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Robot-assisted versus open radical cystectomy in patients receiving perioperative chemotherapy for muscle-invasive bladder cancer: the oncologists' perspective from a multicentre study

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Abstract

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Background—Little is known about the outcomes of robot-assisted radical cystectomy (RARC) compared to open radical cystectomy (ORC) combined with perioperative chemotherapy for muscle-invasive urothelial bladder cancer (UBC).

Objective—We aimed to evaluate the surgical and oncological outcomes of two cystectomy approaches in multimodal treatment.

Design, Setting, Participants—Data from 28 centres were collected for cystectomies performed between January 2000 and July 2013.

Intervention—RARC or ORC combined with perioperative chemotherapy for UBC.

Outcome measures and statistical analysis—Fisher's exact tests, χ^2 tests, and Wilcoxon rank sum tests were used to compare the RARC or ORC groups. Logistic and Cox regression analyses were performed to evaluate potential prognostic factors.

Results and limitations—A total of 688 patients (n=603 ORC and n=85 RARC) were analysed; 60.6% received neoadjuvant chemotherapy, and 45.1% adjuvant chemotherapy. No significant difference was found in the baseline characteristics between the surgical groups. Median time from surgery to adjuvant chemotherapy was 1.9 months for both RARC and ORC groups. The median (interquartile range, IQR) number of removed lymph nodes was 21 (14–35) with RARC and 13 (8–21) with ORC (p<0.001); results were confirmed in subgroup analyses. No difference was found in multivariable analyses in the rate of positive surgical margins (p=0.54 and p=0.78), rate of neobladder diversion (p=0.33 and p=0.51), relapse-free survival (p=0.31 and p=0.23), and overall survival (p=0.63 and p=0.69). The retrospective nature of the data was the major limitation.

Conclusions—In this study, no differences in efficacy outcomes or ability to deliver adjuvant chemotherapy were observed between RARC and ORC. The increasing use of RARC is justifiable from an oncological viewpoint.

Patient summary—In a retrospective study of patients who received perioperative chemotherapy for UBC, we found no difference in key outcomes between RARC and ORC. Performing RARC seems to be justifiable in the multidisciplinary setting.

Keywords

Urothelial carcinoma; Cystectomy; Robot-assisted surgery; Muscle-invasive disease; Perioperative chemotherapy

Introduction

Urothelial bladder cancer (UBC) is a highly aggressive disease. It is the 5th most common cancer in the Western world and the second most common malignancy of the urinary tract, after prostate cancer.[1] For patients who present with a localized high-risk disease, i.e., patients who have a non-muscle-invasive tumour but do not improve with standard conservative treatments or those having or developing muscle-invasive disease, radical cystectomy is the mainstay of curative treatment. Key negative prognostic factors include regional lymph node spread and the local extent of the disease. For this reason, achievement of negative surgical margins and the extent of the lymph node dissection (i.e., the number of

lymph nodes removed in radical cystectomy) are important to the outcome; this is the topic of several articles on UBC treatment.[2–6]

For patients with muscle-invasive tumours, systemic therapy increases the probability of cure. Administration of neoadjuvant chemotherapy improves overall survival (Level 1 evidence) and should be considered whenever cisplatin-based regimens can be safely administered, according to the guidelines of the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN).[7,8] However, pre-operative therapy is underutilized worldwide for many reasons, and neoadjuvant chemotherapy is administered in approximately 20% of cases.[8,9] Conversely, adjuvant chemotherapy has been the subject of many controversial and negative studies, yet it is still frequently administered. Recent data from a large clinical trial, a population-based study and a meta-analysis have supported its use in selected patients with high-risk features.[11,12]

Advances in technology have facilitated the spread of minimally invasive techniques to perform radical cystectomies, and robot-assisted laparoscopic approaches have been developed and improved in many centres. Robust literature reporting the safety outcomes of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) is already available. Key parameters, including length of hospital stay, intraoperative blood loss, and both early and delayed post-surgical complications, have been described.[13,14] Most of these data represent patients who were offered surgery with no additional therapy; to date, limited information about the comparative results of RARC and ORC is available for patients who were administered perioperative chemotherapy. For example, the time between chemotherapy administration and surgery, or *vice versa*, is of paramount importance to outcome. This interval is also needed to identify differences, if any, in the above-mentioned surgical parameters in patients who have received multimodal treatment. With the aim of comparing the most important surgical and oncological results between RARC and ORC in the context of multimodal disease management, an international, multicentre, retrospective study was carried out.

