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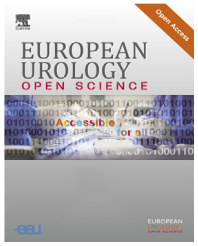

European Association of Urology

Surgery in Motion: Open Science

Retzius-sparing Robot-assisted Radical Prostatectomy in High-risk Prostate Cancer Patients: Results from a Large Single-institution Series

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Abstract

Background: Retzius-sparing (RS) robot-assisted radical prostatectomy represents a valid surgical treatment option for prostate cancer (PCa) patients. However, the available evidence on the role of RS in high-risk (HR) PCa setting is sparse.
Objective: To describe our RS technique for HR-PCa patients and to evaluate intra-, peri-, and postoperative oncological and functional outcomes.
Design, setting, and participants: A total of 340 D'Amico HR-PCa patients underwent RS at a single high-volume centre between 2011 and 2020.
Surgical procedure: Surgical procedures were performed by five experienced robotic surgeons.
Measurements: Complications were collected according to the standardised methodology proposed by the European Association of Urology guidelines. Postoperative outcomes were evaluated in patients with complete follow-up data (n = 320). Biochemical recurrence (BCR) was defined as two consecutive prostate-specific antigen values of $\geq$0.2 ng/ml. Urinary continence (UC) recovery was defined as the use of zero or one safety pad. Kaplan-Meier and multivariable logistic and Cox regression models were performed.
Results and limitations: Fourteen patients (4%) experienced intraoperative complications and 52 90-d complications occurred in 44 patients (14%), of whom 24 had

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Clavien-Dindo 3a/b. Final pathology reported 49% International Society of Urological Pathology (ISUP) grade 4–5, 55% ≥pT3a, and 28.8% positive surgical margins (PSMs; 9.4% focal and 19.4% extended PSMs). The median follow-up was 47 mo. Overall, 35.3% and 1.3% harboured BCR and died from PCa. At 4 yr of follow-up, BCR-free survival and additional treatment-free survival were 63.6% and 56.6%, respectively. ISUP 4–5 at biopsy (odds ratio [OR]: 2.6), prostate volume (OR: 1.03), partial or full nerve sparing (OR: 1.9), and full bladder neck preservation (OR: 2.2) were independent predictors of PSMs. Pathological ISUP 4–5 (hazard ratio [HR]: 1.5) and PSMs (HR: 2.3) were independent predictors of BCR. Pathological ISUP 4–5 (HR: 1.5), PSMs (HR: 2.4), pT ≥3b (HR: 1.8), and pN ≥1 (HR: 1.8) were independent predictors of additional treatment. Immediate UC recovery was recorded in 53% patients. The 1- and 2-yr UC recovery and erectile function recovery were, respectively, 84% and 85%, and 43% and 50%.

Conclusions: RS in HR-PCa patients allows optimal intra-, peri-, and postoperative outcomes. The RS approach should be considered a valid surgical treatment option for HR-PCa patients in expert hands.

Patient summary: Relying on the largest cohort of high-risk prostate cancer patients treated with Retzius sparing (RS), we observed that the RS approach is safe and allows optimal cancer control, without significantly compromising functional outcomes.

1. Introduction

High-risk prostate cancer (PCa) is burdened by an increased risk of prostate-specific antigen (PSA) failure, need for secondary therapy, metastatic progression, and death from PCa [1,2]. According to the European Association of Urology (EAU) guidelines, radical prostatectomy with extended pelvic lymph node dissection is a reasonable option in selected high-risk PCa patients, as part of potential multimodal therapy [1]. Among different surgical approaches, Retzius-sparing robot-assisted radical prostatectomy (RS-RARP) has been considered a valid surgical treatment option for PCa patients [1,3–7]. However, differently from the anterior robot-assisted radical prostatectomy (RARP) and retropubic open prostatectomy, clinicians are sceptic regarding a possible role of the posterior approach (ie, RS-RARP) in the high-risk PCa setting, given the lack of high-level evidence on this subset of patients and a concern that RS-RARP may confer an increased positive surgical margin (PSM) rate [1,6]. The majority of the available studies on RS-RARP focused exclusively on low- and intermediate-risk PCa [1,3,4,6,8–10]. High-risk PCa patients are generally under-represented, and their oncological and functional outcomes are generally clustered with those with less aggressive disease [7,11–14]. To date, only one study [15] exclusively relied on a cohort of high-risk PCa patients and only two [16,17] performed subanalyses in this subset of patients treated with the RS-RARP approach. However, these reports are limited by the small sample size, short follow-up, and absence of a standardised methodology to report complications [18,19]. Therefore, the safety profile of RS-RARP in high-risk PCa patients in terms of oncological and functional outcomes, and postoperative complications have not been explored deeply. To overcome these issues, we relied on the largest series of high-risk PCa patients treated with RS-RARP at a single high-volume centre, to illustrate the step-by-step surgical technique and report perioperative, intermediate-term oncological and functional outcomes.

2. Patients and methods

2.1. Study population

The current study is a retrospective, single-centre, multiple-surgeon, case-series analysis that relied on the database that collected data on 1906 consecutive PCa patients treated with RS-RARP at a single high-volume European centre (ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy) between January 2011 and December 2020. For the purpose of our study, we exclusively focused on D'Amico high-risk PCa patients (clinical stage ≥T2c, biopsy Gleason scores 8–10, or PSA levels >20 ng/ml) [20] treated with RS-RARP and pelvic lymph node dissection (PLND). Overall, 340 high-risk PCa patients were identified. All patients had complete intra- and perioperative data. All patients underwent preoperative computed tomography (CT) and bone scan [1]. Overall, 143 (42.1%) patients underwent preoperative multiparametric magnetic resonance imaging (mpMRI).

Analyses on postoperative outcomes were performed only in patients with available follow-up data (n = 320). All specimens were assessed by three dedicated uropathologists. The study protocol was approved by the institutions' medical ethics committees, and all patients provided informed consent.

