Central European Journal of Urology

ORIGINAL PAPER

UROLOGICAL ONCOLOGY

Robotic-assisted, laparoscopic, and open radical cystectomy: surgical data of 1400 patients from The Italian Radical Cystectomy Registry on intraoperative outcomes

Angelo Porreca[1], Luca Di Gianfrancesco[1], Walter Artibani[2], Gian Maria Busetto[3], Giuseppe Carrieri[3], Alessandro Antonelli[4], Lorenzo Bianchi[5], Eugenio Brunocilla[5], Aldo Massimo Bocciardi[6], Marco Carini[7], Antonio Celia[8], Giovanni Cochetti[9], Andrea Gallina[10], Ettore Mearini[9], Andrea Minervini[11], Riccardo Schiavina[5], Sergio Serni[7], Daniele D'Agostino[12], Erica Debbi[1], Paolo Corsi[1], Alessandro Crestani[1]

[1]*Oncological Urology, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy*
[2]*Department of Urology, Policlinico Abano Terme, Abano Terme, Italy*
[3]*Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy*
[4]*Department of Urology, Azienda Ospedaliera Universitaria Integrata, Verona, Italy*
[5]*Department of Urology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*
[6]*Struttura Complessa Urologia, ASST, Grande Ospedale Metropolitano Niguarda, Milano, Italy*
[7]*Unit of Oncologic Minimally-Invasive Urology and Andrology, Careggi Hospital, Firenze, Italy*
[8]*Department of Urology, San Bassiano Hospital, Bassano Del Grappa, Italy*
[9]*Department of Urology, University of Perugia, Perugia, Italy*
[10]*Department of Urology and Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, URI, Urological Research Institute, Milano, Italy*
[11]*Department of Urology, Careggi Hospital, University of Florence, Firenze, Italy*
[12]*Department of Urology, Ospedale Villa Salus, Mestre, Italy*

Citation: Porreca A, Di Gianfrancesco L, Artibani W, et al. Robotic-assisted, laparoscopic, and open radical cystectomy: surgical data of 1400 patients from The Italian Radical Cystectomy Registry on intraoperative outcomes. Cent European J Urol. 2022; 75: 135-144.

Article history
Submitted: Dec. 2, 2021
Accepted: April 4, 2022
Published online: May 4, 2022

Corresponding author
Luca Di Gianfrancesco
Department of Oncological Urology
Istituto Oncologico Veneto (IOV) IRCCS
sede di Castelfranco Veneto
Treviso, Italy
phone: +39 3202167165
luca.digianfrancesco@iov.veneto.it

Introduction The Italian Radical Cystectomy Registry (Registro Italiano Cistectomie – RIC) aimed to analyse outcomes of a multicenter series of patients treated with radical cystectomy (RC) for bladder cancer.

Material and methods An observational, prospective, multicenter, cohort study was performed to collect data from RC and urinary diversion via open (ORC), laparoscopic (LRC), or robotic-assisted (RARC) techniques performed in 28 Italian Urological Departments. The enrolment was planned from January 2017 to June 2020 (goal: 1000 patients), with a total of 1425 patients included. Chi-square and t-tests were used for categorical and continuous variables. All tests were 2-sided, with a significance level set at $p < 0.05$.

Results Overall median operative-time was longer in RARCs (390 minutes, IQR 335–465) than ORCs (250, 217–309) and LRCs (292, 228–350) ($p < 0.001$). Lymph node dissection (LND) was performed more frequently in RARCs (97.1%) and LRCs (93.5%) than ORCs (85.6%) ($p < 0.001$), with extended-LND performed 2-fold more frequently in RARCs (61.6%) ($p < 0.001$). The neobladder rate was significantly higher (more than one-half) in RARCs. The median estimated blood loss (EBL) rate was lower in RARCs (250 ml, 165–400) than LRCs (330, 200–600) and ORCs (400, 250–600) ($p < 0.001$), with intraoperative blood transfusion rates of 11.4%, 21.7% and 35.6%, respectively ($p < 0.001$). The conversion to open rate was slightly higher in RARCs (6.8%) than LRCs (4.3%). Intraoperative complications occurred in 1.3% of cases without statistically significant differences among the approaches.

Conclusions Data from the RIC confirmed the need to collect as much data as possible in a multicenter manner. RARCs proves to be feasible with perioperative complication rates that do not differ from the other approaches.

Key Words: radical cystectomy ‹› bladder cancer ‹› robotic-assisted ‹› intraoperative outcomes ‹› multicenter registry

Cent European J Urol. 2022; 75: 135-144
doi: 10.5173/ceju.2022.0284

INTRODUCTION

In selected cases of high-risk non-muscle invasive bladder cancer (NMIBC) or muscle invasive bladder cancer (MIBC) the optimal oncological is reached with radical cystectomy (RC) [1, 2]: moreover, it is considered the gold standard. This surgery is complex, with significant morbidity, and it essentially consists of two phases, the destructive phase (removal of the bladder and the lymph nodes) and the reconstructive phase (urinary diversion), and each step is prone to complications. Therefore, RC is preferably performed in referral centers where the experience of the surgeon and the facilities allow to minimize the burden of this complex surgery.

Open RC (ORC) has represented the gold standard approach for a long time; recently, the increased introduction of new technologies has led to minimally invasive approaches such as laparoscopic RC (LRC), and robotic-assisted RC (RARC) becoming more and more applied in this field.

