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ORIGINAL ARTICLE

Challenging cases in high-risk prostate cancer patients treated with Retzius-sparing robot-assisted radical prostatectomy

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Abstract

Objective To evaluate the relationship between enlarged prostate, bulky median lobe (BML) or prior benign prostatic hyperplasia (BPH) surgery and perioperative functional, and oncological outcomes in high-risk (HR) prostate cancer (PCa) patients treated with Retzius-sparing robot-assisted radical prostatectomy (RS-RARP).

Methods 320 HR-PCa patients treated with RS-RARP between 2011 and 2020 at a single high-volume center. The relationship between prostate volume, BML, prior BPH surgery and perioperative outcomes, Clavien–Dindo (CD) grade ≥ 2 90-day postoperative complications, positive surgical margins (PSMs), and urinary continence (UC) recovery was evaluated respectively in multivariable linear, logistic and Cox regression models. Complications were collected according to the standardized methodology proposed by EAU guidelines. UC recovery was defined as the use of zero or one safety pad.

Results Overall, 5.9% and 5.6% had respectively a BML or prior BPH surgery. Median PV was 45 g (range: 14–300). The rate of focal and non-focal PSMs was 8.4% and 17.8%. 53% and 10.9% patients had immediate UC recovery and CD ≥ 2. The 1- and 2-yr UC recovery was 84 and 85%. PV ($p = 0.03$) and prior BPH surgery ($p = 0.02$) was associated with longer operative time. BML was independent predictor of time to bladder catheter removal ($p = 0.001$). PV was independent predictor of PSMs (OR: 1.02; $p = 0.009$). Prior BPH surgery was associated with lower UC recovery (HR: 0.5; $p = 0.03$).

Conclusion HR-PCa patients with enlarged prostate have higher risk of PSMs, while patients with prior BPH surgery have suboptimal UC recovery. These findings should help physicians for accurate preoperative counseling and to improve surgical planning in case of HR-PCa patients with challenging features.

Keywords High-risk prostate cancer · Robot-assisted radical prostatectomy · Retzius-sparing · Challenging scenarios · Functional outcomes

Introduction

Retzius-sparing robot-assisted radical prostatectomy (RS-RARP) represents a valid surgical treatment option for prostate cancer (PCa) patients [1]. It allows the maximal

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preservation of the structures of the Retzius space advocated to play a pivotal role in the continence mechanism [2], with consequent excellent functional outcomes in low- and intermediate-risk PCa patients. This advantage does not come at a significant oncological cost in expert hands [3–5]. Recent evidence suggested that RS-RARP is also feasible and safe in the specific setting of high-risk PCa patients [6] and in several atypical scenarios, such as enlarged prostate, bulky median lobe (BML), and previous benign prostate hyperplasia (BPH) surgery [7–9] with optimal oncological and functional outcomes. In these scenarios, the posterior approach may be more technically challenging, with consequent higher risk of postoperative complications and suboptimal perioperative oncological and functional outcomes [1, 10]. However, this has never been evaluated in the specific setting of high-risk PCa patients treated with RS-RARP. Under this light, relying on a large series of high-risk PCa patients treated at a single high-volume center, we hypothesized that patients presenting with one of the aforementioned challenging features have worse perioperative, oncological, and functional outcomes.

Materials and methods

Population

All consecutive patients with diagnosis of D'Amico high-risk PCa (clinical stage ≥ T2c, biopsy Gleason score 8–10, or PSA levels > 20 ng/mL) [11] submitted to RS-RARP and pelvic lymph node dissection (PLND) at a single high-volume European institution (ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy) between January 2011 and December 2020 were recruited ($n = 340$). All RS-RARP procedures were performed with a four-arm da Vinci Si Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) with a trans-peritoneal approach, as previously described [6], by five experienced robotic surgeons. Patients' data were extracted from a retrospective database and only patients with complete pre-, peri- and postoperative data were included. Overall, 320 assessable patients were identified. The study protocol received the approval by the institutional medical ethics committee and all patients provided informed consent.

Evaluated variables and study endpoints

All patients underwent preoperative multi-parametric MRI or trans-rectal ultrasound of the prostate (TRUS). The distance between the bladder neck and the highest portion of the median prostatic lobe was assessed in MRI T2-weighted mid-sagittal images and TRUS mid-sagittal images. The bladder neck was defined as the proximal opening of the prostatic urethra. BML was defined as a distance ≥ 10 mm between the bladder neck and the highest portion of the median prostatic lobe [8, 12].