2.2. Surgical technique

All RS-RARP procedures were performed with a four-arm da Vinci Si Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) with a transperitoneal approach by five experienced robotic surgeons, who had previously performed at least 50 RS-RARP in low- and intermediate-risk PCa patients. Patients were placed in the 30° Trendelenburg position. Six laparoscopic trocars were inserted, as described previously

(Supplementary Fig. 1) [10]. Specifically, a right periumbilical incision for the camera port was performed and the pneumoperitoneum was induced by the Veress needle until 15 mmHg CO_2. The 12-mm camera port (port 1, C) was placed. The 8-mm trocar for the right robotic arm (port 2, R) was placed 10 cm lateral and 1 cm caudal to the first port. The 8-mm trocar for the left robotic arm (port 3, ML) was positioned 8 cm lateral and 3 cm cranial to the camera port, whereas the 8-mm trocar for the other left robotic arm (port 4, LL) was placed 4 cm cranial and 2 cm medial to the left iliac crest. A first 5-mm assistant port (port 5, A1) was placed between ports 1 and 2 and 3 cm cranially, and a second 12-mm assistant port (port 6, A2) was placed 5–6 cm cranial to the right iliac crest and 3 cm lateral to port 2. Thereafter, the da Vinci SI robot was docked with a 30° downward lens, and monopolar curved scissors (port 2), a Cadiere forceps (port 3), and a Maryland bipolar forceps (port 4) were used. A needle driver was used from port 2 during the vesicourethral anastomosis. If necessary, a 15-cm 2.0 Prolene Ethicon straight needle (Pansadoro's stitch) was placed on the epiploic appendices from the 5-mm assistant trocar, in order to straighten the rectum and increase the surgical field. The peritoneum is lifted up with the Cadiere forceps and a 10-cm incision of the parietal peritoneum at the anterior surface of the Douglas pouch was performed (Fig. 1A). The vasa deferentia were isolated, dissected, and pulled towards the midline with the Maryland bipolar forceps in order to expose and isolate the seminal vesicles. Differently from RS-RARP for low- and intermediate-risk PCa, parts of the Denonvillier's fascia (DVF) and of the perirectal fat are left attached to the seminal vesicles. Two transabdominal suprapubic stitches placed by the assistant were used to lift and support the bladder and retract the seminal vesicles (Fig. 1B). The vasa deferentia were lifted upwards by the Cadiere forceps. With a 30° upward lens, the DVF was incised starting from an extrafascial layer. The subsequent dissection plane was decided based on the combination of digital rectal examination, preoperative PSA, preoperative mpMRI, and biopsy International Society of Urological Pathology (ISUP) grade group. In case of organ-confined disease on the posterior surface of the prostate, after incision of the DVF, we can approximate to the prostatic capsule in order to reach an intra/interfascial plane. In case of non–organ-confined disease localised on the posterior surface of the prostate, the DVF is pushed upwards with the posterior surface of the prostate. In more advanced cases, the surgeon might choose to push not only the DVF, but also part of the perirectal fat upwards with the specimen. The dissection was carried out forward to the prostatic apex. Once the posterior aspect of the prostate was isolated, an extrafascial plane was developed ipsilateral to the tumour, by placing the Maryland bipolar forceps laterally to the prostate in order to identify the levator ani fascia (Fig. 1C). Hem-o-lok clips were placed on the prostatic pedicles, and a wide dissection was carried out forward to the prostatic apex maintaining an extrafascial plane. According to the extension of the disease, unilateral or bilateral extrafascial dissection was performed. Specifically, in case of unilateral disease, a unilateral intra/interfascial nerve sparing was performed in a standard fashion on the side without tumour burden, as described previously [10]. A full nerve-sparing preservation [21] was attempted in case of unilateral ≤T2 disease with a low-grade tumour at biopsy or in case of an anterior tumour at mpMRI.

The prostate was pushed downwards by the Cadiere forceps and the vesicoprostatic junction was identified. The bladder neck was approached starting from its dorsal surface, where a layer represented by the vesicoprostatic muscle covers the circular muscle fibres of the bladder. These fibres were bluntly dissected/incised laterally towards the apex of the prostate as far as possible (Fig. 1D) before bladder neck incision. During this step, it is crucial to push the bladder upwards with the Maryland in order to better identify the vesicoprostatic junction. Complete bladder neck preservation was generally attempted except in case of an anterior tumour and/or median lobe and/or enlarged prostate volume. In case of small bladder neck, two quickly absorbable sutures (Vycril rapide 3-0) can be placed at 6 and 12 o'clock in the bladder neck, in order to fix the mucosa and easily identify the bladder neck orifice during the vesicourethral anastomosis. The anterior surface of the prostate was bluntly isolated from the Santorini plexus whenever oncologically safe. In case of an anterior tumour, the Santorini plexus can be resected partially or completely. A sharp and blunt apical dissection of the prostate was performed, ventrally and laterally, to improve visualisation of the apical borders and avoid entering into the prostate. The apex of the prostate was isolated from the urethra, and the latter was incised carefully (Fig. 1E). Thereafter, a standard Van Velthoven vesicourethral anastomosis was performed [20]. Two separate 15-cm barbed sutures (V-loc 3-0) were used starting from 12 o'clock up to the left anterior quarter (Fig. 1F). Then the right half circle of the suture was carried out up to 6 o'clock, and the posterior left quarter was then completed from 9 to 6 o'clock. In case of wide bladder neck, 23-cm V-loc may be used. The bladder was filled with 120 ml sterile saline solution to perform the leak test for the vesicourethral anastomosis. The transurethral catheter was removed, and a suprapubic tube was inserted under direct vision. In case of bladder cancer history or very wide bladder neck, the transurethral catheter is maintained and the suprapubic tube is not placed. Finally, an extended or superextended PLND was performed based on clinician preference [1]. A unique QR code was generated and linked to the high-resolution video clip.

2.3. Outcomes

Our primary goal was to substantiate the technical reproducibility and safety profile of RS-RARP in the specific setting of high-risk PCa patients. Specifically, we focused on the following:

(1) Oncological outcomes as PSMs, biochemical recurrence (BCR), and need for additional treatments after RS-RARP. A PSM was defined as the presence of inked cells at the edge of the surgical specimen [1]. PSMs were characterised as focally positive (≤1 mm in length) or extensively positive (>1 mm in length) [22]. During follow-up after surgery, serum PSA measurement was tested at 3, 6, and 12 mo, then every 6 mo for 3 yr, and then annually [1]. BCR was defined as two consecutive PSA values of ≥0.2 ng/ml [1]. Additional treatment use was defined as any administration of radiotherapy or hormonal therapy in the adjuvant or salvage setting after RS-RARP, according to the clinical judgement of each treating physician and after discussion with the patient regarding the benefits and possible side effects. The cause of death was defined by the attending urologist or oncologist who followed the patients and/or death certificate.