Surely, RARC represents a challenging procedure that can be improved with specific training and a skilled robotic team [3]. However, RARC is a suitable technique for both older and younger patients [4] and has shown promising rates of peri-operative and short-term outcomes compared to ORC: lower rates of minor perioperative complications, decreased blood loss and transfusion rate, faster gastrointestinal recovery, and shorter length of stay [5]. Despite several studies reporting comparable long-term oncological outcomes for RARC versus ORC [6–9], data on the long-term functional outcomes is sparse. No studies have directly compared urinary continence or sexual potency in patients receiving neobladder after RARC versus ORC.

Not least, the economic burden of RARC is heavier than open surgery due to higher supply costs, but an effective cost-effective analysis is lacking to date.

In a systematic review, Novara et al. demonstrated the safety, acceptable operative time other than relatively lower estimated blood loss (EBL), and relatively low transfusion rate for RARC compared to ORC and LRC [10].

Most intra-abdominal surgical procedures in urology are now performed robotically worldwide. The transition is gradual due to the high cost of the technology and the associated learning curve. The hope is that with more competition in the robotic technology space, the advent of new robotic companies will bring the overall costs down and will reduce the robotic technology healthcare disparities.

The Italian Radical Cystectomy Registry (Registro Italiano Cistectomie – RIC) Protocol [11] aimed to accurately and comprehensively assess the outcomes of RC in order to improve current clinical knowledge. The aim of this study was to analyse intraoperative outcomes of a multicenter series of patients treated with RC for bladder cancer.

MATERIAL AND METHODS

Study design and inclusion criteria

An observational, prospective, multicenter, cohort study was performed in order to constitute the RIC, a protocol with the aim to collect data from RC and urinary diversion via open, laparoscopic, or robotic-assisted technique performed in the most important urological Departments of Italy.

Inclusion criteria: male and female patients ≥18 years old, histologically proven diagnosis of bladder cancer deserving of RC surgery (according to EAU guidelines), signed informed consent.

The enrolment was planned to be performed from January 1st 2017 to June 30th 2020, with a goal of 1000 patients, based on power calculations. The enrolment was discontinued before the planned deadline with the inclusion of 1400 patients.

The RIC is an electronic registry of the 28-participating clinical centers. At each center, patient data was collected in accordance with Italian privacy laws, and entered into an online database by a coordinating physician. Data collection and entering was done using the Data Collection Form, which was designed by the Scientific and Steering Committees. The Data Collection Form was designed using either prespecified or open-ended responses for each question, to ensure homogeneity between centers.

Patients' data were securely stored and kept anonymously using identification codes. The database was password protected. As data sharing is becoming increasingly important, the data was regularly transferred to a globally-accessible online platform. The trial was registered retrospectively on ClinicalTrials.gov on 14/01/2020 with reference number NCT04228198. Data collection was conducted in accordance with the World Medical Association Declaration of Helsinki. This study was approved on 25/06/2020 by Ethical Committee of the University of Padova (number: 0042389). All patients provide signed, informed consent.

Participating centers

All Italian urological departments that currently provide care for RC patients using all three (open, robotic-assisted, laparoscopic) approaches were invited to participate, on a voluntary basis, without additional funding for the centers or participants.

Patients underwent laparoscopic, robotic or open approach at the discretion of the surgeon.
A physician at each center was assigned the management of the recruitment of patients, data collection, the entering of the data into the registry, the data security and the anonymity of the patients. Patients were enrolled at 28 centers across Italy.

Timeline and data collection

The scheduled enrolment of patients was performed as described in Figure 1. Patients' baseline and preoperative characteristics are described in Table 1.
We collected surgical data on total surgery time, type of urinary diversion, median time for urinary diversion, conversion to open surgery, intraoperative bleeding, nerve sparing technique, lymphadenectomy (including its extension).
The post-surgery follow-up was demanded to a subsequent evaluation (the scheduled follow-up is actually ongoing, and at this time is still incomplete).

