

Influence of operative time and blood loss on surgical margins and functional outcomes for laparoscopic versus robotic-assisted radical prostatectomy: a prospective analysis

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Introduction The aim of this article was to analyze whether operative time and blood loss during radical prostatectomy (RP) can significantly influence surgical margins (SM) status and post-operative functional outcomes.

Material and methods We prospectively analyzed prostate cancer (PC) patients undergoing RP, using robot-assisted (RARP) or laparoscopic (LRP) procedures. Blood loss was defined using the variation in hemoglobin (Hb, g/dl) values from the day before surgery and no later than 4 hours after surgery.

Results From a whole population of 413 cases considered for RP, 67% underwent LRP and 33.0% RARP. Positive SM (SM+) were found in 33.9% of cases. Mean surgical operative time was 172.3 ±76 min (range 49–485), whereas blood loss was 2.3 ±1.2 g/dl (range 0.3–7.6). Operative time and blood loss at RP were not significantly correlated ($r = -0.028275$; $p = 0.684$). SM+ rates significantly ($p = 0.002$) varied by operative time; a higher SM+ rate was found in cases with an operative time <120 min (41.2%) and >240 min (53.4%). The risk of SM+ significantly increased 1.70 and 1.94 times in cases with an operative time <120 min and >240 min, respectively, independently to the surgical approach. The rate of erectile dysfunction (ED) varied from 22.4% to 60.3% between <120 min and >240 min procedures ($p = 0.001$). According to blood loss, SM+ rates slightly but significantly ($p = 0.032$) varied; a higher rate of SM+ was found in cases with a Hb variation between 2–4 g/dl (35.9%).

Conclusions Independently to the surgical approach, operative time, more than blood loss at RP, represents a significant variable able to influence SM status and post-operative ED.

Key Words: prostatic neoplasm <> robot-assisted prostatectomy <> laparoscopic prostatectomy <> surgical margins <> blood loss <> operative time

INTRODUCTION

Robot-assisted radical prostatectomy (RARP) has become the most frequently used technique for the surgical management of non-metastatic prostate cancer (PC) [1, 2, 3], yet its advantage over a laparoscopic (LRP) procedure in different post-operative outcomes remains under debate [4]. Indeed, the European Urological Association (EAU) guidelines [5] recommended to inform PC patients qualified for surgery that no surgical approach (open versus LRP versus RARP) has clearly shown superiority in terms of both functional and oncologic results. However, some clinical trials [6–10] showed that RARP can offer better results than LRP in terms of potency recovery and surgical margins (SM) in pathologically organ-confined PC. Although positive SM (SM+) after RP are uniformly considered an adverse outcome associated with failure of surgery to achieve cure of PC, its clinical relevance and management remain under debate [11, 12]. SM+ rate in contemporary RARP series is 15% (range 6.5–32%), which is higher in men with a more advanced pathologic stage and equivalent to the rate reported in prior open and LRP series [11]. The likelihood of SM+ is strongly influenced by the surgeon's experience, irrespective of the surgical approach. Technical modifications using the robotic platform and the role of frozen-section analysis to reduce SM+ rate continue to evolve. SM+ are associated with a two-fold increased hazard of biochemical relapse, yet their association with more robust clinical end-points is still controversial. Data on additional clinical and pathologic predictors of SM+ have been largely inconclusive. Most authors believe that factors that make surgery more difficult – increased body mass index [13], large prostate [14], previous surgery for prostatic hyperplasia [15, 16] – have a negligible impact. To date, only few data regarding a possible influence of operative time and blood loss during surgery on SM status with different RP approaches are available in the literature [17, 18, 19].

The aim of the present prospective trial is to analyze whether operative time and blood loss during surgery can significantly influence surgical margins status and post-operative functional outcomes at RARP and LRP, and whether this impact is independent to other clinical and pathological variables.

MATERIAL AND METHODS

This is a prospective trial on PC patients submitted to RP, using RARP or LRP. A real-life setting was analyzed at our Urological Departments, using homogeneous criteria for the management of PC cases.

Population

Patients with a histological diagnosis of prostatic adenocarcinoma considered for RP as primary therapeutic option were consecutively included in the analysis. The protocol was approved by our internal ethical committee and all patients gave their informed consent for each procedure. All diagnostic and therapeutic procedures reflected our routine clinical practice at high-volume Departments for the management of PC disease. Inclusion criteria were: histological diagnosis of adenocarcinoma, no distant metastases at clinical staging, RP as the chosen primary treatment option, estimated life-expectancy of ≥ 10 years. Exclusion criteria were: androgen deprivation therapies, chemotherapies, pelvic radiation therapies or treatments with other agents that could influence prostate tumor growth. From January 2018 to January 2021, 413 consecutive patients with PC submitted to RP in our Departments of Urology corresponding to the defined inclusion and exclusion criteria were included in our analysis (Table 1).

Clinical parameters

The whole population of 413 cases is described in Table 1. All cases were submitted to a standard random 14-cores biopsy (Bx) of the prostate. In cases submitted to multiparametric magnetic resonance imaging of the prostate (mpMRI) with Prostate Imaging-Reporting Data System (PI-RADS) score 3–5, random Bx was associated with targeted samples on sites indicated by mpMRI [20–24]. Before surgery, clinical staging and risk category (D'Amico and EAU classification) assessment was homogeneously performed, using total prostate-specific antigen (PSA) determination and imaging (mpMRI, CT and bone scan) [5]. All patients were submitted to a laparoscopic or robotic RP, following EAU guidelines for indications [5]. Blood loss at surgery was defined using the variation in hemoglobin (Hb, g/dl) serum values from the day before surgery and no later than 4 hours after surgery. All patients were followed at regular intervals to determine time to biochemical (confirmed total PSA progression ≥ 0.2 ng/ml), radiological (radiologically confirmed), local or distant progression, as recommended by the EAU guidelines [5]. Post-operative functional complications, such as urethral stricture, urinary incontinence (UI) and erectile dysfunction (ED) were analyzed during a follow-up of 12 months. A UI was defined as a persistent urinary leakage ≥ 5 g at pad test. A significant ED was defined as an International Index of Erectile Function-5 (IIEF-5) score between 1–10.