(2) Intraoperative and 90-d postoperative complications. Intraoperative complications were categorised according to the Intraoperative Adverse Incident Classification (EAUiaiC) proposed by the European Association of Urology ad hoc Complications Guidelines Panel [19]. Postoperative complications were collected based on patient chart review done by a dedicated data manager and were graded according to the Clavien-Dindo classification system [23]. From July 2020 to January 2021, a retrospective collection system for 90-d postoperative complications was performed based on patient interview done by four medical doctors who were not involved in the treatment. The quality criteria for accurate and comprehensive reporting of surgical outcomes recommended by the EAU guidelines on reporting and grading of complications were fulfilled (Supplementary Table 1) [18].

As secondary endpoints, functional outcomes were evaluated: immediate continence recovery was defined as the use of zero or one safety pad per day at transurethral/suprapubic catheter removal. All patients

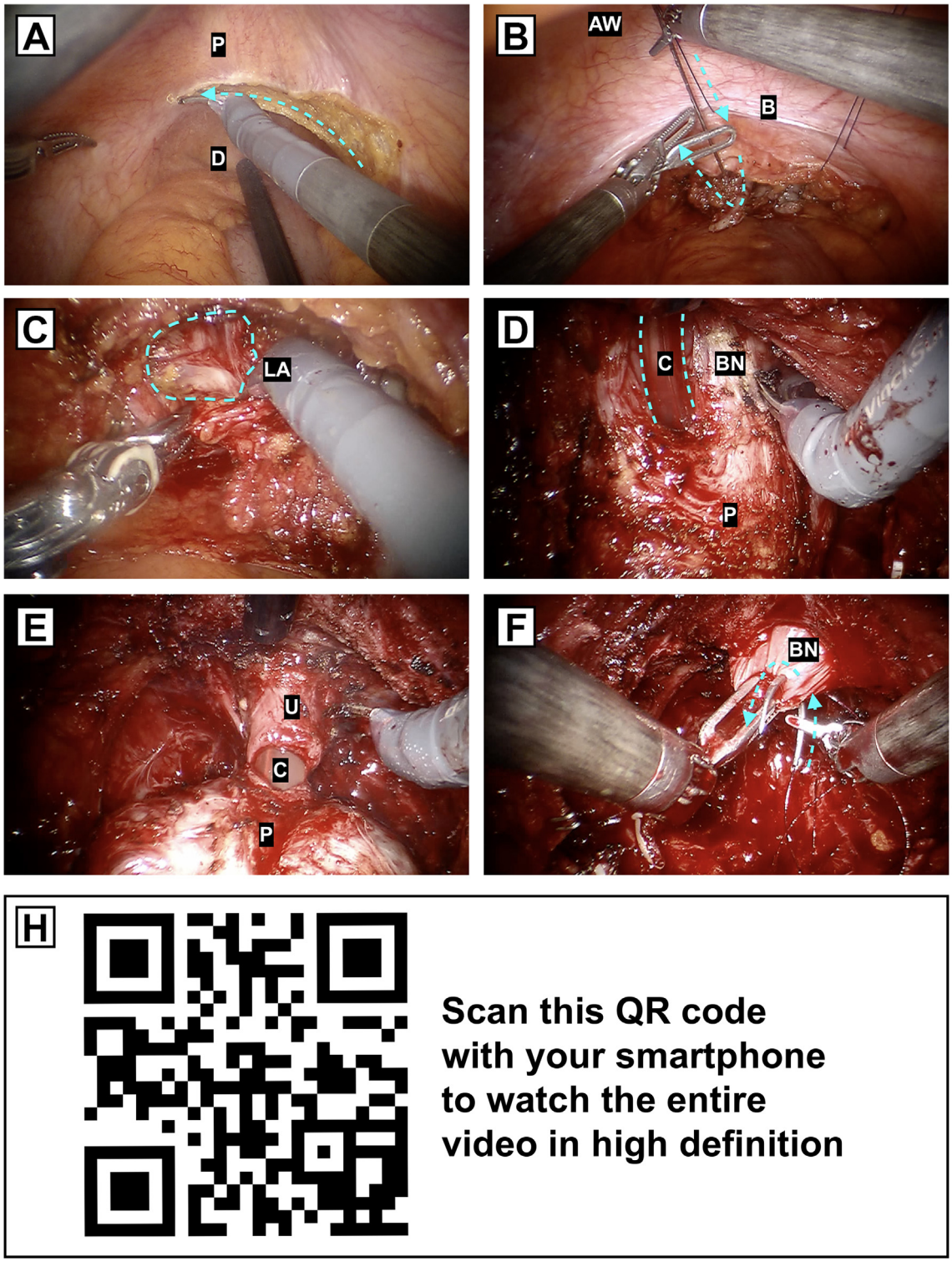

Fig. 1 – Surgical procedure: (A) peritoneal incision; (B) bladder suspension; (C) identification of levator ani fascia; (D) opening of the bladder neck; (E) incision of the urethra; and (F) vesicourethral anastomosis (first step). B = bladder; BN = bladder neck; C = catheter; D = Douglas pouch; LA = levator ani fascia; P = prostate; U = urethra.

with a transurethral catheter undergo cystogram before catheter removal. Urinary continence (UC) recovery was defined as the use of zero or one safety pad per day at the last follow-up. Recovery of sexual function (SF) was assessed in preoperatively potent men who underwent full or partial nerve sparing with complete follow-up data (n = 111) and was defined as satisfactory erections for sexual intercourse (defined as erections hard enough for penetration more than half the time) with and without the use of phosphodiesterase-5 inhibitors or intracavernosal injections postoperatively. Continence and SF recovery were 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. Follow-up phone calls were also performed by four medical doctors who were not involved in the treatment.

2.4. Statistical analyses

Statistical analyses consisted of four analytical steps. First, medians and interquartile ranges (IQRs) as well as frequencies and proportions were reported for continuous and categorical variables, respectively. Second, Kaplan-Meier analyses were used to calculate the probability of freedom from BCR and additional treatment use and their corresponding 95% confidence interval (CI). Patients without records of BCR were censored on the date of the last time they were known to be free of BCR, in accordance with the guidelines for reporting statistics [24]. In BCR analysis, adjuvant therapies were censored as an event.

Third, three separate sets of multivariable logistic and Cox regression models were fitted to evaluate the predictors of PSMs, BCR, and additional treatment use. In the multivariable logistic regression model testing for PSMs, adjustment variables were selected a priori and consisted of PSA, prostate volume, ISUP grade group at biopsy, clinical tumour stage cT, nerve-sparing technique, and bladder neck preservation. The adjustment for case-mix in multivariable Cox regression models testing for BCR and additional treatment use included the following variables that were selected a priori: pathological tumour stage, pathological ISUP grade group, PSMs, and pathological nodal stage pN, along with adjuvant treatment for BCR. Finally, we estimated UC and SF recovery using the Kaplan-Meier method. 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 $p < 0.05$.