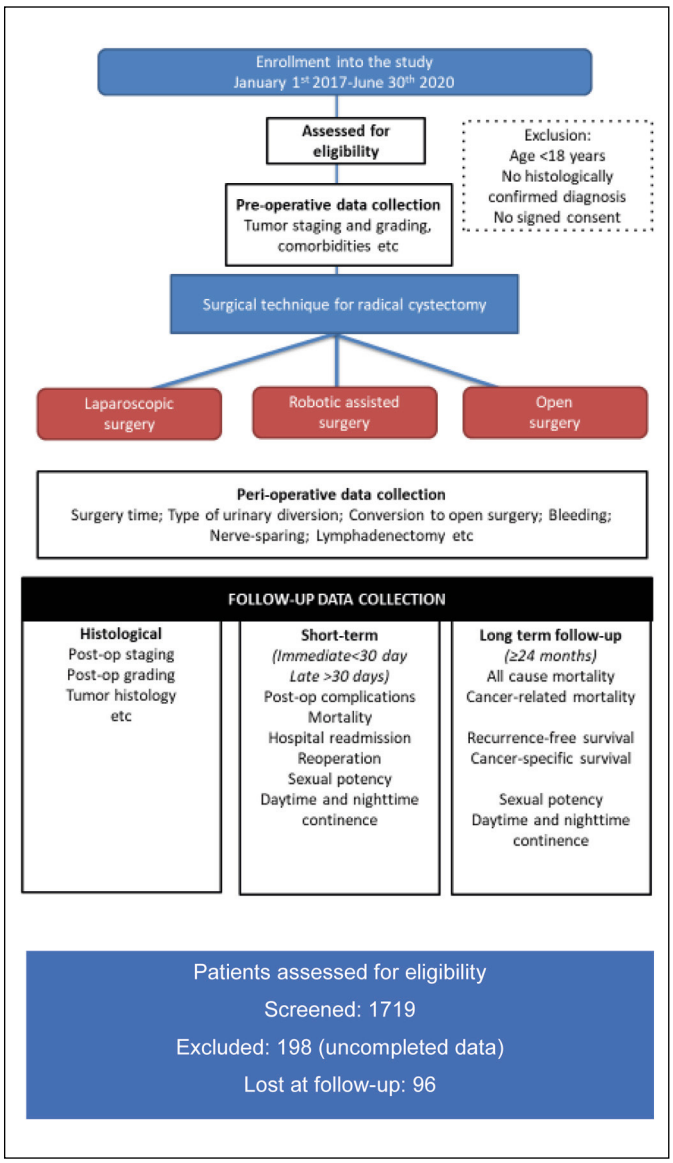

Figure 1. *Scheduled enrollment of patients.*

Statistical analysis

Data were cleaned and checked for discrepancies by a statistician before analysis and dissemination. Chi-square and t-tests were used to compare categorical and continuous variables, respectively, between surgical technique groups. Statistical analyses were performed using Stata-SE 15 (StataCorp LP, College Station, TX, USA). All tests were 2-sided with a significance level set at $p < 0.05$.

RESULTS

A total of 1425 patients were enrolled (1009 ORCs, 368 RARCs, 46 LRCs). Surgical characteristics are reported in Table 2.
Overall median operative time (OT) was longer for RARC [390 minutes (IQR 335-465)] than ORC [250 (217–309)] and LRC [292 (228–350)], with statistically significant differences ($p < 0.001$). Similar results were reported regarding each surgical step. The median cystectomy surgical time was longer for RARC [140 minutes (IQR 115–180)] than the other two approaches [90 minutes (60–120) for ORC and 100 minutes (72–135) for LRC], with statistically significant differences ($p < 0.001$).
Lymph node dissection (LND) was performed in more cases during RARC (97.1%) and LRC (93.5%) than ORC (85.6%), with statistically significant differences ($p < 0.001$). Moreover, LND was not performed up to 2–3 fold in ORC (14.5%) than in the two other types of RC.
Regarding the type of LND, the limited dissection rate was similar among the three types of RC, while the rate of extended dissection was more than 2-fold higher in case of RARC (61.6%) compared to the two other RC types with statistically significant differences ($p < 0.001$). The median time of LND was higher in case of RARC (80 minutes, IQR 60–100) than the two other types of RC, and in particular up to 2-fold higher by comparing RARC to ORC.
The nerve sparing technique was performed in nearly one-third of RARC cases, while with regards to the other two techniques, almost all patients did not undergo the nerve-sparing technique.
In the RARC group the rate of neobladders was significantly higher (more than one-half) compared to the two other approaches where the non-continent diversion was preferred in up to the 80% of cases.