Table 1. Characteristics of the whole population submitted to radical prostatectomy [mean \pm SD, median (range), number of cases (%)]

Patients, n°	413
Age (years)	
mean \pm SD	65.6 \pm 6.0
median (range)	67 (47–72)
BMI	
mean \pm SD	26.35 \pm 4.5
median (range)	26 (17.0–39.0)
D'Amico Risk Class, n° (%)	
low-risk	132 (32.0)
intermediate-risk	174 (42.1)
high-risk	107 (25.9)
Pre-operative total PSA (ng/ml)	
mean \pm SD	9.92 \pm 9.51
median (range)	7.24 (1.7–73.5)
Surgical technique at RP, n° (%)	
LRP	277 (67.0)
RARP	136 (33.0)
NS technique at RP, n° (%)	
performed	208 (50.4)
monolateral	91 (43.7)
bilateral	117 (56.3)
eLND performed at RP, n° (%)	134 (32.4)
Pathological stage (T), n° (%)	
pT2	246 (59.6)
pT3a	110 (26.6)
pT3b	57 (13.8)
Pathological stage (N), n° (%)	
N0	396 (95.9)
N1	17 (4.1)
ISUP grading, n° (%)	
1	85 (20.6)
2	159 (38.5)
3	113 (27.3)
4	26 (6.3)
5	30 (7.3)
SM at surgery, n° (%)	
negative	273 (66.1)
positive	140 (33.9)
Operative time (min)	
mean \pm SD	172.3 \pm 76
median (range)	155 (49–485)
Hb variation after surgery (g/dl)	
mean \pm SD	2.3 \pm 1.2
median (range)	2 (0.37–6)
Blood transfusion, n° (%)	23 (6%)
Hospitalization time (days)	
mean \pm SD	4.9 \pm 2.2
median (range)	4 (1–18)
Post-operative catheterization time (days)	
mean \pm SD	12.2 \pm 4.0
median (range)	11 (6–28)
Biochemical progression, n° (%)	34 (8.2)
Post-operative urethral strictures, n° (%)	4 (1.0)
Post-operative UI, n° (%)	48 (11.6)
Postoperative ED, n° (%)	163 (48.0)*

RP – radical prostatectomy; BMI – body mass index; PSA – prostate-specific antigen; LRP – laparoscopic RP; RARP – robot-assisted RP; eLND – extended lymph node dissection; ISUP – International Society of Urological Pathology; SM – surgical margins; NS – nerve-sparing; Hb – hemoglobin; UI – urinary incontinence; ED – erectile dysfunction

* % computed on 340 cases for whom erectile function data were available

Pathologic evaluation

All histological specimens from prostatic Bx and RP were analyzed by our two uro-pathologists (FMM and AC) with a long experience in the PC field. Gleason score and grade groups according to the World Health organization (WHO)/ISUP 2014 guidelines at Bx and at surgery, pathologic staging using TNM classification, SM status were routinely defined in all cases. In particular, SM were considered positive when carcinoma was transected by an inked SM; this could be in a setting of organ-confined or extracapsular disease.

Surgical procedure

Surgical technique was not assigned randomly. As routine clinical practice in our Departments, each procedure (RARP and LRP) was discussed with the patient and performed by the same surgeons who had a high expertise in each approach, consistent with best practice. All surgeons had ≥ 10 years of experience and had performed ≥ 500 procedures with both approaches. All surgical procedures were performed using the same intraperitoneal standard technique for RP. A nerve-sparing (NS) (intrafascial, monolateral or bilateral) procedure was performed on individual surgeon discretion, based on risk classes, the risk of extracapsular disease and after discussion with the patient on the probability to maintain potency balanced with possible harm [25]. In particular, for either RARP or LRP: patients with clinical high-risk of ipsilateral extracapsular disease were excluded from a NS surgery; extended lymph node dissection (eLND) was performed in all high-risk cases and in the intermediate-risk class in cases with $\geq 5\%$ probability for positive nodes; intra-operative evaluation of SM was not performed; both RARP and LRP were performed using a standard surgical intraperitoneal technique, with the same surgical steps. Operative time was defined in minutes (min), from the beginning to the end of the surgical procedure.

Statistical analysis and outcomes

For statistical evaluation, the SPSS Statistics program was used. Descriptive statistical methods, such as number of cases, mean \pm SD, median and range were used. For the comparison of quantitative data and pairwise intergroup comparisons of variables a Mann Whitney test or ANOVA one-way test were performed. For comparison of qualitative data Fisher's Exact test and chi-square test were used. Pearson correlation analysis was also performed. Univariate and multivariate Cox proportional analysis

considering clinical and pathological parameters were used. Statistical significance was evaluated at $p < 0.05$.

Primary outcomes were to determine differences in SM status and post-operative functional outcomes according to operative time and blood loss results in cases submitted to a RARP or LRP procedure. Secondary outcomes were to determine the independent role of these two parameters on SM and functional outcomes, when considered together with other clinical and pathological variables.

RESULTS

Baseline characteristics of the whole population of 413 cases considered for RP are described in Table 1. An intermediate- and high-risk PC was

present in 42.1% and 25.9% of cases, respectively. In particular, 277 (67%) cases underwent LRP and 136 (33.0%) RARP procedures. An eLND was performed in 134 (32.4%) cases, whereas a NS technique in 208 (50.4%). At the final pathologic evaluation, extracapsular disease (pT3) was found in 40.4% of cases. SM+ were found in 140 (33.9%) cases. Mean surgical operative time was 172.3 ± 76 min (range 49–485 min), whereas blood loss, defined as mean Hb variation after surgery, was 2.3 ± 1.2 g/dl (range 0.3–7.6 g/dl). During a post-operative 12-month follow-up, rates of urethral stricture, UI or ED were 1%, 11.6% and 48%, respectively; considering only the NS cohort, rate of ED was 23.1% (48/208 cases) [36.3% and 12.8% for patients who underwent monolateral (33/91 cases) and bilateral (15/117 cases) approach, respectively].