Patients and Methods

Patient selection

The Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC) is a retrospective study encompassing individual patient-level data from individuals with muscle-invasive or advanced urothelial carcinoma or non-urothelial histology who have received systemic therapy during the course of their disease. This contemporary database includes data gathered from hospitals in the United States, Europe, Israel, and Canada. The RISC study was approved by the ethics committee at each participating institution.

In July 2016, data were extracted to select patients with the following characteristics: the primary tumour site being the bladder, any tumour histology (i.e., pure or prevalent urothelial carcinoma or non-urothelial variant histologies), administration of cisplatin- or carboplatin-containing neoadjuvant and/or adjuvant chemotherapy, and having undergone radical RARC or ORC. Data analysis was performed externally by a senior statistician (GP).

Statistical analyses

The study objective was to compare surgical performance and oncological outcome measures between RARC and ORC. Assessment of surgical quality relied upon the following endpoints: number of removed lymph nodes, achievement of pathologically assessed positive surgical margins, and frequency of performed neobladder diversion. Survival endpoints such as recurrence-free survival (RFS) and overall survival (OS), as well as the time from neoadjuvant chemotherapy to surgery and from surgery to the start of adjuvant chemotherapy, were used to assess oncological outcomes. Patients who underwent surgery from January 2000 to July 2013 were included in the analysis. Patient, disease, and outcome characteristics were summarized using descriptive statistics with frequencies and percentages used for categorical variables and medians and inter-quartile range (IQR) for continuous variables. Fisher's exact tests, χ^2 tests, and Wilcoxon rank sum tests were used to determine whether factors were different between patients undergoing ORC versus RARC. Logistic regression (for dichotomous outcomes) and Cox regression analyses (for time-to-event outcomes) were performed to evaluate potential prognostic factors. Complete case analysis was performed, and no imputation was performed for missing data. However, to account for the absence of a substantial amount of data due to the retrospective nature of this analysis, multiple supportive models were constructed for each outcome to explore the robustness of effects. Additionally, multivariable models were based on pre-specified factors that were hypothesized to be clinically important. All tests were two-sided, and statistical significance was defined as a p-value of 0.05 or less. All analyses were performed in SAS version 9.2.

Results

Patient, disease, and treatment characteristics and outcomes

The study flow chart is presented in Figure 1. Of 3,024 registered cases, 729 patients were initially identified. Of these, 41 patients were excluded due to missing information, leaving 688 patients (85 in the RARC group and 603 in the ORC group, treated from January 2000 to July 2013 at 28 contributing centres) who were suitable for analyse. Summary statistics, which describe patient, disease, and treatment characteristics, are presented in Table 1. Almost half of the patients from the RARC group (49.4%) came from 2 centres (City of Hope Comprehensive Cancer Center [COH] and Fox Chase Cancer Center); otherwise, there were no statistically significant differences between the groups according to the other analysed factors. Both neoadjuvant and adjuvant chemotherapy regimens consisted of cisplatin-based chemotherapy in the majority of cases, and there were no cases treated with variant histology-directed chemotherapy.

Tables 2 and 3 show the distribution of key factors between the two groups. Overall, the number of removed lymph nodes was greater with RARC than with ORC: 21 (IQR: 14–34.5) vs. 13 (8–21, $p<0.001$). The difference remained significant in subgroup analysis. No difference was found in the rate of positive surgical margins (overall, $p=0.59$) or neobladder ($p=0.33$). These results remained consistent across patient subgroups.

Among the survival outcomes, no statistically significant differences were found in the median time from the end of neoadjuvant chemotherapy to cystectomy (3.68 months for RARC vs. 3.52 months for ORC, $p=0.51$) and from cystectomy to the initiation of adjuvant chemotherapy: 1.9 months (range 0.4–4.2) for RARC and 1.9 (0.07–5.7) for ORC ($p=0.98$). The number of removed lymph nodes did not significantly change over the years (i.e., 2000 to 2006, 2007–2010, and 2011) in both groups: for RARC, Spearman's correlation coefficient=0.075, p -value=0.50; for ORC, Spearman's correlation coefficient=0.03, p -value=0.56. Finally, after a median follow-up of 2.3 years, RFS and OS events in the RARC vs. ORC groups were: 35 (47.6%) and 331 (54.9%), and 26 (30.6%) and 251 (41.6%), respectively. There were no significant differences in survival outcomes: 1-year and 5-year RFS were 70.3% (95%CI: 59–79.1) and 52.1% (95%CI: 39–63.7) in the RARC group and 68.3% (95%CI: 64.3–72) and 32.2% (95%CI: 27.4–37.1) in the ORC group, respectively ($p=0.31$). For OS, the 1-year and 5-year estimates were 86% (95%CI: 76.2–92) and 48.4 (28.4–65.8) for RARC and 84.7% (95%CI: 81.4–87.4) and 44.3% (95%CI: 38.9–49.5) for ORC ($p=0.33$).