3. Results

3.1. Preoperative characteristics

Table 1 summarises the descriptive characteristics of our cohort. The median age and body mass index were, respectively, 67 yr (IQR: 62–71) and 26 kg/m^2 (IQR: 24–28). Of the patients, 50% had a Charlson comorbidity index of 2. The median PSA was 9 ng/ml (IQR: 6.3–20). Overall, 106 (31.2%), 165 (48.5%), and 54 (15.8%) patients harboured clinical ≥T3 disease, biopsy ISUP grade group 4, and biopsy ISUP grade group 5, respectively.

3.2. Intra-/perioperative characteristics and cancer control outcomes

The median operative time and estimated blood loss were 200 min (IQR: 141–240) and 200 ml (IQR: 100–300), respectively. Overall, 294 (86.5%) and 131 (38.5%) patients underwent, respectively, full bladder neck preservation and partial or full nerve sparing (Table 1 and Supplementary Table 2). All patients received PLND (95.9% extended vs 4.1% superextended). Two patients (0.6%) received intraoperative transfusion. The median hospital stay and catheter removal were 3 d (IQR: 2–4) and 7 d (IQR: 7–8), respectively.

Pathological T stages were T3a and ≥pT3b in, respectively, 107 (31.5%) and 81 (23.8%) patients. Pathological ISUP grade groups were 4 and 5 in 99 (29.1%) and 69 (20.3%) patients, respectively.

PSMs were noted in 98 (28.8%) patients (9.4% focal vs 19.4% extended PSMs), and 16.7% of patients had nodal disease. At a multivariable logistic regression analysis, prostate volume (odds ratio [OR]: 1.03, 95% CI: 1.01–1.04, $p = 0.001$), ISUP 4–5 grade group at prostate biopsy (OR: 2.6, 95% CI: 1.4–4.3, $p = 0.002$), partial or full nerve sparing (OR: 1.9,

Table 1 – Descriptive characteristics of 340 high-risk prostate cancer patients treated with a Retzius-sparing approach at a single European high-volume centre.

Preoperative variables (n = 340)	
Age (yr), median (IQR)	67 (62–71)
BMI (kg/m^2), median (IQR)	26 (24–28)
ASA score, *n* (%)	
1	79 (23.2)
2	136 (40)
3	109 (32.1)
4	16 (4.7)
5	0
Charlson comorbidity index, *n* (%)	
0–1	56 (16.5)
2	170 (50)
3	114 (33.5)
Previous abdominal surgery, *n* (%)	125 (36.8)
Previous surgery for BPH, *n* (%)	18 (5.3)
PSA at RS-RARP (ng/ml), median (IQR)	9 (6.3–20)
Clinical tumour stage, *n* (%)	
≤cT2a	72 (21.2)
cT2b	97 (28.5)
cT2c	65 (19.1)
≥cT3	106 (31.2)
ISUP grade group at prostate biopsy, *n* (%)	
1	40 (11.8)
2	39 (11.5)
3	42 (12.4)
4	165 (48.5)
5	54 (15.8)
Prostate volume (ml), median (IQR)	40 (30–50)
Intra- and perioperative variables (n = 340)	
Operative time (min), median (IQR)	200 (141–240)
Median lobe, *n* (%)	19 (5.6)
Bladder neck preservation, *n* (%)	
Full preservation	294 (86.5)
Partial preservation	40 (11.8)
Wide dissection	6 (1.7)
Nerve-sparing technique [a], *n* (%)	
Full NS	81 (23.8)
Partial NS	50 (14.7)
Non NS	209 (61.5)
Lymph node dissection [b], *n* (%)	
Extended	326 (95.9)
Superextended	14 (4.1)
Abdominal drain, *n* (%)	0
Urine drain, *n* (%)	
Urethral catheter	53 (15.6)
Suprapubic catheter	287 (84.4)
Estimated blood loss (ml), median (IQR)	200 (100–300)
Intraoperative transfusions, *n* (%)	2 (0.6)
Hospital stay (d), median (IQR)	3 (2–4)
Catheter removal (d), median (IQR)	7 (7–8)
Pathological tumour stage, *n* (%)	
pT2	152 (44.7)
pT3a	107 (31.5)
≥pT3b	81 (23.8)
Pathological ISUP grade group, *n* (%)	
1	23 (6.8)
2	67 (19.7)
3	82 (24.1)
4	99 (29.1)
5	69 (20.3)
Surgical margins, *n* (%)	
Negative margins	242 (71.2)
Overall positive margins	98 (28.8)
Focal	32 (9.4)
Extended	66 (19.4)
Total lymph nodes removed, median (IQR)	20 (16–25)
Pathological nodal stage, *n* (%)	
pN0	283 (83.3)
pN1	57 (16.7)
Postoperative variables (n = 320)	
Adjuvant therapy, *n* (%)	
Overall	89 (27.8)
ADT	18 (5.6)
RT	27 (8.4)

(*continued on next page*)

ADT + RT	44 (13.7)
Salvage therapy, *n* (%)	
Overall	83 (25.9%)
ADT	22 (6.9)
RT	35 (10.9)
ADT + RT	26 (8.1)
Follow-up (mo), median (IQR)	47 (24–70)

ADT = androgen deprivation therapy; ASA = American Society of Anesthesiologists; BMI = body mass index; BPH = benign prostate hyperplasia; IQR = interquartile range; ISUP = International Society of Urological Pathology; NS = nerve sparing; PSA = prostate-specific antigen; RS-RARP = Retzius-sparing robot-assisted radical prostatectomy; RT = radiation therapy.

[a] Nerve sparing was coded according to the recommendations of the Pasadena Consensus Panel [21].

[b] Pelvic lymph node dissection templates were defined as follows: extended = obturator, external, and internal iliac lymph nodes; superextended = obturator, presacral, external, internal, and common lymph nodes.

95% CI: 1.2–3.4, $p = 0.02$), and full bladder neck preservation (OR: 2.2, 95% CI: 1.1–4.5, $p = 0.03$) were independent predictors of PSMs (Table 2).

A total of 113 (35.3%) patients harboured BCR. The median (IQR) time to BCR was 15 (6–40) mo. The median (IQR) follow-up for patients who did not experience BCR was 47 (24–70) mo. The 4-yr probabilities of freedom from BCR and additional treatment were, respectively, 63.6% (95% CI: 58–70; Fig. 2A) and 56.6% (95% CI: 51–63; Fig. 2B). Overall, ten patients died during follow-up, four of them from PCa.