History of previous BPH surgery was investigated during preoperative assessment and defined as previous transurethral resection of the prostate (TURP) or holmium/thulium laser enucleation of the prostate or simple open/minimally invasive prostatectomy. Prostate volume (PV) was defined as prostate weight at final pathology and considered as a continuous variable.

The endpoint of this study was to evaluate the relationship between PV, BML, prior BPH surgery and perioperative, oncological, and functional outcomes, in the specific setting of high-risk PCa patients. Specifically, we focused on:

(a) Perioperative outcomes as surgical operative time, intraoperative blood loss, length of hospitalization and time to bladder catheter removal. A suprapubic tube is inserted under direct vision when the vesico-urethral anastomosis is completed. In case of bladder cancer history or very wide bladder neck the transurethral catheter is maintained and the suprapubic tube is not placed.
(b) Oncological outcomes as positive surgical margins (PSMs). Focal and extended PSMs were defined as the presence of inked cells at the edge of the surgical specimen, for ≤ 1 mm and > 1 mm in length, respectively [1];
(c) 90-day complications. Postoperative complications were collected based on patient chart review done by a dedicated data manager and were graded according to Clavien–Dindo classification system [13]. From July 2020 to January 2021 four medical doctors who were not involved in the treatment, performed patients' interviews to retrospectively collect 90-day postoperative complications. Postoperative complications were graded according to Clavien–Dindo classification system [13] and reported according to the standardized methodology proposed by the European Association of Urology ad hoc Complications Guidelines Panel in 2012 (Supplementary table 1a) [14–18];
(d) Functional outcomes as urinary continence (UC) recovery. Immediate UC recovery was defined as the use of zero or one safety pad per day at catheter removal. UC recovery was defined as the use of zero or one safety pad per day at last follow-up. Continence recovery was assessed at each follow-up visit, namely at 3, 6, and 12 mo after surgery, then every 6 mo for 3 yr, and then annually.

Statistical analysis

Median and interquartile ranges (IQR) as well as frequencies and proportions were reported for continuous and

categorical variables, respectively. Seven separate sets of multivariable linear, logistic and Cox regression models were fitted to assess the relationship between challenging scenarios (i.e., PV, BML, prior BPH surgery) and operative time, intraoperative blood loss, length of hospitalization, time to bladder catheter removal, PSMs, at least one postoperative CD ≥ 2 and UC recovery. Adjustment variables were selected a priori. In multivariable models testing for perioperative outcomes, adjustment variables consisted of BMI, ISUP grade group at biopsy (1–3 vs 4–5), clinical T stage (≤ T2 vs. ≥ T3), previous abdominal surgery and surgical experience (SE). SE was coded as the number of prior RS-RARP performed by each surgeon at the time of the index patient's operation, as previously done [19, 20]. In multivariable models predicting PSMs, adjustment variables consisted of ISUP grade group at biopsy, clinical T stage, nerve sparing technique (non-nerve sparing vs. full or partial nerve sparing) and SE. In multivariable models testing for CD ≥ 2, adjustment variables consisted of Charlson comorbidity index (CCI) and SE. In multivariable models predicting UC recovery, covariates of interest were age at surgery, nerve sparing technique, CCI and SE. For all statistical analyses, R software environment for statistical computing and graphics (version 3.6.3) was used. All tests were two-sided with a level of significance set at $p < 0.05$.

Results

Descriptive characteristics of the study population

Table 1 resumes the characteristics of the entire population. Median age and BMI were 66 years (IQR: 61–71) and 26 kg/mq (IQR: 24–28), respectively. Fifty percent of the patients had a CCI of 2. Overall, 121 (37.8%) and 18 patients (5.6%) had a history of previous abdominal surgery and previous surgery for BPH (TURP for all cases) respectively. Median PSA at RS-RARP was 8.8 ng/ml (IQR 6.2–20). Overall, 99 patients (30.9%) had ≥ clinical T3 disease and 204 patients (63.8%) ISUP grade ≥ 4 at prostate biopsy.

Intra-, peri- and post-operative outcomes

Median operative time and estimated blood loss were 200 min (IQR: 145–240) and 200 ml (IQR: 100–300), respectively (Table 1). A full nerve sparing was performed in 78 patients (24.4%). Nineteen patients (5.9%) harbored BML and the median prostate volume was 45 g (range 14–300). The median hospital stay and time to bladder catheter removal were 3 days (IQR 2–4) and 7 days (IQR 7–8), respectively. Supplementary Table 2a–b reported perioperative outcomes of patients with history of BPH surgery and with BML.