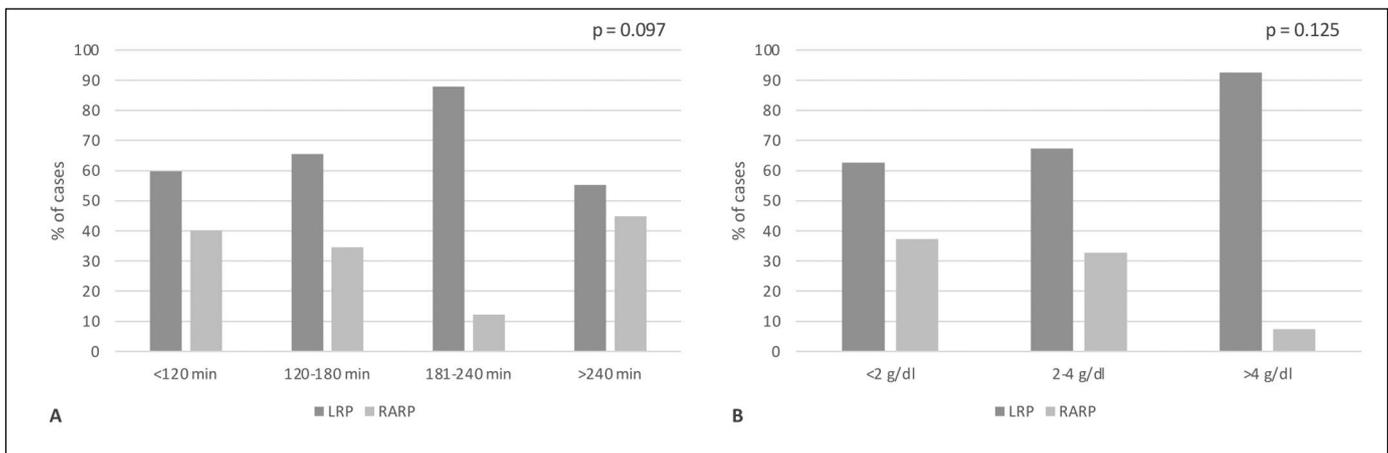


Figure 1. Bar-chart showing the percentage of patients submitted to robot-assisted radical prostatectomy (RARP) and laparoscopic radical prostatectomy (LRP) in the different groups, according to: **A)** operative time (<120 min; 120–180 min; 181–240 min; >240 min) ($p = 0.097$); **B)** serum hemoglobin (Hb) variation after surgery (<2 g/dl, 2–4 g/dl, >4 g/dl) ($p = 0.125$). ANOVA one-way test.

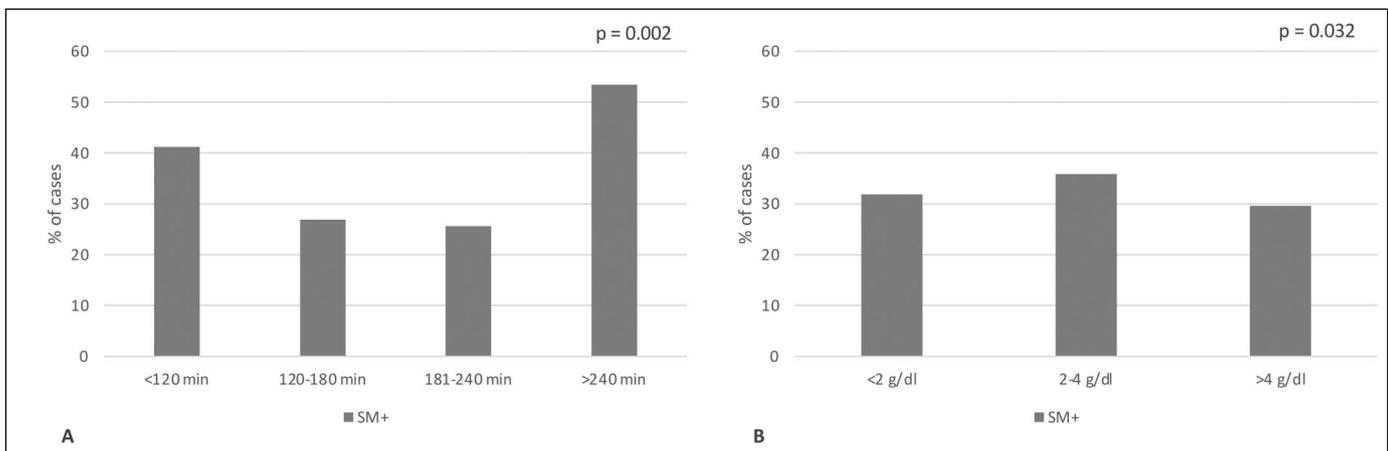


Figure 2. Bar-chart showing the positive surgical margins (SM+) rate in the different groups, according to: **A)** operative time (<120 min; 120–180 min; 181–240 min; >240 min); ($p = 0.002$); **B)** serum hemoglobin (Hb) variation after surgery (<2 g/dl, 2–4 g/dl, >4 g/dl) ($p = 0.032$). ANOVA one-way test.

Table 2. Characteristics of the population submitted to radical prostatectomy stratified by operative time [mean \pm SD, median (range)]. Number of cases (%). ANOVA one-way test]