Table 1. *Patients' baseline and pre-operative characteristics*

	Overall n = 1425	Open n = 1009	Robotic n = 368	Laparoscopic n = 46	P value
Age	71 (64, 77)	72 (65, 78)	67 (60, 74)	76 (65, 77)	<0.001
BMI	26.0 (23.7, 28.1)	26.0 (23.7, 28.2)	26.0 (23.8, 28.3)	24.2 (23.1, 25.6)	0.002
Sex, n (%)					
Female	267 (18.7%)	206 (20.4%)	54 (14.6%)	7 (15.2%)	0.018
Male	1156 (81.1%)	803 (79.6%)	314 (84.9%)	39 (84.8%)	
Missing	2 (0.1%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	
ASA score, n (%)					
1	105 (7.4%)	42 (4.2%)	61 (16.5%)	2 (4.3%)	<0.001
2	582 (40.8%)	396 (39.2%)	162 (43.8%)	24 (52.2%)	
3	579 (40.6%)	476 (47.2%)	87 (23.5%)	16 (34.8%)	
4	65 (4.6%)	58 (5.7%)	4 (1.1%)	3 (6.5%)	
5	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	
Missing	93 (6.5%)	37 (3.7%)	56 (15.1%)	0 (0.0%)	
Preoperative T stage, n (%)					
Ta	50 (3.5%)	35 (3.5%)	14 (3.8%)	1 (2.2%)	0.040
T1	268 (18.8%)	199 (19.7%)	59 (15.9%)	10 (21.7%)	
T2	911 (63.9%)	633 (62.7%)	250 (67.6%)	28 (60.9%)	
T3	70 (4.9%)	51 (5.1%)	15 (4.1%)	4 (8.7%)	
T4a	36 (2.5%)	33 (3.3%)	2 (0.5%)	1 (2.2%)	
T4b	10 (0.7%)	10 (1.0%)	0 (0.0%)	0 (0.0%)	
Tis	43 (3.0%)	28 (2.8%)	14 (3.8%)	1 (2.2%)	
Missing	37 (2.6%)	20 (2.0%)	16 (4.3%)	1 (2.2%)	
Preoperative grade, n (%)					
G1	34 (2.4%)	27 (2.7%)	7 (1.9%)	0 (0.0%)	<0.001
G2	69 (4.8%)	45 (4.5%)	16 (4.3%)	8 (17.4%)	
G3	1259 (88.4%)	905 (89.7%)	317 (85.7%)	37 (80.4%)	
Missing	63 (4.4%)	32 (3.2%)	30 (8.1%)	1 (2.2%)	
Concomitant CIS, n (%)					
No	1171 (82.2%)	842 (83.4%)	286 (77.3%)	43 (93.5%)	<0.001
Yes	221 (15.5%)	154 (15.3%)	64 (17.3%)	3 (6.5%)	
Missing	33 (2.3%)	13 (1.3%)	20 (5.4%)	0 (0.0%)	
Neoadjuvant chemotherapy, n (%)					
No	1241 (87.1%)	911 (90.3%)	284 (76.8%)	46 (100.0%)	<0.001
Yes	157 (11.0%)	87 (8.6%)	70 (18.9%)	0 (0.0%)	
Missing	27 (1.9%)	11 (1.1%)	16 (4.3%)	0 (0.0%)	
Preoperative BCG, n (%)					
No	1114 (78.2%)	818 (81.1%)	254 (68.6%)	42 (91.3%)	<0.001
Yes	281 (19.7%)	180 (17.8%)	97 (26.2%)	4 (8.7%)	
Missing	30 (2.1%)	11 (1.1%)	19 (5.1%)	0 (0.0%)	
Palliative cystectomy, n (%)					
No	1272 (89.3%)	895 (88.7%)	338 (91.4%)	39 (84.8%)	<0.001
Yes	127 (8.9%)	108 (10.7%)	12 (3.2%)	7 (15.2%)	
Missing	26 (1.8%)	6 (0.6%)	20 (5.4%)	0 (0.0%)	
Diabetes, n (%)					
No	1126 (79.0%)	806 (79.9%)	287 (77.6%)	33 (71.7%)	<0.001
Yes	247 (17.3%)	187 (18.5%)	47 (12.7%)	13 (28.3%)	
Missing	52 (3.6%)	16 (1.6%)	36 (9.7%)	0 (0.0%)	
Hypertension, n (%)					
No	593 (41.6%)	423 (41.9%)	152 (41.1%)	18 (39.1%)	<0.001
Yes	790 (55.4%)	577 (57.2%)	185 (50.0%)	28 (60.9%)	
Missing	42 (2.9%)	9 (0.9%)	33 (8.9%)	0 (0.0%)	
Cardiopathy, n (%)					
No	1036 (72.7%)	726 (72.0%)	280 (75.7%)	30 (65.2%)	<0.001
Yes	346 (24.3%)	273 (27.1%)	57 (15.4%)	16 (34.8%)	
Missing	43 (3.0%)	10 (1.0%)	33 (8.9%)	0 (0.0%)	
COPD, n (%)					
No	1169 (82.0%)	832 (82.5%)	300 (81.1%)	37 (80.4%)	<0.001
Yes	208 (14.6%)	166 (16.5%)	34 (9.2%)	8 (17.4%)	
Missing	48 (3.4%)	11 (1.1%)	36 (9.7%)	1 (2.2%)	

Table 1. *Continued*

	Overall n = 1425	Open n = 1009	Robotic n = 368	Laparoscopic n = 46	P value
History of transient ischemia, n (%)					
No	1303 (91.4%)	938 (93.0%)	323 (87.3%)	42 (91.3%)	<0.001
Yes	71 (5.0%)	56 (5.6%)	13 (3.5%)	2 (4.3%)	
Missing	51 (3.6%)	15 (1.5%)	34 (9.2%)	2 (4.3%)	
Anticoagulant, n (%)					
No	871 (61.1%)	623 (61.7%)	224 (60.5%)	24 (52.2%)	<0.001
Yes	503 (35.3%)	376 (37.3%)	105 (28.4%)	22 (47.8%)	
Missing	51 (3.6%)	10 (1.0%)	41 (11.1%)	0 (0.0%)	

n – number of patients; BMI – body mass index; ASA – American Society of Anesthesiology; CIS – carcinoma in situ; BCG – Bacillus Calmette-Guerin; COPD – chronic obstructive pulmonary disease