Results of univariable and multivariable analyses

Logistic regression analyses are presented in Table 4. No factor was significantly prognostic for having positive surgical margins in the multivariable model. Notably, all patients from COH were missing the Charlson comorbidity index. Hence, for multivariable analyses, it was not possible to include the three-site grouping and Charlson index in the model.

As for the rate of urinary diversion type, increasing age and higher Charlson index were less likely to be associated with neobladder ($p=0.002$ for both), while the administration of neoadjuvant chemotherapy was significantly associated with the chance of having a neobladder (OR: 2.42, 95%CI: 1.38–4.27, $p=0.002$). Surgical modality was not associated with any outcome. No interaction effect was observed to be statistically significant between age, Charlson index and neoadjuvant therapy. Cox regression analyses are shown in Table 5. Multivariably, there were no differences in both RFS and OS between the two groups, as shown in Supplementary Figure 1A, B (i.e., all patients) and in Supplementary Figure 2A, B (i.e., patients who received neoadjuvant or adjuvant chemotherapy, separately analysed).

Discussion

We have provided results from one of the few studies assessing surgical and oncological outcomes between RARC and ORC in the context of multidisciplinary patient management in UBC and analysing data from a multicentre international database. In the context of a recommended partnership between surgical and medical disciplines, the advances in techniques for surgical resection did not significantly affect key oncological parameters.

There is an on-going debate among surgical urology specialists as to whether improvements in technology, in particular, the use of robot-assisted cystectomies, will lead to a change in the standard indication for cystectomy in UBC. A vast amount of data is already available that compares robotic with open surgical procedures, focusing mainly on immediate and long-term morbidity issues.[15–23] Results from almost all these studies are retrospective in nature, and the level of evidence is usually low for RARC data. Trends are for longer

operating time and hospital stays for RARC but less intraoperative blood loss compared to ORC, and substantial overlap in mixed post-surgical quality of life parameters may be noted, although these outcomes are highly dependent on the surgical volume of each centre. Of note, similar findings were prospectively reported in a pivotal, randomized study from the United States comparing RARC with ORC. In an analysis of 118 patients, the investigators found no significant reduction in perioperative complications with RARC as compared with ORC (with the use of extracorporeal urinary diversion in both cases), and the trial was closed early owing to futility.[24,25]

Additionally, contradictory results have been presented by several authors with regard to the relative costs of each surgical procedure. In principle, it will remain very difficult to compare the performance of RARC and ORC. In fact, the use of RARC is continually being expanded by technological improvements and as a result is being increasingly used in many centres worldwide. Hence, it is likely that the use of robotic technology will eventually become more common than open procedures in referral centres, although current data have not sufficiently proven the advantages or disadvantages of either technique with respect to oncological and functional outcomes.

In the present analysis, two key oncological findings did not seem to be negatively affected by a robotic surgical technique: the number of lymph nodes removed (otherwise referred to as lymph node yield) and the frequency of positive surgical margins in the radical cystectomy specimens. For the former, we observed a significantly higher median number of lymph nodes in the surgical specimens of the RARC group, although the inherent bias of centre selection and the different sample size between the two groups may account for this result. However, these findings confirm that extended lymph node dissection is possible during RARC, mainly in high-volume centres.[18,19] The number of lymph nodes removed was high throughout the evaluated time frame, and the analysis further supported patient centralization in high-volume centres whenever RARC is planned, especially in combination with perioperative chemotherapy. Of course, an adequate pathological assessment is always implied when reporting the number of lymph nodes removed in radical cystectomy, and the lack of information on such assessments should be recognized as another inherent bias when interpreting results. Another important limitation in determining the number of lymph nodes is variation in pathologists' judgement across centres worldwide.

With regard to the frequency of tumour-positive surgical margins, we found substantial similarity between the surgical techniques, as was observed in an analysis of data from the International Robotic Cystectomy Consortium (IRCC) database.[26]

The above outcomes, along with the comparable number of neobladder diversions in the two groups, were also found in subgroup analyses of data for patients with more advanced and high-risk disease, such as those with high T and N stage UBC. As expected, increasing age and Charlson comorbidity index were inversely associated with the probability of undergoing a neobladder diversion in both univariable and multivariable analyses. Conversely, administration of neoadjuvant chemotherapy seemed to be associated with the possibility of neobladder reconstruction. In centres who have contributed the majority of cases, urologists tend to counsel almost all patients under the age of 70 towards neoadjuvant

chemotherapy and neobladder urinary diversion. Hence, the observed association may ultimately stem from the belief that a younger, healthier patient is a better candidate for neoadjuvant chemotherapy and neobladder urinary diversion.