	Operative time				P value
	<120 min	120–180 min	181–240 min	>240 min	
Patients, n° (%)	102 (24.7)	171 (41.4)	82 (19.8)	58 (14.1)	–
Age (years)					
mean \pm SD	65.0 \pm 6.5	61.1 \pm 6.0	65.7 \pm 6.0	68.0 \pm 4.6	0.0733
median (range)	66 (47–72)	6 (51–72)	67 (48–72)	69 (54–72)	
BMI					
mean \pm SD	25.6 \pm 3.4	26.7 \pm 3.3	26.4 \pm 3.6	26.2 \pm 2.7	0.4945
median (range)	25.2 (19.0–34.2)	26.2 (17.0–39.0)	26 (18.5–37.0)	26.3 (21.7–32.8)	
D'Amico Risk Class, n° (%)					
low	36 (35.3)	48 (28.1)	24 (29.3)	24 (41.4)	0.1717
intermediate	38 (37.2)	77 (45.0)	40 (48.8)	19 (32.7)	
high	28 (27.5)	46 (26.9)	18 (21.9)	15 (25.9)	
Pre-operative total PSA (ng/ml)					
mean \pm SD	7.3 \pm 3.23	10.9 \pm 11.69	10.26 \pm 8.16	9.13 \pm 7.29	0.0568
median (range)	6.9 (1.7–19.0)	7.55 (1.7–73.5)	7.7 (2.6–58.0)	7.2 (13.0–39.0)	
Surgical technique at RP, n° (%)					
LRP	61 (59.8%)	112 (65.5%)	72 (87.8%)	32 (55.2%)	0.0972
RARP	41 (40.2%)	59 (34.5%)	10 (12.2%)	26 (44.8%)	
NS technique at RP, n° (%)					
performed	47 (46.1)	89 (52.0)	37 (45.1)	35 (60.3)	0.0019
monolateral	20 (42.6)	47 (52.8)	14 (37.8)	10 (28.6)	
bilateral	27 (57.4)	42 (47.2)	23 (62.2)	25 (71.4)	
eLND performed at RP, n° (%)	12 (11.8)	58 (33.9)	37 (45.1)	27 (46.5)	0.0614
Pathological stage (T), n° (%)					
pT2	78 (76.5)	89 (52.0)	51 (62.2)	28 (48.3)	0.010
pT3a	17 (16.6)	60 (35.1)	21 (25.6)	12 (20.7)	
pT3b	7 (6.9)	22 (12.9)	10 (12.2)	18 (31.0)	
Pathological stage N1, n° (%)	1 (1.0)	6 (3.5)	6 (7.3)	4 (6.9)	0.0343
ISUP grading, n° (%)					
1	33 (32.3)	30 (17.5)	15 (18.3)	7 (12.0)	0.0613
2	49 (48.0)	65 (38.0)	27 (32.9)	18 (31.0)	
3	17 (16.7)	50 (29.2)	23 (28.0)	23 (39.6)	
4	1 (1.0)	11 (6.4)	8 (9.7)	6 (10.3)	
5	2 (2.0)	15 (8.8)	9 (10.9)	4 (6.9)	
Positive SM at RP, n° (%)	42 (41.2)	46 (26.9)	21 (25.6)	31 (53.4)	0.0022
Operative time (min)					
mean \pm SD	90.27 \pm 16.68	152.8 \pm 16.48	212.0 \pm 16.64	317.2 \pm 55.74	–
median	90	150	210	302	
Hb variation after surgery (g/dl)					
mean \pm SD	2.49 \pm 1.16	2.17 \pm 1.7	2.41 \pm 1.12	2.30 \pm 0.96	0.1426
median	2.4 (0.2–5.9)	1.9 (0.3–7.6)	2.3 (0.3–5.7)	2.2 (0.7–6.3)	
Blood transfusion, n° (%)	4 (3.9)	7 (4.1)	5 (6.1)	7 (12.1)	0.1939
Hospitalization time (days)					
mean \pm SD	3.90 \pm 1.84	4.70 \pm 1.90	5.91 \pm 2.46	4.8 \pm 2.46	0.1331
median (range)	4 (2–11)	5 (2–14)	5 (1–18)	5 (3–11)	
Post-operative catheterization time (days)					
mean \pm SD	10.60 \pm 1.87	11.60 \pm 3.50	13.07 \pm 4.47	14.12 \pm 4.17	0.1917
median (range)	10 (7–16)	11 (6–28)	12 (8–28)	12 (8–28)	
Biochemical progression, n° (%)	5 (4.9)	21 (12.3)	6 (7.3)	2 (3.4)	0.1204
Post-operative urethral strictures, n° (%)	1 (0.9)	3 (1.8)	0 (0)	0 (0)	0.4008
Post-operative UI, n° (%)	8 (7.5)	22 (12.9)	10 (12.2)	8 (13.8)	0.9195
Postoperative ED, n° (%)	24 (22.4)	69 (40.3)	35 (42.7)	35 (60.3)	0.0015

RP – radical prostatectomy; BMI – body mass index; PSA – prostate-specific antigen; LRP – laparoscopic RP; RARP – robot-assisted RP; eLND – extended lymph node dissection; ISUP – International Society of Urological Pathology; SM – surgical margins; NS – nerve-sparing; Hb – hemoglobin; UI – urinary incontinence; ED – erectile dysfunction

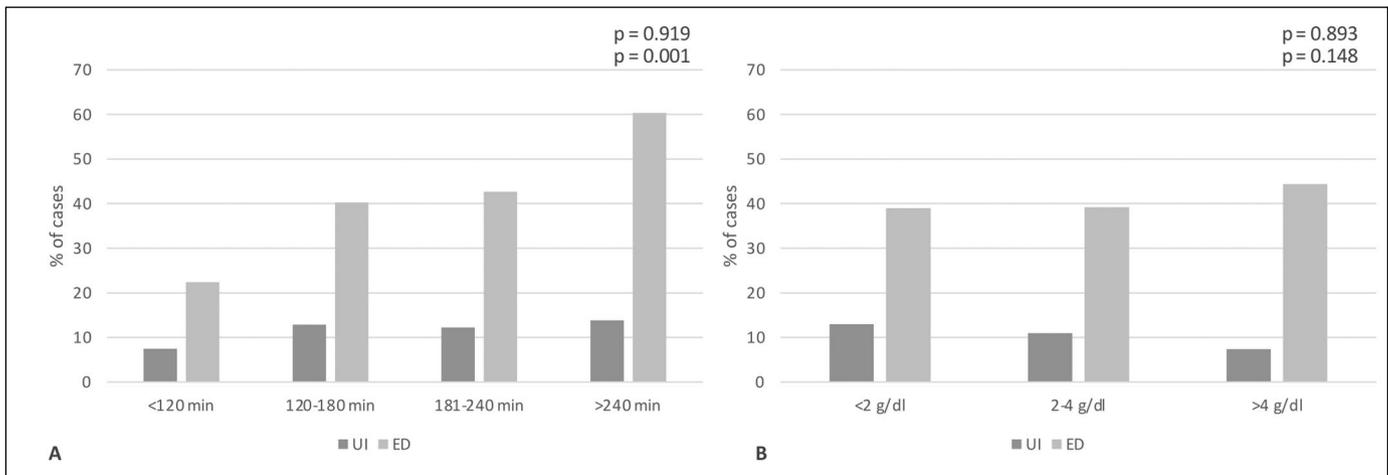


Figure 3. Bar-chart showing the rate of post-operative urinary incontinence (UI) and erectile dysfunction (ED) in the different groups, according to: **A)** operative time (<120 min; 120–180 min; 181–240 min; >240 min); ($p = 0.919$ and 0.001 , respectively); **B)** serum hemoglobin (Hb) variation after surgery (<2 g/dl, 2–4 g/dl, >4 g/dl) ($p = 0.893$ and 0.148 , respectively). ANOVA one-way test.