Table 2. *Surgical characteristics*

	Overall n = 1425	ORC n = 1009	RARC n = 368	LRC n = 46	P value (RARC vs ORC)	P value (RARC vs LRC)
Nerve sparing, n (%)						
No	1257/1425 (88.2%)	966/1009 (95.7%)	246/368 (66.5%)	45/46 (97.8%)		
Unilateral	10/1425 (0.7%)	2/1009 (0.2%)	7/368 (1.9%)	1/46 (2.2%)		
Bilateral	124/1425 (8.7%)	26/1009 (2.6%)	98/368 (26.5%)	0/46 (0.0%)		
Missing	34/1425 (2.4%)	15/1009 (1.5%)	19/368 (5.1%)	0/46 (0.0%)		
PLND, n (%)						
Not performed	160/1425 (11.2%)	146/1009 (14.5%)	11/368 (3.0%)	3/46 (6.5%)		
Iliac ott ext bil	914/1425 (64.1%)	693/1009 (68.7%)	186/368 (50.3%)	35/46 (76.1%)		
Iliac ott ext presacral bil	327/1425 (22.9%)	164/1009 (16.3%)	155/368 (41.9%)	8/46 (17.4%)		
Missing	24/1425 (1.7%)	6/1009 (0.6%)	18/368 (4.9%)	0/46 (0.0%)		
PLND type, n (%)						
Not performed	173/1425 (12.1%)	150/1009 (14.9%)	20/368 (5.4%)	3/46 (6.5%)		
Limited	86/1425 (6.0%)	64/1009 (6.3%)	18/368 (4.9%)	4/46 (8.7%)		
Standard	601/1425 (42.2%)	493/1009 (48.9%)	82/368 (22.2%)	26/46 (56.5%)		
Extended	526/1425 (36.9%)	287/1009 (28.4%)	228/368 (61.6%)	11/46 (23.9%)		
Missing	39/1425 (2.7%)	15/1009 (1.5%)	22/368 (5.9%)	2/46 (4.3%)		
Diversion, n (%)						
Open	1079/1425 (75.7%)	1009/1009 (100%)	69/368 (18.6%)	10/46 (21.7%)		
Robotic	295/1425 (20.8%)	0/1009 (0.0%)	295/368 (79.7%)	0/46 (0.0%)		
Laparoscopic	36/1425 (2.7%)	0/1009 (0.0%)	3/368 (0.8%)	36/46 (78.3%)		
Missing	3/1425 (0.01%)	0/1009 (0.0%)	3/368 (0.8%)	0/46 (0.0%)		
Frozen section, n (%)						
Normal urethra	333/1425 (23.4%)	180/1009 (17.8%)	148/368 (40.0%)	5/46 (10.9%)		
CIS urethra	11/1425 (0.8%)	6/1009 (0.6%)	5/368 (1.4%)	0/46 (0.0%)		
Normal Bundle	1/1425 (0.1%)	1/1009 (0.1%)	0/368 (0.0%)	0/46 (0.0%)		
Missing	35/1425 (2.5%)	15/1009 (1.5%)	20/368 (5.4%)	0/46 (0.0%)		
Urinary diversion, n (%)						
Ileal conduit	540/1425 (38.2%)	430/1009 (43.0%)	101/368 (27.4%)	9/46 (20.0%)		
Neobladder	435/1425 (30.8%)	205/1009 (20.5%)	216/368 (58.7%)	14/46 (31.1%)		
Ucs	437/1425 (30.9%)	364/1009 (36.4%)	51/368 (13.9%)	22/46 (48.9%)		
Total Surgical Time, min (IQR)	283 (217, 360)	250 (197, 309)	368 (335, 465)	292 (228, 350)	<0.001	<0.001
Cystectomy Surgical Time, min (IQR)	100 (60, 140)	90 (60, 120)	140 (115, 180)	100 (72, 135)	<0.001	<0.001
LND Surgical Time, min (IQR)	50 (30, 65)	40 (20, 60)	80/368 (60, 100)	60 (40, 83)	<0.001	<0.001
Diversion Surgical Time, min (IQR)	70 (40, 115)	60 (30, 90)	134/368 (100, 194)	100 (60, 125)	<0.001	<0.001

n – number of patients; RARC – robotic-assisted radical cystectomy; ORC – open radical cystectomy; LRC – laparoscopic radical cystectomy; PLND – pelvic lymph node dissection; CIS – carcinoma in situ; IQR – interquartile range; Ucs – ureterocutaneostomy

The diversion was performed with the same approach of RC for the majority of the cases of RARC and LRC, with comparable rates (79.7% and 78.3%, respectively).

Regarding the median urinary diversion time, it was significantly higher in RARC (134 minutes, IQR 100–194) compared to LRC (100 min, IQR 60–125) and ORC (60 min, IQR 30–90) ($p < 0.001$).

Regarding the intraoperative EBL, the median rate was significantly lower in RARC (250 ml, IQR 165–400) than in the two other approaches: 400 ml (IQR 250–600) for ORC, and 330 ml (IQR 200–600) for LRC) (p <0.001).
The rate of conversion to open procedure was slightly higher in case of RARC compared to LRC (6.8% vs 4.3%, respectively).
Intraoperative blood transfusion rate was 11.4%, 21.7% and 35.6% for RARC, LRC and ORC approach respectively (p <0.001).
Intraoperative complications (Table 3) occurred in 18/1425 cases (1.3%). No statistically significant differences were detected between three groups. Regarding intraoperative complications requiring conversion to open, no cases were recorded in the RARC group, three cases of rectal injury and two cases of vascular injury received an intracorporeal suture.
After match-pairing, 34 patients for each approach (ORC, RARC, LRP) were selected and compared. The statistically significant differences demonstrated for overall population were confirmed after match-pairing analysis (Table 4).

DISCUSSION

The results of the Italian Radical Cystectomy registry show that minimally invasive RC is feasible with

Table 3. *Intraoperative complications*

Conversion to open, n (%)	Overall	ORC	RARC	LRC	P value (RARC vs ORC)	P value (RARC vs LRP)
No	n/a	n/a	319/368 (86.2%)	44/46 (95.7%)		
Yes	n/a	n/a	25/368 (6.8%)	2/46 (4.3%)		<0.001
Missing data	n/a	n/a	26/368 (7.0%)	0/46 (0.0%)		
Intraoperative complications, n (%)						
Number	18/1425 (1.3%)	11/1009 (1.1%)	5/368 (1.4%)	2/46 (4.3%)	<0.001	<0.001
Type	Rectal injury: 11/1425 (0.8%) Vascular injury 7/1425 (0.5%)	Rectal injury: 7/1009 (0,7%) Vascular injury: 4/1009 (0.4%)	Rectal injury: 3/368 (0.8%) Vascular injury: 2/368 (0,5%)	Rectal injury: 1/46 (2,2%) Vascular injury: 1/46 (2.2%)		
Treatment		Suture	Suture	Conversion to open Suture		
Estimate blood loss, mL (IQR)	390 (200, 600)	400 (250–600)	250 (165–400)	330 (200–600)	<0.001	<0.001
Intraoperative blood transfusion, n (%)	411/1425	359/1009 (35.6%)	42/368 (11.4%)	10/46 (21.7%)	<0.001	<0.001

n – number of patients; ORC – open radical cystectomy; RARC – robotic-assisted radical cystectomy; LRC – laparoscopic radical cystectomy; IQR – interquartile range