The presence of certain biases may have affected other results. Most of these limitations are ultimately due to the nature of our data. First, the RISC database collects information on the outcomes of different systemic therapies in UBC (i.e., from neoadjuvant therapy to salvage therapy after chemotherapy failure). It is therefore plausible that a selection of patients trending to worse outcomes is generally seen when analysing surgical outcomes, which usually represent early stages of disease. However, despite the retrospective nature of this study, it is likely that this bias was equally distributed in the two groups. For the same reason, many surgical details like the extent of lymph node dissection or the type of urinary diversion performance (i.e., intra- vs. extracorporeal), as well as histological details like the presence of lymphovascular invasion or concomitant *carcinoma in situ* component, were not captured in our database. Indeed, a totally intracorporeal orthotopic urinary diversion could dramatically increase operative times and, consequently, have an impact on surgical outcomes. Second, despite the large numbers overall, the number of RARC cases was not high enough to enable highly powered analyses, and this bias may have further affected the results of the subgroup analyses. Additionally, data for RARC cases were collected from a limited number of centres, reflecting the fact that complex surgical techniques are usually provided by a few high-volume centres, both in and outside clinical trials. Third, we were unable to provide data regarding safety outcomes because these data were not captured in the RISC database. Robust literature is already available on safety outcomes in general, from both the surgical and oncological viewpoints; however, prospective reporting of side effects after chemotherapy plus robotic surgery is needed.

In the field of robotic surgery, enormous efforts are being made to enhance the urologists' learning curve as well as to lower the incidence of postoperative complications and shorten the length of hospital stays and patient recovery time.[27] In our study, we obtained information on one very important safety parameter that also yields oncological value—the time from cystectomy to the initiation of adjuvant chemotherapy—and no difference between the groups was observed.

Finally, as an observation outside the aim of this study, an increasing Charlson comorbidity index was strongly associated with poorer survival, both RFS and OS. Incorporation of this still underused factor into new decision-making tools before administering perioperative chemotherapy is encouraged as outlined in recent guidelines.[28] Additional prognostic factor analyses are suggested in order to compare the prognostic utility of the Charlson index with that of other comorbidity scores.

Conclusions

In summary, we have presented the results of a retrospective analysis comparing key oncological outcomes between RARC and ORC in patients with muscle-invasive UBC who received complementary neoadjuvant or adjuvant chemotherapy. The results showed a substantial overlap in all these parameters irrespective of the type of surgery, although some

biases due to the nature of the study should be acknowledged. Our study provides further evidence supporting robot-assisted procedures in a multidisciplinary setting, although the issues related to cost-effectiveness when performing robotic procedures remain open to debate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study flow chart, with counts and reasons for patient selection.

Table 1

Patient and disease characteristics according to the type of surgery

Characteristic	Statistic	RARC	ORC	p-value
N		85	603	
Treatment centre	COH	22 (25.9)	6 (1.0)	<0.001
	FCCC	20 (23.5)	72 (11.9)	
	Other	43 (50.6)	525 (87.1)	
Age	mean (std)	62.0 (10.3)	63.4 (9.3)	0.26
Gender	N (%) male	65 (76.5)	479 (79.4)	0.57
Smoking status	current smoker	21 (24.7)	142 (23.5)	0.97
	former smoker	36 (42.3)	252 (41.8)	
	never smoker	23 (27.1)	150 (24.9)	
	missing	5 (5.9)	59 (9.8)	
Charlson comorbidity index	N (%) 2	28 (45.2)	286 (48.4)	0.69
Histology	TCC	62 (72.9)	441 (73.1)	0.95
	TCC with variants	10 (11.8)	65 (10.8)	
	Other	13 (15.3)	97 (16.1)	
Clinical T stage	<i>in situ</i> , 0, 1	4 (4.7)	23 (3.8)	0.25
	2	45 (52.9)	338 (56.1)	
	3,4	16 (18.8)	190 (31.5)	
	missing	20 (23.6)	52 (8.6)	
Clinical N stage	0	40 (47.1)	290 (48.2)	0.47
	1–3	9 (10.6)	90 (14.9)	
	missing	36 (42.3)	223 (36.9)	
Pathologic T stage	<i>in situ</i> , 0, 1	27 (31.8)	136 (22.6)	0.16
	2	13 (15.3)	126 (20.9)	
	3,4	45 (52.9)	319 (52.9)	
	missing	-	22 (3.6)	
Pathologic N stage	0	45 (52.9)	278 (46.1)	0.64
	1–3	37 (43.5)	260 (43.1)	
	missing	3 (3.6)	65 (10.8)	
Neoadjuvant CT	N (%) Yes	53 (63.9)	344 (60.1)	0.55
Cisplatin-based CT		41 (82.0)	256 (42.4)	
Carboplatin-based CT		2 (2.3)	39 (6.4)	
No platinum-based CT		7 (8.2)	41 (6.7)	
Unknown		3 (3.5)	8 (1.3)	