Differences in clinical and pathologic parameters according to operative surgical time

The whole population was stratified on the basis of the operative surgical time in 4 groups: operative time <120 min, between 120–180 min, between 181–240 min, and >240 min (Table 2). The distribution of cases by surgical technique did not significantly vary among the 4 groups (Figure 1A). In particular, 22.0% and 33.0% of LRP and RARP were in the operative time group <120 min, and 40.4% and 43.3% in the operative time group of 120–180 min, respectively. SM+ rates significantly ($p = 0.002$) varied among the 4 groups, and a higher SM+ rate was found in cases with an operative time <120 min (41.2%) and >240 min (53.4%) (Figure 2A). Hospitalization and catheterization time did not significantly vary by operative time. Post-operative urinary stricture and UI rates did not significantly vary according to operative time, whereas the rate of ED varied from 22.4% to 60.3% between <120 min and >240 min surgical time ($p = 0.001$) (Figure 3A).

Differences in clinical and pathologic parameters according to blood loss at surgery

In this analysis, cases were stratified in 3 groups according to Hb serum levels variation after surgery, as a parameter to describe blood loss during RP: <2 g/dl, between 2–4 g/dl, and ≥ 4 g/dl (Table 3). The distribution of cases by surgical technique did not significantly vary among the 3 groups (Figure 1b). In particular, 38.2% and 46.3% of LRP and RARP cases, respectively, were in the Hb variation group

<2 g/dl and 52.7% and 52.2% in the Hb group between 2–4 g/dl. SM+ rates slightly but significantly ($p = 0.032$) varied among the 3 groups, and a higher SM+ rate was found in cases with a Hb variation between 2–4 g/dl (35.9%) (Figure 2b). Hospitalization and catheterization time did not significantly vary according to blood loss and Hb variation, as well as all post-operative functional evaluations (urinary stricture, UI and ED) (Figure 3b).

Correlations among operative time or surgical blood loss and the other clinical and pathologic parameters

According to Pearson analysis (Table 7), operative time and blood loss at RP were not significantly correlated ($r = -0.028275$; $p = 0.684$). Similarly, operative time and blood loss at RP were neither significantly correlated to surgical techniques (LRP versus RARP, NS procedure or eLND) nor with post-operative urethral stricture or UI rates. On the contrary, operative time was significantly correlated with SM+ ($r = 0.51957$; $p = 0.037$) and post-operative ED rates ($r = 0.38460$; $p = 0.044$).

Logistic regression analysis: predictors for surgical margins status and functional results after surgery

Table 4 shows a logistic regression analysis assessed to identify variables able to condition SM status in our population. On univariate analysis, the risk of SM+ did not significantly vary according to the surgical technique (LRP versus RARP: OR = 1.70; 95%CI 0.37–2.22; $p = 0.161$) (NS procedure: OR = 1.17;

Table 3. Characteristics of the population submitted to radical prostatectomy stratified on the basis of hemoglobin (Hb) variation after surgery [mean \pm SD, median (range). Number of cases (%). ANOVA one-way test]

	Hb variation			P value
	<2 g/dl	2–4 g/dl	>4 g/dl	
Patients, n° (%)	169 (41.0)	217 (52.5)	27 (6.5)	–
Age (years)				
mean \pm SD	65.6 \pm 5.7	65.8 \pm 6.0	67.4 \pm 6.3	0.4926
median (range)	66 (47–72)	67 (48–72)	69 (52–72)	
BMI				
mean \pm SD	26.8 \pm 3.3	26.1 \pm 3.4	25.3 \pm 2.4	0.1212
median (range)	26.3 (19.0–36.8)	25.6 (17.0–39.0)	25.3 (18.5–26.9)	
D'Amico Risk Class, n° (%)				
low	43 (25.5)	81 (37.3)	8 (29.6)	0.0951
intermediate	82 (48.5)	79 (36.4)	13 (48.2)	
high	44 (26.0)	57 (26.3)	6 (22.2)	
Pre-operative total PSA (ng/ml)				
mean \pm SD	11.14 \pm 11.5	9.05 \pm 7.23	8.34 \pm 2.80	0.0864
median (range)	7.36 (2.8–7.4)	6.9 (1.7–73.5)	7.6 (4.3–6.5)	
Surgical technique at RP, n° (%)				
LRP	106 (62.7)	146 (67.3)	25 (92.6)	0.1248
RARP	63 (37.3)	71 (32.7)	2 (7.4)	
NS technique at RP, n° (%)				
performed	84 (49.7)	112 (51.6)	12 (44.4)	0.0060
monolateral	49 (58.3)	39 (34.8)	3 (25.0)	
bilateral	35 (41.7)	73 (65.2)	9 (75.0)	
eLND performed at RP, n° (%)	55 (32.5)	74 (34.1)	5 (18.5)	0.0712
Pathological stage (T), n° (%)				
pT2	94 (55.6)	132 (60.8)	20 (74.1)	0.4122
pT3a	54 (32.0)	52 (24.0)	4 (14.8)	
pT3b	21 (12.4)	33 (15.2)	3 (11.1)	
Pathological stage (N), n° (%)				
N0	159 (94.1)	210 (96.8)	27 (100)	0.5981
N1	10 (5.9)	7 (3.2)	0 (0)	
ISUP grading, n° (%)				
1	29 (17.1)	48 (22.1)	8 (29.6)	0.1411
2	67 (39.6)	83 (38.3)	9 (33.3)	
3	48 (28.5)	58 (26.7)	7 (25.9)	
4	11 (6.5)	15 (6.9)	0 (0)	
5	14 (8.3)	13 (6.0)	3 (11.2)	
Positive SM at RP, n° (%)	54 (31.9)	78 (35.9)	8 (29.6)	0.0324
Operative time (min)				
mean \pm SD	68.7 \pm 63	176.4 \pm 86.3	161 \pm 58.5	0.5991
median	157 (60–360)	155 (49–485)	150 (65–310)	
Hb variation after surgery (g/dl)				
mean \pm SD	1.3 \pm 0.4	2.8 \pm 0.6	5.1 \pm 1.0	–
median (range)	1.3 (0.3–1.9)	2.7 (2.0–4.0)	4.8 (4.1–7.6)	
Blood transfusion, n° (%)	4 (2.4)	15 (6.9)	4 (14.8)	0.0733
Hospitalization time (days)				
mean \pm SD	4.7 \pm 1.9	5.0 \pm 2.5	5.6 \pm 2.6	0.1227
median (range)	4 (1–13)	4 (2–18)	5 (2–14)	
Post-operative catheterization time (days)				
mean \pm SD	11.4 \pm 3.2	12.7 \pm 4.2	13.5 \pm 5.3	0.30692
median (range)	11 (6–26)	12 (7–28)	11 (8–28)	
Biochemical progression, n° (%)	15 (8.9)	16 (7.4)	3 (11.1)	0.4992
Post-operative urethral strictures, n° (%)	2 (1.2)	1 (0.5)	1 (3.7)	0.2118
Post-operative UI, n° (%)	22 (13.0)	24 (11.0)	2 (7.4)	0.8930
Postoperative ED, n° (%)	66 (39.0)	85 (39.2)	12 (44.4)	0.1478