Table 1 Demographic, clinical and pathological characteristics of 320 high-risk prostate cancer patients treated with Retzius-sparing approach at a single European high-volume center

Pre-operative variables	Population, *n*	320
	Age, years, median (IQR)	66 (61–71)
	BMI, kg/mq, median (IQR)	26 (24–28)
	Charlson comorbidity index, *n* (%)	
	0–1	56 (17.5)
	2	161 (50.3)
	3	103(32.2)
	Previous abdominal surgery, *n* (%)	121 (37.8)
	Previous surgery for BPH, *n* (%)	18 (5.6)
	PSA at RS-RARP, ng/ml, median (IQR)	8.8 (6.2–20)
	Clinical tumor stage, *n* (%)	
	≤ cT2a	67 (20.9)
	cT2b	95 (29.7)
	cT2c	59 (18.5)
	≥ cT3	99 (30.9)
	ISUP grade group at prostate biopsy, *n* (%)	
	1	39 (12.2)
	2	37 (11.6)
	3	40 (12.5)
	4	158 (49.4)
	5	46 (14.3)
Intra- and peri-operative variables	Operative time, mins, median (IQR)	200 (145–240)
	Bulky Median Lobe, *n* (%)	19 (5.9)
	Bladder neck preservation, *n* (%)	
	Full preservation	279 (87.2)
	Partial preservation	36 (11.3)
	Wide dissection	5 (1.5)
	Nerve sparing technique, *n* (%)	
	Full NS	78 (24.4)
	Partial NS	44 (13.8)
	Non-NS	198 (61.8)
	Lymph node dissection, *n* (%)	
	Extended*	308 (96.2)
	Super-extended*	12 (3.8)
	Estimated blood loss, ml, median (IQR)	200 (100–300)
	Hospital stay, days, median (IQR)	3 (2–4)
	Catheter removal, days, median (IQR; range)	7 (7–8; 3–34)
	Pathological tumor stage, *n* (%)	
	pT2	143 (44.7)
	pT3a	101 (31.6)
	≥ pT3b	76 (23.7)
	Pathological ISUP grade group, *n* (%)	
	1	21 (6.6)

Table 1 (continued)

Pre-operative variables	Population, *n*	320
	2	62 (19.4)
	3	77 (24.1)
	4	94 (29.4)
	5	66 (20.5)
	Surgical margins, *n* (%)	
	Negative margins	236 (73.8)
	Overall positive margins	84 (26.2)
	Focal	27 (8.4)
	Extended	57 (17.8)
	Total lymph nodes removed, median (IQR)	20 (16–25)
	Pathological nodal stage, *n* (%)	
	pN0	268 (83.8)
	pN1	52 (16.2)
	Prostate volume, ml, median (range)	45 (14–300)
	Follow-up, months, median (IQR)	47 (24–70)

BMI body mass index, *BPH* benign prostate hyperplasia, *PSA* prostate-specific antigen, *ISUP* international society of urological pathology, *RS-RARP* Retzius-sparing robot-assisted radical prostatectomy

*Pelvic lymph node dissection templates were defined as follows: extended = obturator, external, and internal iliac lymph nodes; super-extended = obturator, presacral, external, internal, and common lymph nodes

At multivariable linear regression analysis, PV ($p = 0.03$) and previous BPH surgery (estimate 43.4, $p = 0.02$) were independent predictors of operative time (Table 2). BML was the only independent predictor of time to bladder catheter removal (estimate 1.7, $p = 0.001$), after accounting for multiple confounders (Table 2). Conversely, PV, BML and prior BPH surgery were not associated with neither blood loss nor length of stay (all $p \geq 0.4$; Table 2).

The final pathology revealed pathological ≥ T3b disease in 76 patients (23.7%), pathological ≥ ISUP grade 4–5 in 160 patients (50%) and PSM rate of 26.2% (Table 1). PSMs were focal in 27 patients (8.4%) and extended in 57 patients (17.8%). Supplementary Table 2a–b reported the pathology of patients with history of BPH surgery and with BML.

At multivariable logistic regression model predicting PSMs, PV reached the independent predictor status (OR: 1.02; $p = 0.009$, Table 3). Conversely, BML and prior BPH surgery did not predict higher PSMs (all $p \geq 0.1$). Overall, 52 90-day postoperative complications occurred in 44 patients (44/320 = 14%; Supplementary Table 1b). Eleven percent had at least one postoperative CD ≥ 2. At multivariable logistic regression model predicting 90-day CD ≥ 2, PV, BML and previous BPH surgery did not reach the independent predictor status (all $p \geq 0.2$; Table 3).