Characteristic	Statistic	RARC	ORC	p-value
Adjuvant CT	N (%) Yes	31 (36.9)	271 (46.3)	0.13
Cisplatin-based CT		21 (24.7)	187 (31.0)	
Carboplatin-based CT		6 (7.1)	54 (8.9)	
No platinum-based CT		2 (2.3)	16 (2.6)	
Unknown		2 (2.3)	14 (2.3)	
Neoadjuvant and adjuvant CT	N (%) Yes [‡]	3 (3.7)	26 (4.7)	1.00

Abbreviations: COH: City of Hope Comprehensive Cancer Center; CT: chemotherapy; FCCC: Fox Chase Cancer Center; ORC: open radical cystectomy; RARC: robot-assisted radical cystectomy; std: standard deviation; TCC: transitional cell carcinoma.

[‡]Denominator is represented by patients with known adjuvant and neoadjuvant chemotherapy status

Table 2

Unadjusted rate of removed lymph-nodes by clinical stage, pathological stage, and use of neoadjuvant chemotherapy for open versus robot-assisted radical cystectomy

	RARC	ORC	p-value
Median (IQR) Number of removed lymph nodes			
Overall	21 (14, 34.5)	13 (8, 21)	<0.001
Selected RARC centres only	21 (14, 34.5)	15 (8, 23)	<0.001
Clinical T stage			
• <i>in situ, 0, 1</i>	25 (19, 32)	12.5 (7, 17.5)	0.040
• 2	20.5 (14.5, 35)	15 (9, 22)	<0.001
• 3,4	21.5 (11, 30)	12 (7, 20)	0.020
Clinical N stage			
• 0	21 (14, 30)	15 (8, 22)	<0.001
• 1–3	16 (10, 23)	13 (6, 20)	0.35
Pathologic T stage			
• <i>in situ, 0, 1</i>	20.5 (13, 33)	14 (8, 21)	0.012
• 2	22 (16, 30)	12 (8, 22)	0.006
• 3,4	21 (14, 36)	14 (8, 21)	<0.001
Pathologic N stage			
• 0	19.5 (14, 35)	15 (8, 22)	<0.001
• 1–3	22 (15, 35)	14 (8, 22)	<0.001
Neoadjuvant CT			
• <i>No</i>	23 (19, 37)	13 (8, 23)	<0.001
• <i>Yes</i>	18.5 (14, 33.5)	14 (8, 21)	<0.001

Abbreviations: CI: confidence intervals; CT: chemotherapy; IQR: interquartile range; OR: odds ratio; ORC: open radical cystectomy; RARC: robot-assisted radical cystectomy

Table 3

Unadjusted rate of neobladder urinary diversion and positive surgical margins by clinical stage, pathological stage, and use of neoadjuvant chemotherapy for open versus robot-assisted radical cystectomy