Table 4. *Perioperative outcomes stratified for different approach after match-pairing*

	Overall n = 102	ORC n = 34	RARC n = 34	LRC n = 34	P value (RARC vs ORC)	P value (RARC vs LRC)
Intraoperative complications, n (%)						
Number	2/102 (2%)	1/34 (2.9%)	0/34 (0%)	1/34 (2.9%)	n/a	n/a
Type	Rectal injury: 2/102 (2%)	Rectal injury: 1/34 (2.9%)	Rectal injury: 0/34 (0%)	Rectal injury: 1/34 (2.9%)		
Treatment		Suture	Suture	Conversion to open Suture		
Estimate Blood Loss, mL (IQR)	380 (195. 590)	410 (270–620)	250 (165–410)	345 (210–605)	<0.001	<0.001
Total Surgical Time, min (IQR)	270 (205. 350)	260 (240. 307)	395 (340. 470)	295 (240. 370)	<0.001	<0.001
Cystectomy Surgical Time, min (IQR)	105 (60. 145)	90 (60. 120)	145 (120. 180)	105 (69. 140)	<0.001	<0.001
LND Surgical Time, min (IQR)	50 (30. 65)	40 (20. 60)	85 (60. 100)	60 (40. 83)	<0.001	<0.001
Diversion Surgical Time, min (IQR)	73 (45. 115)	60 (30. 90)	134 (100. 194)	100 (60. 125)	<0.001	<0.001

n – number of patients; ORC- open radical cystectomy; RARC – robotic-assisted radical cystectomy; LRP – laparoscopic radical cystectomy; IQR – interquartile range; LND – lymph node dissection

good perioperative profile in terms of intraoperative outcome. RARC and LRC show lower EBL compared to ORC. RARC is characterized by longer median OT probably explained by the learning curve of robotic approach other than by urinary diversion type utilized. Orthotopic neobladder is more likely used during robotic procedures.

RC actually represents one of the most complex urological surgery, and the increasingly technological improvement represents the way to the employment of minimally invasive approaches to this major surgery. There are currently very few randomized control trials (RCTs) comparing the three considered approaches, and previous non-randomized studies had small sample sizes and short follow-up. The RCTs are the preferred study design for evaluating treatment efficacy, but there is also the need of comparison-effective studies: there are multiple factors that determine the choice and outcomes of surgical techniques in real-life clinical settings, including complex clinical decision making, patient and hospital characteristics, and surgical expertise. The RIC aimed to provide data to this rapidly developing field by creating a nationwide, multicenter registry with two-year post-surgery follow-up of bladder cancer patients treated with RC, with a comprehensive data collection on multiple outcomes.

A direct comparison of RARC to ORC and LRC was not optimal based on previously published RCTs [12, 13]; surgical RCTs are difficult to perform successfully, leading to methodological and practical issues: several biases might arise from low accrual rate, preferences of the patients, different skills of surgeons and team, different standardisation of the technique among centers and difficulties regarding the blinding of the procedures [14]. These reasons lead to the choice of a comparative effectiveness design alternative to an optimal surgical RCT.

The ORC is a well-developed technique and it has represented the standard treatment for many years. RARC is increasingly performed [15], since many urologists are trained mainly in minimally invasive technique: the laparoscopic RC is challenging, therefore RARC might be the only minimally invasive alternative.

Recent systematic reviews comparing ORC and RARC reported lower rates of blood loss and an approximately one-day shorter length of hospital stay (LOS) in case of RARC, but with longer operative time. The complication rates seemed similar for both approaches but all published reviews suffer from low quality data.

In the systematic review performed by Novara et al., despite the post-operative complications being common, the authors reported a low risk of intraoperative complications. In their cumulative analyses, authors demonstrated a shorter operative time with ORC, whereas blood loss and transfusion rates were significantly lower with RARC than with ORC. Conversely, rates for any grade and grade 3 complication at 90 days were slightly lower with RARC than with ORC. Similarly, transfusion rates were lower with RARC than with LRC, as were any grade and grade 3 complication rates [10].

In a systematic review and meta-analysis, Sathianathen et al. confirmed less frequent intraoperative blood transfusion rates (13% vs 34%, $p < 0.0001$) and our results appeared comparable, in particular for what concerned the comparison between RARC and ORC (11.4% vs 35.6%, $p < 0.0001$, respectively) [16].

Despite the major limitation of the low level of evidence of the studies included in recent systemic reviews, most findings were corroborated by a recent Cochrane review incorporating data from all five published RCTs, where the time to recurrence, the positive surgical margin rates and grade 3–5 complications appeared comparable for RARC and ORC, whilst transfusion rate was likely lower after RARC [17].

Similar conclusions were confirmed by the Pasadena Consensus Panel (a group of experts on RC, LND and urinary reconstruction) [18], with additional data regarding the increased costs associated with RARC.