Overall, 53% of patients had immediate UC recovery at bladder catheter removal. The 1- and 2-yr UC recovery was 84 and 85%, respectively. UC recovery rates at bladder catheter removal, at 1 and at 2 yr from surgery for patients with BML and prior BPH surgery were displayed by Supplementary Table 2a–b. At multivariable Cox regression model, previous BPH surgery was significantly associated with urinary continence recovery (HR: 0.5; $p = 0.03$; Table 4).

Discussion

Several commendable retrospective series [21–28] corroborated by four systematic reviews of the literature [3–5, 28] provided evidence that RS-RARP is technically reproducible and oncologically safe, with a special mention to its extraordinary functional outcomes (i.e., immediate UC recovery) [29]. Under this light, since 2020, the European Association of Urology (EAU) guidelines have included RS-RARP as treatment surgical option for PCa patients [1]. Nevertheless, none of the available evidence evaluated the potential detrimental effect of previous surgery for BPH, enlarged prostate and BML on perioperative, intermediate-term oncological and functional outcomes in the specific setting of high-risk PCa patients. Relying on a large series of high-risk PCa patients treated at a single high-volume center, we hypothesized that high-risk PCa patients with one of the aforementioned challenging features have worse perioperative

Table 2 Multivariable linear regression models predicting operative time, blood loss, length of stay and time to catheter removal in 320 prostate cancer patients treated with Retzius-sparing robot-assisted radical prostatectomy between 2011 and 2020 at a single high-volume center

	Operative time		Intraoperative Blood loss		Length of stay		Time to catheter removal	
	Estimate (95%CI)	*p*-value	Estimate (95%CI)	*p*-value	Estimate (95%CI)	*p*-value	Estimate (95%CI)	*p*-value
Prostate volume	–	0.03	–	0.8	–	0.7	–	0.9
Bulky median lobe	−18.5 (−54 to 17)	0.3	24 (−40 to 80)	0.5	− 0.3 (−1.09 to 1.02)	0.9	1.7 (1–3)	0.001
Previous BPH surgery	43.4 (5.9–80)	0.02	−10 (−89 to 99)	0.8	−0.47 (− 1.6 to 0.6)	0.4	−0.1 (−1.3 to 1.1)	0.5

All models were adjusted for BMI, ISUP grade group at biopsy (1–3 vs 4–5), clinical T stage (≤T2 vs. T3), previous abdominal surgery and surgical experience

Table 3 Multivariable logistic regression models predicting positive surgical margins and 90-day Clavien–Dindo ≥ 2 in 320 prostate cancer patients treated with Retzius-sparing robot-assisted radical prostatectomy between 2011 and 2020 at a single high-volume center

	Positive surgical margins		Clavien–Dindo ≥ 2	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Prostate volume	1.02 (1.01–1.03)	0.009	0.98 (0.96–1.01)	0.2
Bulky median lobe	4.2 (0.9–10.6)	0.1	2.02 (0.7–5.5)	0.2
Previous BPH surgery	1.4 (0.5–4.8)	0.5	0.3 (0.02–1.9)	0.3
ISUP grade group at biopsy				
1–3	Ref	–	–	–
4–5	2.4 (1.4–4)	0.002		
Clinical T stage				
≤ T2	Ref	–	–	–
≥ T3	0.7 (0.4–1.3)	0.3		
Nerve sparing				
No nerve sparing	Ref	–	–	–
Full or partial nerve sparing	1.9 (1.1–3.5)	0.01		
Charlson Comorbidity Index	Ref	–	–	–
Surgical experience	1.01 (0.9–1.02)	0.6	0.97 (0.96–0.99)	0.04

Table 4 Multivariable Cox regression models predicting urinary continence recovery in 320 prostate cancer patients treated with Retzius-sparing robot-assisted radical prostatectomy between 2011 and 2020 at a single high-volume center

	HR (95% CI)	*p*-value
Prostate volume	0.9 (0.8–1.1)	0.3
Bulky median lobe	1.1 (0.6–1.9)	0.6
Previous BPH surgery	0.5 (0.3–0.8)	0.03
Age at surgery	0.8 (0.7–0.9)	0.02
Nerve sparing		
No nerve sparing	Ref	–
Full or partial nerve sparing	1.2 (1.01–1.5)	0.04
Charlson Comorbidity Index	0.7 (0.4–1.1)	0.2
Surgical experience	0.9 (0.9–1.2)	0.5

outcomes. Our findings partially confirmed our hypothesis, and several noteworthy observations are highlighted.