	RARC, N (%)	ORC, N (%)	RARC vs ORC OR (95%CI)	p-value
Neobladder urinary diversion				
Overall	23/83 (27.7)	127/556 (22.8)	1.29 (0.77, 2.18)	0.33
Selected RARC centres only	23/83 (27.7)	80/359 (22.3)	1.34 (0.78, 2.30)	0.31
Clinical T stage				
• <i>in situ</i> , 0, 1	1/4 (25.0)	3/22 (13.6)	2.11 (0.2, 27.58)	0.51
• 2	10/44 (22.7)	80/322 (24.8)	0.89 (0.42, 1.88)	0.85
• 3,4	4/16 (25.0)	34/177 (19.2)	1.40 (0.43, 4.62)	0.52
Clinical N stage				
• 0	11/39 (28.2)	47/279 (16.9)	1.94 (0.90, 4.17)	0.12
• 1–3	2/9 (22.2)	18/81 (22.2)	1.00 (0.19, 5.24)	1.00
Pathologic T stage				
• <i>in situ</i> , 0, 1	12/27 (44.4)	26/131 (19.9)	3.23 (1.35, 7.73)	0.012
• 2	3/13 (23.1)	40/120 (33.3)	0.60 (0.16, 2.30)	0.55
• 3,4	8/43 (18.6)	60/296 (20.3)	0.90 (0.40, 2.04)	1.00
Pathologic N stage				
• 0	13/45 (28.9)	45/268 (16.8)	2.01 (0.98, 4.14)	0.063
• 1–3	9/36 (25.0)	67/242 (27.7)	0.87 (0.39, 1.95)	0.84
Neoadjuvant CT				
• No	8/28 (28.6)	60/204 (29.4)	0.96 (0.40, 2.30)	1.00
• Yes	14/53 (26.4)	56/323 (17.3)	1.71 (0.87, 3.36)	0.13
Positive surgical margins				
Overall	12/82 (14.6)	65/532 (12.2)	1.23 (0.63, 2.40)	0.59
Selected RARC centres only	12/82 (14.6)	43/340 (12.7)	1.18 (0.59, 2.36)	0.59
Clinical T stage				
• <i>In situ</i> , 0, 1	1/4 (25.0)	4/18 (22.2)	1.17 (0.09, 14.52)	1.00
• 2	5/45 (11.1)	34/315 (10.8)	1.03 (0.38, 2.80)	1.00
• 3,4	3/15 (20.0)	23/168 (13.7)	1.58 (0.41, 6.02)	0.45
Clinical N stage				
• 0	4/40 (10.0)	34/272 (12.5)	0.78 (0.26, 2.32)	0.80
• 1–3	1/9 (11.1)	10/81 (12.4)	0.89 (0.10, 7.86)	1.00
Pathologic T stage				
• <i>in situ</i> , 0, 1	0/27 (0.0)	0/128 (0.0)	-	1.00
• 2	1/12 (8.3)	11/116 (9.5)	0.87 (0.10, 7.37)	1.00
• 3,4	11/43 (25.6)	54/286 (18.9)	1.48 (0.70, 3.12)	0.31
Pathologic N stage				

	RARC, N (%)	ORC, N (%)	RARC vs ORC OR (95%CI)	p-value
• <i>0</i>	4/45 (8.9)	16/264 (6.1)	1.51 (0.48, 4.75)	0.51
• <i>1–3</i>	8/35 (22.9)	43/231 (18.6)	1.30 (0.55, 3.05)	0.64
Neoadjuvant CT				
• <i>No</i>	4/27 (14.8)	33/193 (17.1)	0.84 (0.27, 2.60)	1.00
• <i>Yes</i>	7/53 (13.2)	30/314 (9.6)	1.44 (0.60, 3.47)	0.46

Abbreviations: CI: confidence intervals; CT: chemotherapy; IQR: interquartile range; OR: odds ratio; ORC: open radical cystectomy; RARC: robot-assisted radical cystectomy

Univariable and multivariable logistic regression analyses for positive margin status and neobladder diversion type endpoints

Table 4

Characteristic	Univariable analysis			Multivariable analysis (N=382)		
	Statistic	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	p-value
Probability of having positive margins						
Treatment centre	COH	1.39 (0.46, 4.18)				
	FCCC	1.20 (0.63, 2.29)	0.75			
	Other	Ref.				
Age	/decade	1.07 (0.83, 1.39)	0.59	1.09 (0.77, 1.52)		0.64
Gender	female vs male	1.36 (0.79, 2.36)	0.27			
Smoking status	current smoker	1.23 (0.58, 2.62)				
	former smoker	1.80 (0.95, 3.41)	0.15			
	never smoker	Ref.				
Charlson comorbidity index	2 versus 0–1	1.35 (0.82, 2.22)	0.24	1.81 (0.93, 3.51)		0.081
Histology	TCC	0.91 (0.49, 1.71)		1.15 (0.38, 3.53)		
	TCC with variants	0.46 (0.16, 1.34)	0.33	0.78 (0.17, 3.48)		0.77
	Other	Ref.		Ref.		
Clinical T stage	in situ, 0, 1	1.78 (0.60, 5.23)		2.10 (0.48, 9.14)		
	2	0.73 (0.43, 1.25)	0.18	1.12 (0.55, 2.31)		0.62
	3,4	Ref.		Ref.		
Clinical N stage	0 vs 1–3	1.00 (0.49, 2.04)	0.99	0.97 (0.44, 2.17)		0.95
Pathologic T Stage	in situ, 0, 1					
	2	Not Defined				
	3,4					
Pathologic N Stage	0 vs 1–3	0.29 (0.17, 0.50)	<0.001			