Furthermore, Rai et al. reported comparable rates of positive surgical margins, as a surrogate for oncological outcome, between RARC and ORC, although with low certainty [17].

Regarding LRC, Tang et al. in a review including sixteen studies, reported similar conclusions as described for RARC [19]. Moreover, Albisinni et al. in a multicenter study, confirmed significantly longer operative time, fewer overall complications, less blood transfusions and analgesic use, less blood loss and a shorter LOS for LRC compared to ORC [20].

One of the most interesting data concerned the LND issue: it was performed more frequently in RARC (in almost all cases, up to 97.1%) and with a 2-fold higher rate of extended dissection compared to the other two approaches. This data might be justified by the lower disease stage of the cases performed with the robotic-assisted approach, but surely it reflected the need of an accurate and extended LND not only in terms of accurate diagnosis but also in a prognostic point of view.

In our study LND was most frequently performed during RARC compared to ORC and LRC group. The absence of LND in 14.5% of patients in ORC group is essentially due to the high number of palliative surgeries presents in this group.

Controversies in evaluating the clinical significance of LND still concern RC in general, and they are generally related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument. In general, studies comparing LND vs no LND reported a better oncological outcome for the LND group [21]. To date, the optimal extent of LND has not been established yet. In two high-volume center studies, the authors reported no difference in outcome between extended and super-extended LND [22]. In the LEA trial [23] the extended LND failed to show a significant advantage over limited LND in RFS, CSS, and OS but, differently, Mandel et al. and Bi et al., in meta-analyses, reported a beneficial outcome for (super)extended compared to limited or standard LND [24, 25].

Moreover, Koppie et al. showed how the survival rates increase with the number of dissected lymph nodes [26], but regarding the optimal minimum number to be removed during surgery there are no data from RCTs. In retrospective studies, the removal of at least ten lymph nodes has been postulated as sufficient for evaluation of lymph node status, as well as being beneficial for OS [27]. In conclusion, extended LND might have a therapeutic benefit compared to less extensive LND, but due to study bias no firm conclusions have been drawn to date [28].

Among the advantages of RARC there are the higher manoeuvrability and the image amplification: these allowed to perform nerve sparing technique in nearly one-third of cases and the orthotopic continent neobladder in more than one-half of cases, and these rates appeared to be significantly higher compared to the other two techniques.

RARC surely represents a costly procedure, but the non-inferiority in terms of surgical outcomes and the increasing opportunities from different and more and more competitive robotic-industry products might overcome the economic aspects. An open question concerns how the complications translate into costs and quality-adjusted life years, and if it possible to build scenarios in which RARC might become a gold standard treatment in terms of cost-effectiveness or at least cost-neutrality [29].

Furthermore, in a cohort of 267 patients treated with RARC and intracorporeal (ICUD) or extracorporeal (ECUD) urinary diversion, Mazzone et al. reported how Age-adjusted Charlson Comorbidity Index (ACCI) was associated with an increased risk of Clavien Dindo ≥2 (OR: 1.2, p = 0.006), by identifying a significant interaction term between ACCI and approach type (p = 0.04), where patients with ICUD had lower risk of CD ≥2 relative to those with ECUD with increasing ACCI. The authors tried to identify a recommendation from which patients might benefit more from the RARC approach [30].

The limitations of the study consisted of: short follow-up, different number of cases performed in different centers (with different surgical volumes), potential different protocols of reporting complications and different perioperative protocols, the cohorts were not balanced in terms of surgeon's experience, patient and tumour characteristics, the lack of propensity score matching and multiple regression analyses and aimed to control for the most important group differences and potential confounders. Nonetheless, statistics cannot replace prospective RCTs. Furthermore, not all surgeons conducted both RARC and ORC and no mid- or long-term follow-up was included to compare the oncological outcomes, which are currently ongoing.

CONCLUSIONS

RC still represents a challenging procedure and RARC is gaining its role in this important issue, despite some disadvantages but also thanks to a lot of advantages. Moreover, the initial results are corroborating what reported in the international background.

Data from the RIC Italian registry confirmed the need and the usefulness to collect as much data as possible in a multicenter manner. In the next years, this longitudinal study might represent a benchmark and the base for every further research in the context of RC.

DATA SHARING STATEMENT

Will individual participant data be available (including data dictionaries)?
Yes

What data in particular will be shared?
Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices).

What other documents will be available?
Study protocol, statistical analysis plan, informed consent form, clinical study report, analytic code.

When will data be available (start and end dates)?
Immediately following publication. No end date.

With whom?
Researchers who provide a methodologically sound proposal.

For what types of analyses?
To achieve aims in the approved proposal.

By what mechanism will data be made available?
Proposals should be directed to luca.digianfrancesco@iov.veneto.it. To gain access, data requestors will need to sign a data access agreement

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING DETAILS

The Italian Radical Cystectomy Registry is an observational, non-profit study. AB Medica provided an unconditional grant solely for the maintenance of the database. AB Medica has no involvement in the acquisition, control, or management of the data. The registry and all data are exclusively owned by the Steering Committee.