First, when the relationship between PV, BML, prior BPH surgery and perioperative outcomes was assessed, we observed that higher PV and previous BPH surgery significantly influenced operative time while blood loss and hospitalization did not suffer from any deviation from the usual ranges. As foreseeable, BML significantly increased the time to bladder catheter removal.

Second, we demonstrated that in terms of oncological safety, patients with enlarged prostate have significantly higher risk of PSMs (OR 1.02; $p = 0.009$), even if the clinical significance might be scarce. Conversely, neither BML nor previous BPH surgery may affect the reliability of RS-RARP in terms of PSMs. Noteworthy, we failed to observe a relationship between SE and PSMs, suggesting that the learning process might be longer than expected [30] also in expert hands, as demonstrated in other settings [20]. Nevertheless, the rate of PSMs observed in the current report, is in line with those reported for high-risk PCa patients treated with anterior approach [31, 32]. Our results are in contrast with previous findings that provided evidence that larger prostates were not significantly associated with higher risk of PSMs in PCa patients treated with RS-RARP [7]. However, the authors mainly relied on low- and intermediate-risk PCa patients [7]. Our findings should not rule out the need for surgical approach (i.e., RS-RARP) in high-risk PCa patients with enlarged prostate, given the excellent results in terms of functional outcomes (i.e., 1- and 2-yr UC recovery was 84 and 85%). The implementation of new imaging technologies for image-guided surgery on daily clinical practice that allow real-time understanding of surgical anatomy, might help to reduce the rate of PSMs especially in high-risk PCa patients with enlarged prostate treated with RS-RARP [33].

Third, when considering 90-d complications, we failed to observe an association with an increased risk of CD ≥ 2 for all three challenging scenarios (i.e., PV, BML, prior BPH surgery). Of note, SE is crucial to reduce the risk of CD ≥ 2 (OR 0.97, p value 0.04). The reliability of our findings is strengthened by the standardized methodology used to collect postoperative complications [14]. Although authors are still reluctant to use the mentioned methodology [17, 18], evidence suggested that its implementation is key to increase the complications rate detected relative to a collection system based on patient chart review and allowed to identify complications after discharge that would have been missed otherwise [16]. As consequence, our analysis represents the strongest study in terms of quality of complications report after RS-RARP.

Fourth, when functional outcomes were assessed, we observed that high-risk PCa patients who underwent previous BPH surgery have a consistently lower probability

of UC recovery, after accounting for multiple confounders ($p = 0.03$). This might be explained by the presence of sticky tissue and less definable planes that made the surgery trickier. Conversely, enlarged prostate and BML did not impact on UC recovery. These findings are crucial to improve patient counseling, minimizing the regret and maximizing the satisfaction.

Unfortunately, our findings cannot be compared with other studies being the first to assess the relationship between previous surgery for BPH, enlarged prostate and BML and perioperative, intermediate-term oncological and functional outcomes in the specific setting of high-risk PCa patients.

Finally, our study is not devoid of limitations. This surgery is high-skill demanding and maybe not reproducible in centers without a consistent caseload and experience with the technique or for surgeons still in their learning process. The study is based on a retrospective analysis with all its inherent limitations, among whom the possibility of recall bias, considered the large span of time covered by our observations. Multi-centric studies relying on larger series are warranted, eventually comparing similar scenarios faced by different approaches.

Conclusion

In our RS-RARP series, high-risk PCa patients with enlarged prostate have higher risk of PSMs, while patients with prior BPH surgery have suboptimal UC recovery. These findings should help physicians for accurate preoperative counseling and to improve surgical planning (i.e., wider surgical resection) in case of high-risk PCa patients with enlarged prostates.

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Author contributions Tappero: Project development, Data analysis, Manuscript writing. Dell'Oglio: Project development, Data analysis, Manuscript writing. Longoni: Data collection, Data analysis. Buratto: Data collection. Palagonia: Data collection, Data analysis. Scilipoti: Data collection. Vecchio: Data collection. Martiriggiano: Data collection. Secco: Project development, Data analysis. Olivero: Project development, Data analysis. Barbieri: Data collection. Napoli: Data collection. Strada: Data collection. Petralia: Critical revision of the manuscript, Important intellectual content. Di Trapani: Critical revision of the manuscript, Important intellectual content. Bocciardi: Project development, Critical revision of the manuscript, Important intellectual content, Supervision. Galfano: Project development, Manuscript writing, Supervision.

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Declarations

Conflict of interest The authors declare that there is no conflict of interests.

Ethics consent statement Due to the anonymously coded design of the employed database, study-specific Institutional Review Board ethics approval was not required.

Patient consent statement, permission to reproduce material from other sources and clinical trial registration Not applicable.

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