At multivariable Cox regression analysis predicting BCR, the pathological ISUP 4–5 grade group (hazard ratio [HR]: 1.5, 95% CI: 1.01–2.2, $p = 0.04$) and PSMs (HR: 2.3, 95% CI: 1.5–3.5, $p < 0.001$) reached the independent predictor status (Table 3). Pathological ISUP 4–5 grade group (HR: 1.5, 95% CI: 1.01–2, $p = 0.04$), PSMs (HR: 2.4, 95% CI: 1.7–3.4, $p < 0.001$), pT stage ≥3b (HR: 1.8, 95% CI: 1.2–2.7, $p = 0.002$), and pN stage 1 (HR: 1.8, 95% CI: 1.2–2.6, $p = 0.003$) were independent predictors of additional treatment after RS-RARP (Table 3).

Table 2 – Multivariable logistic regression model predicting positive surgical margins in 340 high-risk prostate cancer patients treated with a Retzius-sparing approach at a single European high-volume centre.

Variables	Positive surgical margins	
	OR (95% CI)	*p* value
PSA	0.99 (0.98–1.01)	0.6
Prostate volume	1.03 (1.01–1.04)	**0.001**
ISUP grade group at biopsy		
1–3	Ref.	
4–5	2.6 (1.4–4.3)	**0.002**
Clinical tumour stage		
≤cT2	Ref.	
≥cT3	0.7 (0.4–1.3)	0.3
Nerve-sparing technique		
Non-NS	Ref.	
Partial or full NS	1.9 (1.2–3.4)	**0.02**
Bladder neck preservation		
Wide dissection or partial preservation	Ref.	
Full preservation	2.2 (1.1–4.5)	**0.03**

CI = confidence interval; ISUP = International Society of Urological Pathology; NS = nerve sparing; OR = odds ratio; PSA = prostate-specific antigen; Ref. = reference.

3.3. Complications

A total of 14 intraoperative complications were reported in 14 patients (Table 4). Intraoperative complications were represented by injury of the epigastric artery during trocar positioning ($n = 6$), injury of the iliac vessels during PLND ($n = 3$), injury of the ureter during PLND ($n = 2$), complete dissection of the left obturator nerve ($n = 1$), and injury of the bladder nearby the right ureteral orifice that required double J stent positioning ($n = 1$) and below the bladder neck ($n = 1$).

Table 5 shows the 90-d postoperative complications. Overall, 52 postoperative complications occurred in 44 patients (44/320 = 14%). The overall rates of Clavien-Dindo I and II were 5.3% ($n = 17$) and 3.4% ($n = 11$), respectively. The most common Clavien-Dindo I and II were represented by prolonged catheterisation due to urethrovesical leakage ($n = 17$; 5.3%) and urinary tract infection requiring antibiotic therapy ($n = 7$; 2.2%). Twenty-two patients (6.9%) experienced Clavien-Dindo IIIa (19 lymphocele treated with percutaneous drainage and three acute urinary retention requiring bladder catheterisation). Two patients (0.6%) had Clavien-Dindo IIIb for reoperation to drain abdominal haematoma and revise the urethrovesical anastomosis ($n = 1$), and to remove a needle fragment in the pelvic area ($n = 1$). No perioperative deaths were reported.

3.4. Functional outcomes

Immediate UC recovery was observed in 53% (169/320) of patients. The 1- and 2-yr UC recovery were 84% (95% CI: 79–87) and 85% (95% CI: 81–89), respectively (Fig. 2C).

Among men who were preoperatively potent ($n = 252$) and underwent full or partial nerve sparing with complete follow-up data ($n = 111$), the 1- and 2-yr SF recovery were 43.1% (95% CI: 33–51) and 50% (95% CI: 39–58), respectively (Fig. 2D). Among those patients who had SF recovery during the study period, 53% used phospodiesterase-5 inhibitors, 4% used penile injection, and 43% had spontaneous erection.

4. Discussion

High-level evidence evaluating the role of RS-RARP in high-risk PCa patients is unavailable. Only few retrospective studies [15–17] attempted to circumvent this lack of data relying on a small sample size, short follow-up, and no standardised methodology to report complications according to the EAU guidelines [1,18,19]. Our objective was to evaluate whether the safety profile of RS-RARP observed in low- and intermediate-risk PCa [4–7] is also substantiated in the specific setting of high-risk disease. We described our surgical technique and presented the largest cohort of high-risk PCa patients treated with RS-RARP at a single high-volume centre.

First, our results demonstrated that RS-RARP is a safe approach in terms of oncological outcomes. Specifically, the rate of PSMs was 28.8% (9.4% focal vs 19.4% extended PSMs), which is in line with those reported by the largest available series on D'Amico high-risk PCa treated with anterior RARP at tertiary care referral centres (PSM rate range: 25.3–34.8%) [25]. Kumar et al [26] and Abdollah et al [27]