Characteristic	Univariable analysis			Multivariable analysis (N=382)		
	Statistic	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	
Neoadjuvant CT	No vs Yes	1.80 (1.11, 2.94)	0.018	1.67 (0.88, 3.16)	0.12	
Adjuvant CT	No vs Yes	0.45 (0.27, 0.74)	0.002			
Neoadjuvant and adjuvant CT	No vs Yes	0.39 (0.15, 1.02)	0.054			
Neoadjuvant CT	cisplatin-based vs other	0.70 (0.32, 1.53)	0.38			
Adjuvant CT	cisplatin-based vs other	0.99 (0.47, 2.11)	0.98			
Surgery type	ORC vs RARC	0.81 (0.42, 1.58)	0.54	1.18 (0.39, 3.58)	0.78	
Probability of having neobladder diversion type						
	Univariable analysis			Multivariable analysis (N=388)		
Treatment centre	COH	1.96 (0.89, 4.29)				
	FCCC	0.37 (0.19, 0.73)	0.003			
	Other	Ref.				
Age	/decade	0.62 (0.51, 0.76)	<0.001	0.65 (0.49, 0.85)	0.002	
Gender	female vs male	0.25 (0.13, 0.46)	<0.001			
Smoking status	current smoker	0.54 (0.32, 0.92)				
	former smoker	0.66 (0.42, 1.02)	0.052			
	never smoker	Ref.				
Charlson comorbidity index	2 versus 0–1	0.62 (0.42, 0.91)	0.015	0.39 (0.22, 0.70)	0.002	
Histology	TCC	0.97 (0.59, 1.58)		1.35 (0.51, 3.61)		
	TCC with variants	0.55 (0.25, 1.20)	0.25	1.19 (0.34, 4.19)	0.81	
	Other	Ref.		Ref.		
Clinical T stage	in situ, 0, 1	0.74 (0.24, 2.28)		0.82 (0.16, 4.26)		
	2	1.33 (0.87, 2.04)	0.28	1.52 (0.84, 2.75)	0.32	

Characteristic	Univariable analysis			Multivariable analysis (N=382)		
	Statistic	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	
	3,4	Ref.		Ref.		
Clinical N stage	0 vs 1–3	0.78 (0.4, 1.38)	0.40	0.89 (0.46, 1.69)		0.71
Pathologic T Stage	in situ, 0, 1	1.26 (0.80, 1.98)				
	2	1.90 (1.21, 2.99)	0.020			
	3,4	Ref.				
Pathologic N Stage	0 vs 1–3	0.61 (0.41, 0.89)	0.011			
Neoadjuvant CT	No vs Yes	1.81 (1.24, 2.66)	0.002	2.42 (1.38, 4.27)		0.002
Adjuvant CT	No vs Yes	0.51 (0.35, 0.74)	<0.001			
Neoadjuvant and adjuvant CT	No vs Yes	0.88 (0.34, 2.26)	0.78			
Neoadjuvant CT	cisplatin-based vs other	0.79 (0.43, 1.44)	0.43			
Adjuvant CT	cisplatin-based vs other	0.81 (0.45, 1.48)	0.49			
Surgery type	ORC vs RARC	0.77 (0.46, 1.30)	0.33	0.75 (0.33, 1.74)		0.51

Abbreviations: COH: City of Hope Comprehensive Cancer Center; CI: confidence intervals; CT: chemotherapy; FCCC: Fox Chase Cancer Center; ORC: open radical cystectomy; RARC: robot-assisted radical cystectomy