RP – radical prostatectomy; BMI – body mass index; PSA – prostate-specific antigen; LRP – laparoscopic RP; RARP – robot-assisted RP; eLND – extended lymph node dissection; ISUP – International Society of Urological Pathology; SM – surgical margins; NS – nerve-sparing; Hb – hemoglobin; UI – urinary incontinence; ED – erectile dysfunction

Table 4. Univariate and multivariate step wise regression model analysis regarding predictive value of different characteristics in terms of surgical margins results [odds ratio (OR); 95% confidential interval (CI) and p value]

Covariates	Univariate			Multivariate		
	OR	95%CI	p value	OR	95%CI	p value
Age (years)						
50–60	Ref	–	–			
61–70	0.64	0.37–1.11	0.116			
71–75	0.98	0.51–1.88	0.946			
BMI						
15–25	Ref	–	–			
26–30	0.97	0.60–1.57	0.912			
>30	1.70	0.83–3.51	0.148			
Pre-operative PSA (ng/ml)						
<4.0	Ref	–	–	Ref	–	–
4.0–10.0	1.63	0.67–3.93	0.281	2.38	0.88–6.43	0.088
>10.0	3.00	1.19–7.55	0.020	3.57	1.25–10.16	0.017
Risk class						
low	Ref	–	–			
intermediate	1.03	0.63–1.69	0.896			
high	1.65	0.97–2.80	0.065			
Surgical technique						
LRP	Ref	–	–			
RARP	1.50	0.37–2.22	0.161			
NS procedure						
no	Ref	–	–			
yes, monolateral	0.75	0.43–1.31	0.312			
yes, bilateral	1.17	0.71–1.92	0.539			
eLND						
no	Ref	–	–			
yes	1.42	0.93–2.18	0.109			
ISUP grading						
1	Ref	–	–	Ref	–	–
2	1.63	0.87–3.03	0.125	1.22	0.58–2.60	0.598
3	2.44	1.28–4.65	0.007	1.34	0.60–2.99	0.482
4	3.56	1.40–9.01	0.007	2.28	0.77–6.74	0.138
5	3.56	1.47–8.63	0.005	1.25	0.37–4.17	0.717
pT stage						
pT2	Ref	–	–	Ref	–	–
pT3a	2.13	1.32–3.43	0.002	1.81	1.03–3.17	0.039
pT3b	3.40	1.88–6.18	<0.0001	2.20	1.03–4.74	0.043
Operative time (min)						
120–180 min	Ref	–	–	Ref	–	–
<120 min	1.70	0.41–2.21	0.020	1.60	0.39–2.67	0.045
181–240 min	0.53	0.30–0.92	0.125	0.73	0.39–1.36	0.323
>240 min	1.94	1.05–3.95	0.034	1.92	1.01–3.88	0.047
Hb variation after surgery (g/dl)						
<2 g/dl	Ref	–	–			
2–4 g/dl	1.00	0.66–1.51	0.992			
>4 g/dl	1.10	0.31–3.89	0.877			

OR – odds ratio; CI – confidential interval; BMI – body mass index; PSA – prostate-specific antigen; RP – radical prostatectomy; LRP – laparoscopic RP; RARP – robot-assisted RP; eLND – extended lymph node dissection; ISUP – International Society of Urological Pathology; NS – nerve-sparing; Hb – hemoglobin

95%CI 0.71–1.92; $p = 0.539$), whereas it significantly increased according to ISUP grading ($p < 0.05$) and pT stage (OR = 2.13 in pT3a and 3.40 in pT3b cases), when compared to pT2 (95%CI 1.32–3.43 and 1.88–6.18, respectively) ($p = 0.002$ and < 0.001 , respectively). Considering the group with an operative time of 120–180 min as standard reference, the risk of SM+ significantly increased 1.70 times (95%CI 0.41–2.21; $p = 0.020$) in cases with an operative

time <120 min and 1.94 times (95%CI 1.05–3.95; $p = 0.034$) in cases with an operative time >240 min. Considering a Hb variation after surgery <2 g/dl as reference, the risk of SM+ showed no significant increases in cases with a Hb variation between 2–4 g/dl and >4 g/dl ($p > 0.05$). On multivariate analysis, only pre-operative PSA, pT stage and operative time remain variables able to independently and significantly determine SM positivity ($p < 0.05$). In particu-

Table 5. Univariate and multivariate step wise regression model analysis regarding predictive value of different characteristics in terms of post-operative urinary incontinence results [odds ratio (OR); 95% confidential interval (CI) and p value]