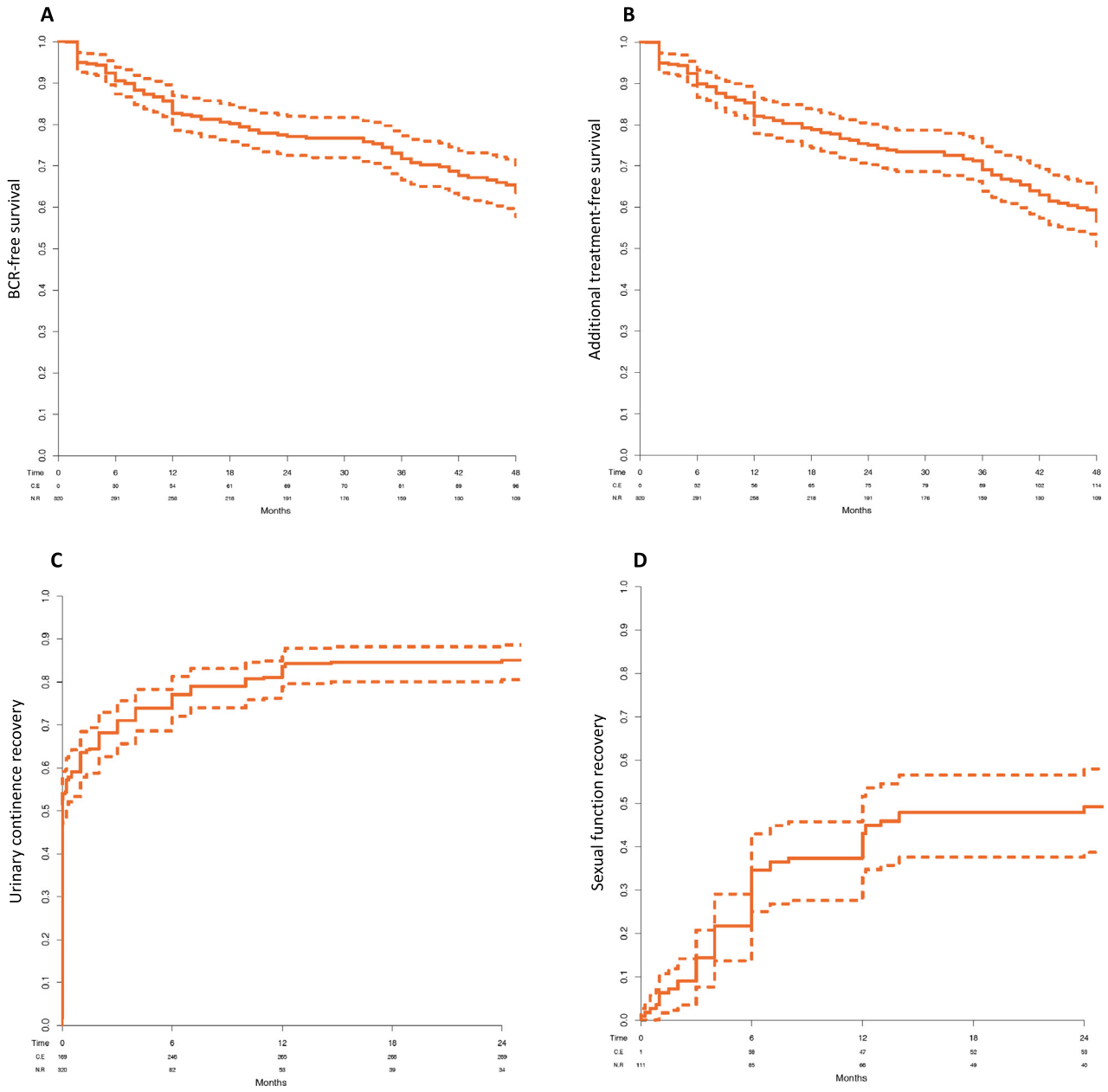

Fig. 2 – Kaplan-Meier plots depicting (A) biochemical recurrence-free survival, (B) additional treatment-free survival, (C) urinary continence recovery, and (D) sexual function recovery after Retzius-sparing robot-assisted radical prostatectomy in high-risk prostate cancer patients. BCR = biochemical recurrence.

analysed 557 and 868 high-risk PCa patients reporting 25.2% and 34% PSM rates, respectively. The rate of PSMs in the largest cohort of high-risk patients (n = 1110) treated with an anterior RARP approach is 34.8% [28]. Our PSMs are in line with those recently reported by Mazzone et al [29] who focused on more aggressive PCa patients (ie, preoperative posterior T3a and T3b at mpMRI) treated with an anterior approach at a single high-volume centre. In the current study, we also observed that patients with enlarged prostate and who harboured ISUP 4–5 grade group at biopsy had a higher risk of PSMs at final pathology. Noteworthy, patients who underwent full or partial nerve sparing and who received full bladder neck preservation had an approximately two-fold higher probability of harbouring PSMs at final pathology. The latter findings strongly suggest that surgeons performing RS-RARP should remain humble in front of high-risk PCa patients and improve surgical planning by performing wider surgical resection. When recurrence was evaluated, we observed that the 4-yr probability of freedom from BCR was 63.6%, in line with previous studies on high-risk PCa patients who underwent an anterior RARP approach [27,28]. Moreover, our analyses showed that high-grade disease and PSMs were independent predictors of inferior BCR and additional treatment after RS-RARP. Likewise, higher pathological stage and lymph node invasion were associated with an increased risk of additional treatment after RS-RARP. Knowledge of these factors may help clinicians improve patient counselling by adopting a risk-stratified approach. Moreover, these findings suggest that high-risk patients with negative surgical

Table 3 – Multivariable Cox regression models predicting biochemical recurrence in 320 high-risk prostate cancer patients treated with the Retzius-sparing approach at a single European high-volume centre.

Variables	Biochemical recurrence		Additional treatment use	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Pathological tumour stage				
≤pT3a	Ref.		Ref.	
≥T3b	1.3 (0.9–2.6)	0.1	1.8 (1.2–2.7)	**0.002**
Pathological ISUP grade group				
1–3	Ref.		Ref.	
4–5	1.5 (1.01–2.2)	**0.04**	1.5 (1.01–2)	**0.04**
Positive surgical margins				
No	Ref.		Ref.	
Yes	2.3 (1.5–3.5)	**<0.001**	2.4 (1.7–3.4)	**<0.001**
Pathological nodal stage				
pN0	Ref.		Ref.	
pN1	1.3 (0.7–2.5)	0.4	1.8 (1.2–2.6)	**0.003**
Adjuvant treatment				–
No	Ref.		–	
Yes	0.6 (0.4–1.3)	0.2		

CI = confidence interval; HR = hazard ratio; ISUP = International Society of Urological Pathology; Ref. = reference.

Table 4 – Summary of intraoperative complications in 340 patients with complete follow-up data treated with Retzius-sparing robot-assisted radical prostatectomy using the EAUiaiC.

Complication and procedure	*n*	%	MF (%)
Injury of the left external iliac vein during LND			
Grade 1	2	0.6	0.6
Injury of the left internal iliac artery during LND			
Grade 1	1	0.3	0.3
Injury of the epigastric artery during trocar positioning [a]			
Grade 0	5	1.5	1.8
Grade 1	1	0.3	
Partial injury of the right ureter during LND			
Grade 2	1	0.3	0.3
Partial injury of the left ureter during LND			
Grade 2	1	0.3	0.3
Complete dissection of the left obturator nerve			
Grade 2	1	0.3	0.3
Injury of the bladder nearby right ureteral orifice that required double J stent positioning			
Grade 2	1	0.3	0.3
Injury of the bladder below the bladder neck			
Grade 1	1	0.3	0.3

EAUiaiC = Intraoperative Adverse Incident Classification by the European Association of Urology ad hoc Complications Guidelines Panel; LND = lymph node dissection; MF = mode frequency.
[a] Grade 0: simple cautery of the vessel; grade 1: small widening of the cutaneous incision and sealing of the artery.

margins, low-grade disease, lower pathological stage, and no lymph node invasion might be optimal candidates for RS-RARP without the need of additional treatment at intermediate-term follow-up. Overall, our results on oncological outcomes overwhelmingly suggest that RS-RARP allows optimal cancer control in high-risk PCa patients and represents a valid alternative to the anterior RARP approach for surgical management of high-risk disease.