References

1. Sylvester RJ, Rodríguez O, Hernández V, et al. European Association of Urology (EAU) Prognostic Factor Risk Groups for Non-muscle-invasive Bladder Cancer (NMIBC) Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An Update from the EAU NMIBC Guidelines Panel. Eur Urol. 2021; 79: 480-488.
2. Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2021; 79: 82-104.
3. Porreca A, Chessa F, Romagnoli D, et al. Robot assisted radical cystectomy with totally intracorporeal urinary diversion: initial, single-surgeon's experience after a modified modular training. Minerva Urol Nefrol. 2018; 70: 193-201
4. Romagnoli D, Bianchi FM, Corsi P, et al. Robot-assisted radical cystectomy with Intracorporeal Orthotopic Ileal Neobladder: a safe strategy in elderly patients? Results of propensity score matching in a single high-volume center. Surg Technol Int. 2019; 34: 302-309.
5. Davis RB, Farber NJ, Tabakin AL, Kim IY, Elsamra SE. Open versus robotic cystectomy: comparison of outcomes. Investig Clin Urol. 2016; 57 (Suppl 1): S36-S43.
6. Kim TH, Sung HH, Jeon HG, et al. Oncological outcomes in patients treated with radical cystectomy for bladder cancer: comparison between open, laparoscopic, and robot-assisted approaches. J Endourol. 2016; 30: 783-791.
7. Snow-Lisy DC, Campbell SC, Gill IS, et al. Robotic and laparoscopic radical cystectomy for bladder cancer: long-term oncologic outcomes. Eur Urol. 2014; 65: 193-200.
8. Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018; 391: 2525-2536.
9. Tan WS, Sridhar A, Ellis G, et al. Analysis of open and intracorporeal robotic assisted radical cystectomy shows no significant difference in recurrence patterns and oncological outcomes. Urol Oncol. 2016; 34: e1-e39.
10. Novara G, Catto JWF, Wilson T, et al. Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. Eur Urol. 2015; 67: 376-401.
11. Porreca A, Palmer K, Artibani W, et al. Protocol of the Italian Radical Cystectomy Registry (RIC): a non-randomized, 24-month, multicenter study comparing robotic-assisted, laparoscopic, and open surgery for radical cystectomy in bladder cancer. BMC Cancer. 2021; 21: 51.
12. Wijburg CJ, Michels CTJ, Oddens JR, et al. Robot assisted radical cystectomy versus open radical cystectomy in bladder cancer (RACE): study protocol of a non-randomized comparative effectiveness study. BMC Cancer. 2018; 18: 861
13. Bochner BH, Dalbagni G, Sjoberg DD, et al. Comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: a randomized clinical trial. Eur Urol. 2015; 67: 1042-1050.
14. Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. Trials. 2009; 10: 9.
15. van der Poel, Jong I-J. Jaarverslag cystectomieregistratie NVU 2017. Tijdschr Urol. 2019; 9: 56-67.
16. Sathianathen NJ, Kalapara A, Frydenberg M, et al. Robotic assisted radical cystectomy vs. open radical cystectomy: systematic review and meta-analysis. J Urol. 2019; 201: 715-720.
17. Rai BP, Bondad J, Vasdev N, et al. Robotic versus open radical cystectomy for bladder cancer in adults. Cochrane Database Syst Rev. 2019; 4: Cd011903.
18. Wilson TG, Guru K, Rosen RC, et al. Best practices in robot-assisted radical cystectomy and urinary reconstruction: recommendations of the Pasadena Consensus Panel. Eur Urol. 2015; 67: 363-375.
19. Tang K, Li H, Xia D, Hu Z, et al. Laparoscopic versus open radical cystectomy in bladder cancer: a systematic review and meta-analysis of comparative studies. PLoS One. 2014; 9: e95667.
20. Albisinni S, Rassweiler J, Abbou CC, et al. Long-term analysis of oncological outcomes after laparoscopic radical cystectomy in Europe: results from a multicentre study by the European Association of Urology (EAU) section of Uro-technology. BJU Int. 2015 115: 937-945.
21. Bruins HM, Veskimae E, Hernandez V, et al. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. Eur Urol. 2014; 66: 1065-1077.
22. Zehnder P, Studer UE, Skinner EC, et al. Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. J Urol. 2011; 186: 1261-1268.
23. Gschwend JE, Heck MM, Lehmann J, et al. Extended Versus Limited Lymph Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results from a Prospective, Randomized Trial. Eur Urol. 2019; 75: 604611.
24. Mandel P, Tilki D, Eslick GD. Extent of lymph node dissection and recurrence-free survival after radical cystectomy: a meta-analysis. Urol Oncol. 2014; 32: 1184-1190.

25. Bi L, Huang H, Fan X, et al. Extended vs non-extended pelvic lymph node dissection and their influence on recurrence-free survival in patients undergoing radical cystectomy for bladder cancer: a systematic review and meta-analysis of comparative studies. BJU Int. 2014; 113: E39-E48.

26. Koppie TM, Vickers AJ, Vora K, Dalbagni G, Bochner BH. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer. 2006; 107: 2368-2374.

27. W Wright JL, Lin DW, Porter MP. The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. Cancer. 2008; 112: 2401-2408.

28. Wang YC, Wu J, Dai B, et al. Extended versus non-extended lymphadenectomy during radical cystectomy for patients with bladder cancer: a meta-analysis of the effect on long-term and short-term outcomes. World J Surg Oncol. 2019; 17: 225.

29. Michels CTJ, Wijburg CJ, Leijte E, Witjes JA, Rovers MM, Grutters JPC. A cost-effectiveness modeling study of robot-assisted (RARC) versus open radical cystectomy (ORC) for bladder cancer to inform future research. Eur Urol Focus. 2019; 5: 1058-1065.

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: 803-812. ■