Covariates	Univariate		
	OR	95%CI	p value
Age (years)			
50–60	Ref	–	–
61–70	1.83	0.73–4.62	0.200
71–75	2.48	0.88–6.95	0.085
BMI			
15–25	Ref	–	–
26–30	0.81	0.40–1.66	0.571
>30	3.34	1.43–7.81	0.005
Pre-operative PSA (ng/ml)			
<4.0	Ref	–	–
4.0–10.0	0.67	0.25–1.77	0.420
>10.0	0.55	0.18–1.64	0.284
Risk class			
Low	Ref	–	–
Intermediate	0.81	0.39–1.69	0.582
High	1.27	0.59–2.75	0.539
Surgical technique			
LRP	Ref	–	–
RARP	0.78	0.41–1.48	0.452
NS procedure			
no	Ref	–	–
yes, monolateral	0.80	0.36–1.77	0.575
yes, bilateral	1.05	0.52–2.12	0.886
eLND			
no	Ref	–	–
yes	0.97	0.50–1.90	0.934
ISUP grading			
1	Ref	–	–
2	0.84	0.37–1.87	0.664
3	0.63	0.25–1.55	0.311
4	0.45	0.09–2.21	0.325
5	1.00	0.28–3.51	0.994
pT stage			
pT2	Ref	–	–
pT3a	1.49	0.77–2.88	0.242
pT3b	0.72	0.26–2.00	0.534
Operative time (min)			
120–180 min	Ref	–	–
<120 min	1.08	0.44–2.65	0.867
181–240 min	1.30	0.61–2.78	0.493
>240 min	1.06	0.43–2.59	0.902
Hb variation after surgery (g/dl)			
<2 g/dl	Ref	–	–
2–4 g/dl	1.17	0.64–2.17	0.607
>4 g/dl	1.15	0.58–2.13	0.475

OR – odds ratio; CI – confidential interval; BMI – body mass index; PSA – prostate-specific antigen; RP – radical prostatectomy; LRP – laparoscopic RP; RARP – robot-assisted RP; eLND – extended lymph node dissection; ISUP – International Society of Urological Pathology; NS – nerve-sparing; Hb – hemoglobin

lar, the effect of operative time on SM+ rates was independent of the surgical approach (LRP or RARP) and the surgeon who performed the procedure. Table 5 and 6 show a logistic regression analysis performed to identify variables able to condition post-

operative UI and ED occurrence in our population. On univariate analysis, the risk of UI and ED did not significantly vary by surgical approach ($p > 0.05$). According to operative time, only the risk of ED significantly increased 2.41 times (95%CI 1.27–4.59; $p = 0.007$) in cases with an operative time > 240 min. Hb variation after surgery as index for blood loss did not significantly condition the risk of either UI or ED ($p > 0.05$). On multivariate analysis, NS procedure ($p = 0.047$) and age ($p = 0.001$), yet not operative time ($p > 0.10$) remained independent variables able to determine ED development.

DISCUSSION

RP is one of the main treatment options for non-metastatic PC and it aims to obtain optimal long-term oncologic results while preserving functional outcomes, such as urinary continence and erectile potency [3, 26]. LRP and RARP have gained widespread acceptance within urological practice. These techniques aim to be associated with less peri-operative morbidity, less intra-operative bleeding, and faster recovery time, when compared to open RP [9]. Moreover, the expectation from RARP is that this technique would allow a better preservation of neurovascular structures involved in erection [6, 8, 9, 27, 28, 29]. However, several systematic reviews, meta-analyses [2, 4, 30, 31] and randomized trials [32,33] have underlined that the different approaches to RP yielded similar post-operative results, so that EAU guidelines [5] recommend informing patients that no surgical approach to RP has clearly shown superiority in terms of both functional and oncologic outcomes. Independently to the surgical approach, several variables have been analyzed as possible predictors and factors able to influence oncologic and functional results after surgery [11–19, 28–35]. Only few data are present in the literature regarding the correlation between blood loss during RP and surgical outcomes. Boehm et al. [17] in a retrospective analysis showed no significant association between blood loss and oncologic outcomes after RP. Similarly, Djavan et al. [18] in a prospective series on open RP concluded that blood loss did not adversely impact SM status and functional outcomes after surgery. On the contrary, Preisser et al. [19] on PC cases submitted to open RP or RARP, sustained that a higher blood loss was able to determine worse functional outcomes (OR = 0.52, $p = 0.04$ for ED; OR = 0.66, $p = 0.002$ for UI).

The aim of the present analysis was to verify whether operative time and surgical blood loss, independently to other well-known clinical and pathological factors and to the surgical approach, were able

Table 6. Univariate and multivariate step wise regression model analysis regarding predictive value of different characteristics in terms of significant post-operative erectile dysfunction (ED) results [relative risk (RR); 95% confidential interval (CI) and p value]

Covariates	Univariate			Multivariate		
	OR	95%CI	p value	OR	95%CI	p value
Age (years)						
50–60	Ref	–	–	Ref	–	–
61–70	2.15	1.20–3.85	0.010	2.10	1.14–3.86	0.017
71–75	4.98	2.43–10.24	<0.0001	4.24	1.98–9.07	0.0001
BMI						
15–25	Ref	–	–			
26–30	1.23	0.77–1.95	0.387			
>30	0.81	0.39–1.67	0.561			
Pre-operative PSA (ng/ml)						
<4.0	Ref	–	–			
4.0–10.0	1.57	0.72–3.47	0.260			
>10.0	2.02	0.86–4.71	0.106			
Risk class						
low	Ref	–	–			
intermediate	0.90	0.54–1.47	0.666			
high	0.99	0.57–1.75	0.985			
Surgical technique						
LRP	Ref	–	–			
RARP	0.87	0.56–1.35	0.537			
NS procedure						
no	Ref	–	–	Ref	–	–
yes, monolateral	0.46	0.27–0.81	0.007	0.58	0.31–1.08	0.085
yes, bilateral	0.42	0.16–0.75	0.005	0.45	0.23–0.84	0.047
eLND						
no	Ref	–	–			
yes	1.16	0.73–1.85	0.530			
ISUP grading						
1	Ref	–	–	Ref	–	–
2	0.53	0.29–0.97	0.040	0.75	0.37–1.52	0.419
3	0.87	0.46–1.65	0.673	0.91	0.41–2.03	0.816
4	1.04	0.40–2.72	0.936	1.18	0.38–3.69	0.773
5	1.04	0.40–2.72	0.936	1.00	0.32–3.17	0.996
pT stage						
pT2	Ref	–	–			
pT3a	0.78	0.48–1.28	0.323			
pT3b	1.30	0.69–2.43	0.412			
Operative time (min)						
120–180 min	Ref	–	–	Ref	–	–
<120 min	0.63	0.34–1.20	0.164	0.64	0.33–1.27	0.203
181–240 min	1.09	0.64–1.88	0.744	1.02	0.58–1.79	0.957
>240 min	2.41	1.27–4.59	0.007	1.75	0.88–3.49	0.109
Hb variation after surgery (g/dl)						
<2 g/dl	Ref	–	–			
2–4 g/dl	1.07	0.54–1.73	0.170			
>4 g/dl	1.20	0.85–1.95	0.085			