Second, the safety profile of RS-RARP in a high-risk setting was also provided by the acceptable rate of intra- and postoperative complications reported. Specifically, 14 intraoperative complications were reported in 14 patients (4%) and 52 postoperative complications occurred in 44 patients (14%), with 7.5% Clavien-Dindo ≥III. The perioperative complication rates found in the available non–population-based studies on high-risk PCa patients treated with an anterior RARP approach range from 4% to 14.3% [25], with the major complication rates ranging from 0.6% to 9.1%. These wide ranges might be explained by variations in recording and reporting of perioperative complication data. The robustness of our data is ensured by the fact that, differently from the aforementioned studies [25], we relied on the standardised methodology proposed by the EAU guidelines to collect postoperative complications [18], which was proved to

Table 5 – Summary of 90-d postoperative complications in 320 patients with complete follow-up data treated with Retzius-sparing robot-assisted radical prostatectomy.

Overall complications (*n* = 52 in 44 patients, 14%)			
Category	Type of complication	*n*	%
Clavien-Dindo I (*n* = 17, 5.3%)	Prolonged catheterisation due to urethrovesical leakage at cystogram	17	5.3
Clavien-Dindo II (*n* = 11, 3.4%)	Urinary tract infection requiring ABT	7	2.2
	Pulmonary thromboembolism	1	0.3
	Deep venous thrombosis	3	0.9
Clavien-Dindo IIIa (*n* = 22, 6.9%)	Lymphocele [a] treated with percutaneous drainage	19	5.9
	Acute urinary retention requiring bladder catheterisation	3	0.9
Clavien-Dindo IIIb (*n* = 2, 0.6%)	Abdominal haematoma treated with explorative laparotomy and revision of the urethrovesical anastomosis	1	0.3
	Videolaparoscopic removal of needle fragment in pelvic area	1	0.3

ABT = antibiotic therapy.
[a] Lymphocele was defined as any clearly definable fluid collection and was considered clinically significant when requiring treatment. Ultrasound examination was used to detect lymphoceles.

avoid missing critical information that could lead to an underestimation of perioperative complications [30–33].

Third, we demonstrated, for the first time ever, that functional outcomes of high-risk PCa patients treated with RS-RARP were not compromised significantly. Indeed, despite the wider excision of the tissue surrounding the prostate, optimal immediate UC recovery (ie, 53%) was recorded. The rate of immediate UC recovery observed is significantly higher than those available in the literature for an anterior RARP approach [34,35], suggesting that RS-RARP is associated with faster and higher UC recovery in the short term also in the high-risk PCa setting. When functional outcomes were evaluated in the longer term, the 1- and 2-yr UC recovery were 84% and 85%, and SF recovery were 43.1% and 50%, respectively. These rates are similar to those reported by the largest available series on high-risk PCa patients treated with an anterior RARP approach (ie, 1- and 2-yr UC: 85.2% and 89.1%; 1- and 2-yr SF recovery: 33.8% and 52.3%) [34].

Our study must be interpreted in light of its limitations. First, our findings were derived from a retrospective review of prospectively collected observational data. Thus, our results must be interpreted within the bounds of the limitations of such data. Second, evolution in postoperative treatment protocols over time might have led to differences in the outcomes that we cannot account for. Third, our findings were derived from a centre with a high annual caseload and from surgeons experienced in RS-RARP. Therefore, our results might not be applicable to smaller centres with a limited surgical volume. Fourth, no validated questionnaires (eg, International Index of Erectile Function—Erectile Function) were used to quantify recovery of potency. Fifth, none of our high-risk PCa patients underwent anterior RARP. Future comparative studies are needed to confirm that RS-RARP is a valid surgical treatment option in the specific setting of high-risk PCa patients. Nonetheless, our study represents the largest report on high-risk PCa patients treated with RS-RARP as the primary treatment modality and the first one that reported intermediate-term oncological and functional outcomes and postoperative complications according to the standardised reporting methodology proposed by the EAU guidelines.

5. Conclusions

RS-RARP in high-risk PCa patients is associated with optimal intra-, peri-, and postoperative outcomes. The Retzius-sparing approach should be considered a valid surgical treatment option for high-risk PCa patients in expert hands.

***Author contributions*:** Paolo Dell'Oglio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dell'Oglio, Tappero, Galfano.
Acquisition of data: Dell'Oglio, Tappero, Longoni, Buratto, Scilipoti, Palagonia.
Analysis and interpretation of data: Dell'Oglio, Tappero, Longoni, Galfano.
Drafting of the manuscript: Dell'Oglio, Tappero, Longoni.
Critical revision of the manuscript for important intellectual content: Dell'Oglio, Tappero, Longoni, Buratto, Scilipoti, Secco, Olivero, Barbieri, Palagonia, Napoli, Strada, Petralia, Di Trapani, Vanzulli, Bocciardi, Galfano.
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Appendix A. Supplementary data

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References

[1] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[2] Yossepowitch O, Eggener SE, Serio AM, et al. Secondary therapy, metastatic progression, and cancer-specific mortality in men with clinically high-risk prostate cancer treated with radical prostatectomy. Eur Urol 2008;53:950–9.
[3] Galfano A, Ascione A, Grimaldi S, Petralia G, Strada E, Bocciardi AM. A new anatomic approach for robot-assisted laparoscopic prostatectomy: a feasibility study for completely intrafascial surgery. Eur Urol 2010;58:457–61.
[4] Checcucci E, Veccia A, Fiori C, et al. Retzius-sparing robot-assisted radical prostatectomy vs the standard approach: a systematic review and analysis of comparative outcomes. BJU Int 2020;125:8–16.
[5] Phukan C, Mclean A, Nambiar A, et al. Retzius sparing robotic assisted radical prostatectomy vs. conventional robotic assisted radical prostatectomy: a systematic review and meta-analysis. World J Urol 2020;38:1123–34.
[6] Rosenberg JE, Jung JH, Edgerton Z, et al. Retzius-sparing versus standard robotic-assisted laparoscopic prostatectomy for the treatment of clinically localized prostate cancer. Cochrane Database Syst Rev 2020;2020:CD013641.
[7] Lee J, Kim HY, Goh HJ, et al. Retzius sparing robot-assisted radical prostatectomy conveys early regain of continence over conventional robot-assisted radical prostatectomy: a propensity score matched analysis of 1,863 patients. J Urol 2020;203:137–44.
[8] Dalela D, Jeong W, Prasad M-A, et al. A pragmatic randomized controlled trial examining the impact of the Retzius-sparing approach on early urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2017;72:677–85.
[9] Menon M, Dalela D, Jamil M, et al. Functional recovery, oncologic outcomes and postoperative complications after robot-assisted radical prostatectomy: an evidence-based analysis comparing the Retzius sparing and standard approaches. J Urol 2018;199:1210–7.
[10] Asimakopoulos AD, Topazio L, de Angelis M, et al. Retzius-sparing versus standard robot-assisted radical prostatectomy: a prospective randomized comparison on immediate continence rates. Surg Endosc 2019;33:2187–96.
[11] Galfano A, di Trapani D, Sozzi F, et al. Beyond the learning curve of the Retzius-sparing approach for robot-assisted laparoscopic

