5.4 (4−8.2)	**0.02**	1,035	(0.965−1.112)	5 (3−7)	5 (3−7)	0.2762		

this context. Absence of this variable probably limits the value of our findings in terms of BCR predictors.

Our work is not without limitations. Its retrospective nature may have affected data quality causing the exclusion of several and underestimation of complications. We included recurrences following different types of primary treatment. However, with the increase of primary options other than external beam radiotherapy [5], we believe the current series well reflects trends of recurrences CaP practitioners have to face in the present era. Importantly, all sRP were carried out by experienced surgeons at high-volume tertiary referral institutions performing >100 primary radical prostatectomies/year. Hence, results in terms of functional outcomes, complications, positive margins and perhaps oncological control overall are likely not reproducible outside of this setting [25,26]. We included some procedures performed before 2005 and thus overall outcomes may not precisely reflect current results. Nonetheless, these patients were a minority and previous large series included surgeries from the eighties [10,11]. Also, more than half of the procedures were performed using an open approach, which is becoming increasingly rare with the expansion of robotic RP. Finally, our series does not fully comply with current guidelines. A minority of patients did not receive confirmatory biopsy before surgery and others underwent the procedure even though they did not fulfil the recommended criteria. However, the vast majority of surgeries were performed before the last guidelines updates. Also, more stringent inclusion would have likely further improved oncological outcomes. We await the results of large prospective series to confirm our findings and to develop predictive models in order to identify men who are more likely to benefit from sRP.

5. Conclusions

sRP is a complex procedure and often reveals at least locally advanced disease with aggressive histology, which may be undergraded by pre-sRP biopsy. When sRP is performed in high-volume centers, surgical margin rate is not negligible but comparable to a first-line setting. At 5 years, a significant proportion of men has no evidence of disease, CaP deaths are rare and overall deaths uncommon. Hence, despite morbidity being significant and higher compared to a first-line setting, the procedure should not be a priori precluded in appropriately selected patients. Future studies are needed to confirm our findings on large prospective cohorts with a longer follow-up.

Compliance with ethical standards

Conflict of interests: None to declare.

Research involving Human Participants and/or Animals: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: For this type of study formal consent is not required. Internal Review Board approval for the present study and for retrospective data collection was obtained according to the policy set by each participant institution, when required.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.11.002.

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