OR – odds ratio; CI – confidential interval; BMI – body mass index; PSA – prostate-specific antigen; RP – radical prostatectomy; LRP – laparoscopic RP; RARP – robot-assisted RP; eLND – extended lymph node dissection; ISUP – International Society of Urological Pathology; NS – nerve-sparing; Hb – hemoglobin

to significantly influence SM status and functional aspects, such as continence and potency after RP. In particular, we focused our attention on SM+ rates more than biochemical progression as oncologic parameter, uniformly considered an adverse outcome associated with failure of surgery.

In our trial, the surgical approach was not assigned randomly, and the number of cases submitted to LRP or RARP was not perfectly balanced, reflecting

a real-life setting in the management of PC. As routine clinical practice in our Departments of Urology, each procedure was performed by the same surgeons who had a high expertise in each approach. The surgical technique was homogeneously intraperitoneal in all cases, and decisions regarding NS procedures or eLND were homogeneously obtained following the same criteria based on international guidelines, so that a possible effect of surgeon's expertise on on-

Table 7. Correlation coefficients (Pearson) among operative time or hemoglobin (Hb) variation and pathological and functional results after surgery

Correlation	Coefficient	P value
Operative time – Hb variation	0.028275	0.6845
Operative time – time of catheterization	0.292138	0.0950
Operative time – days of hospitalization	0.1055449	0.1276
Operative time – surgical technique	0.0397009	0.7568
Operative time – NS procedure	-0.043485	0.6854
Operative time – eLND	0.2591769	0.0733
Operative time – biochemical progression	-0.096264	0.7465
Operative time – SM	0.5195773	0.0367
Operative time – post-operative UI	-0.010127	0.7332
Operative time – post-operative ED	0.3846001	0.0445
Operative time – post-operative urethral stricture	-0.057317	0.6877
Hb variation – time of catheterization	0.1806763	0.5734
Hb variation – days of hospitalization	0.1008983	0.4976
Hb variation – surgical technique	0.0397009	0.7855
Hb variation – NS procedure	0.1539241	0.5743
Hb variation – eLND	-0.041369	0.7845
Hb variation – biochemical progression	-0.026762	0.7749
Hb variation – SM	0.0096756	0.7941
Hb variation – post-operative UI	0.061050706	0.7467
Hb variation – post-operative ED	0.087763961	0.7254
Hb variation – post-operative urethral stricture	0.036394287	0.7488

Hb – hemoglobin; NS – nerve-sparing; eLND – extended lymph node dissection; SM – surgical margins; UI – urinary incontinence; ED – erectile dysfunction

colologic and functional results at RP was verified and excluded from our analysis. As in previous analyses [17, 18], we decided to define blood loss at surgery using the variation in Hb (g/dl) serum values from the day before surgery and no later than 4 hours after surgery, as it could be a more precise parameter than the direct intra-operative evaluation of blood loss - possibly influenced by the presence of other liquids in the counts.

In our population, SM+ were found in 33.9% of cases and surgical operative time and blood loss at RP strongly varied (range 49–485 min and 0.3–7.6 g/dl), with mean values of 172.3 ± 76 min and 2.3 ± 1.2 g/dl, respectively. No significant correlation between these two variables was found ($p = 0.684$).

Blood loss did not significantly change by surgical technique (LRP versus RARP) and SM+ rates slightly yet significantly ($p = 0.032$) varied according to this parameter, without a specific trend: a higher SM+ rate was found in cases with a Hb variation between 2–4 g/dl (35.9%), when compared to lower (<2 g/dl = 31.9%) or higher (>4 g/dl = 29.6%) varia-

tions. In our experience, blood loss was a variable with a limited influence on SM status and no influence on functional post-operative outcomes.

Moreover, operative time did not significantly vary by surgical technique. Indeed, 22.0% and 33.0% of LRP and RARP were in the operative time group <120 min, and 40.4% and 43.3% in the operative time group of 120–180 min, respectively. On the contrary, in our experience, operative time showed a significant ($p < 0.05$) and strong correlation with both SM and post-operative ED, yet not with post-operative UI ($p = 0.733$). In particular, considering an operative time between 120–180 min as reference, SM+ significantly increased from 26.9% to 41.2% in faster (<120 min) RP and to 53.4% in slower (>240 min) RP ($p = 0.002$). Post-operative ED progressively increased according to operative time from 22.4% (<120 min) to 60.3% (>240 min) ($p = 0.001$). On univariate analysis, the risk of SM+ increased 1.70 times in <120 min RP ($p = 0.020$) and 1.94 times in >240 min RP ($p = 0.034$). The risk of post-operative ED increased 2.41 times in ≥ 240 min RP ($p = 0.007$).

In summary, a faster RP, independently from the approach (LRP or RARP), determined a lower rate of ED, but a higher rate of SM+. A slower RP determined a higher rate of both SM+ and post-operative ED. On multivariate analysis, operative time remained a significant independent predictor of SM+, yet not of post-operative ED where other variables (NS procedure and age) interfered on outcomes.

Our study prospectively represents a real-life non-randomized experience in high-volume and high-experience centers for the management of PC, where either a laparoscopic or a robotic-assisted procedure is offered to patients. Limitations of our analysis are mainly represented by the limited follow-up after surgery - that do not consent to obtain results also in terms of biochemical progression and survival.

CONCLUSIONS

Independently to the surgical laparoscopic or robotic approach, operative time more than blood loss at RP represents a significant variable able to influence oncological outcomes in terms of SM+ and post-operative functional results in terms of ED. In particular, a faster than 120 min RP significantly and independently increases the risk of SM+, whereas the incidence of ED progressively, yet not independently to other variables (age and NS procedure) increases according to operative time.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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