radical prostatectomy: oncologic and functional results of the first 200 patients with ≥1 year of follow-up. Eur Urol 2013;64:974–80.
[12] Lim SK, Kim KH, Shin T-Y, et al. Retzius-sparing robot-assisted laparoscopic radical prostatectomy: combining the best of retropubic and perineal approaches. BJU Int 2014;114:236–44.
[13] Umari P, Eden C, Cahill D, Rizzo M, Eden D, Sooriakumaran P. Retzius-sparing versus standard robot-assisted radical prostatectomy: a comparative prospective study of nearly 500 patients. J Urol 2021;205:780–90.
[14] Sayyid RK, Sherwood D, Simpson WG, Terris MK, Klaassen Z, Madi R. Retzius-sparing robotic-assisted laparoscopic radical prostatectomy: racial considerations for 250 consecutive cases. J Robot Surg 2021;15:221–8.
[15] Nyarangi-Dix JN, Görtz M, Gradinarov G, et al. Retzius-sparing robot-assisted laparoscopic radical prostatectomy: functional and early oncologic results in aggressive and locally advanced prostate cancer. BMC Urol 2019;19:113.
[16] Abdel Raheem A, Chang KD, Alenzi MJ, et al. Predictors of biochemical recurrence after Retzius-sparing robot-assisted radical prostatectomy: analysis of 359 cases with a median follow-up period of 26 months. Int J Urol 2018;25:1006–14.
[17] Qiu X, Li Y, Chen M, et al. Retzius-sparing robot-assisted radical prostatectomy improves early recovery of urinary continence: a randomized, controlled, single-blind trial with a 1-year follow-up. BJU Int 2020;126:633–40.
[18] Mitropoulos D, Artibani W, Graefen M, Remzi M, Rouprêt M, Truss M. Reporting and grading of complications after urologic surgical procedures: an ad hoc EAU guidelines panel assessment and recommendations. Eur Urol 2012;61:341–9.
[19] Biyani CS, Pecanka J, Rouprêt M, Jensen JB, Mitropoulos D. Intraoperative Adverse Incident Classification (EAUiaiC) by the European Association of Urology ad hoc Complications Guidelines Panel. Eur Urol 2020;77:601–10.
[20] D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74.
[21] Montorsi F, Wilson TG, Rosen RC, et al. Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. Eur Urol 2012;62:368–81.
[22] Sammon JD, Trinh Q-D, Sukumar S, et al. Risk factors for biochemical recurrence following radical perineal prostatectomy in a large contemporary series: a detailed assessment of margin extent and location. Urol Oncol 2013;31:1470–6.
[23] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–96.
[24] Assel M, Sjoberg D, Elders A, et al. Guidelines for reporting of statistics for clinical research in urology. Eur Urol 2019;75:358–67.
[25] Dell'Oglio P, Stabile A, Gandaglia G, et al. New surgical approaches for clinically high-risk or metastatic prostate cancer. Expert Rev Anticancer Ther 2017;17:1013–31.
[26] Kumar A, Samavedi S, Bates AS, et al. Safety of selective nerve sparing in high risk prostate cancer during robot-assisted radical prostatectomy. J Robot Surg 2017;11:129–38.
[27] Abdollah F, Dalela D, Sood A, et al. Intermediate-term cancer control outcomes in prostate cancer patients treated with robotic-assisted laparoscopic radical prostatectomy: a multi-institutional analysis. World J Urol 2016;34:1357–66.
[28] Abdollah F, Sood A, Sammon JD, et al. Long-term cancer control outcomes in patients with clinically high-risk prostate cancer treated with robot-assisted radical prostatectomy: results from a multi-institutional study of 1100 patients. Eur Urol 2015;68:497–505.
[29] Mazzone E, Dell'Oglio P, Rosiello G, et al. Technical refinements in superextended robot-assisted radical prostatectomy for locally advanced prostate cancer patients at multiparametric magnetic resonance imaging. Eur Urol 2021;80:104–12.
[30] Mazzone E, D'Hondt F, Beato S, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion decreases postoperative complications only in highly comorbid patients: findings that rely on a standardized methodology recommended by the European Association of Urology Guidelines. World J Urol 2021;39:803–12.
[31] Gandaglia G, Bravi CA, Dell'Oglio P, et al. The impact of implementation of the European Association of Urology Guidelines Panel recommendations on reporting and grading complications on perioperative outcomes after robot-assisted radical prostatectomy. Eur Urol 2018;74:4–7.
[32] Dell'Oglio P, Andras I, Ortega D, et al. Impact of the implementation of the EAU guidelines recommendation on reporting and grading of complications in patients undergoing robot-assisted radical cystectomy: a systematic review. Eur Urol 2021;80:129–33.
[33] Cacciamani GE, Maas M, Nassiri N, et al. Impact of pelvic lymph node dissection and its extent on perioperative morbidity in patients undergoing radical prostatectomy for prostate cancer: a comprehensive systematic review and meta-analysis. Eur Urol Oncol 2021;4:134–49.
[34] Abdollah F, Dalela D, Sood A, et al. Functional outcomes of clinically high-risk prostate cancer patients treated with robot-assisted radical prostatectomy: a multi-institutional analysis. Prostate Cancer Prostatic Dis 2017;20:395–400.
[35] Hagman A, Lantz A, Carlsson S, et al. Urinary continence recovery and oncological outcomes after surgery for prostate cancer analysed by risk category: results from the LAParoscopic prostatectomy robot and open trial. World J Urol 2021;39:3239–49.