Table 5

Univariable and multivariable prognostic factor analyses for RFS and OS

Characteristic	Univariable analysis			Multivariable analysis (N=405)		
	Statistic	Hazards Ratio (95% CI)	p-value	Hazards Ratio (95% CI)	p-value	
RFS						
Treatment centre	COH	1.00 (0.57, 1.74)				
	FCCC	0.70 (0.50, 0.97)	0.10			
	Other	Ref.				
Age	/decade	1.12 (1.00, 1.25)	0.050	1.13 (0.97, 1.31)		0.11
Gender	female vs male	0.96 (0.75, 1.24)	0.76			
Smoking status	current smoker	0.70 (0.52, 0.94)				
	former smoker	0.78 (0.61, 1.01)	0.040			
	never smoker	Ref.				
Charlson comorbidity index	2 versus 0–1	1.20 (0.97, 1.48)	0.096	1.40 (1.05, 1.89)		0.024
Histology	TCC	0.68 (0.52, 0.88)		0.61 (0.39, 0.96)		
	TCC with variants	0.79 (0.53, 1.18)	0.014	0.83 (0.46, 1.50)		0.060
	Other	Ref.		Ref.		
Clinical T stage	in situ, 0, 1	1.13 (0.68, 1.88)		0.88 (0.40, 1.93)		
	2	0.75 (0.60, 0.95)	0.027	0.87 (0.64, 1.18)		0.66
	3,4	Ref.		Ref.		
Clinical N stage	0 vs 1–3	0.68 (0.50, 0.91)	0.010	0.62 (0.44, 0.87)		0.006
Pathologic T Stage	in situ, 0, 1	0.25 (0.18, 0.36)				
	2	0.69 (0.53, 0.90)	<0.001			
	3,4	Ref.				
Pathologic N Stage	0 vs 1–3	0.51 (0.41, 0.64)	<0.001			

Characteristic	Statistic	Univariable analysis			Multivariable analysis (N=405)		
		Hazards Ratio (95% CI)	p-value	Hazards Ratio (95% CI)	p-value	Hazards Ratio (95% CI)	p-value
Neoadjuvant CT	No vs Yes	0.96 (0.77, 1.19)	0.69	0.78 (0.58, 1.06)	0.12		
Adjuvant CT	No vs Yes	1.07 (0.87, 1.32)	0.51				
Neoadjuvant and adjuvant CT	No vs Yes	0.62 (0.40, 0.96)	0.031				
Neoadjuvant CT	cisplatin-based vs other	0.66 (0.48, 0.90)	0.009				
Adjuvant CT	cisplatin-based vs other	0.86 (0.62, 1.19)	0.37				
Surgery type	ORC vs RARC	1.20 (0.85, 1.70)	0.31	1.44 (0.79, 2.60)	0.23		
OS							
		Univariable analysis			Multivariable analysis (N=405)		
Treatment centre	COH	0.69 (0.31, 1.54)					
	FCCC	0.90 (0.63, 1.27)	0.56				
	Other	Ref.					
Age	/decade	1.18 (1.03, 1.34)	0.015	1.19 (0.99, 1.43)	0.061		
Gender	female vs male	1.06 (0.80, 1.41)	0.67				
Smoking status	current smoker	0.75 (0.54, 1.05)					
	former smoker	0.72 (0.54, 0.96)	0.065				
	never smoker	Ref.					
Charlson comorbidity index	2 versus 0–1	1.32 (1.04, 1.68)	0.025	1.61 (1.14, 2.27)	0.007		
Histology	TCC	0.62 (0.46, 0.84)		0.47 (0.29, 0.78)	0.004		
	TCC with variants	0.91 (0.59, 1.40)	0.003	0.79 (0.41, 1.52)			
	Other	Ref.		Ref.			
Clinical T stage	in situ, 0, 1	1.18 (0.67, 2.06)	0.019	0.82 (0.32, 2.10)	0.66		
	2	0.72 (0.56, 0.93)		0.85 (0.59, 1.22)			

Characteristic	Univariable analysis		Multivariable analysis (N=405)	
	Statistic	Hazards Ratio (95% CI)	p-value	Hazards Ratio (95% CI)
	3,4	Ref.		Ref.
Clinical N stage	0 vs 1–3	0.64 (0.46, 0.90)	0.011	0.58 (0.39, 0.85)
Pathologic T Stage	in situ, 0, 1	0.31 (0.21, 0.45)	<0.001	
	2	0.78 (0.58, 1.05)		
	3,4	Ref.		
Pathologic N Stage	0 vs 1–3	0.62 (0.48, 0.81)	<0.001	
Neoadjuvant CT	No vs Yes	0.79 (0.62, 1.02)	0.071	0.64 (0.45, 0.92)
Adjuvant CT	No vs Yes	1.12 (0.88, 1.42)	0.36	
Neoadjuvant and adjuvant CT	No vs Yes	0.59 (0.36, 0.95)	0.029	
Neoadjuvant CT	cisplatin-based vs other	0.68 (0.48, 0.98)	0.036	
Adjuvant CT	cisplatin-based vs other	0.80 (0.55, 1.15)	0.23	
Surgery type	ORC vs RARC	1.11 (0.74, 1.66)	0.63	1.14 (0.59, 2.21)

Abbreviations: CHO: City of Hope Comprehensive Cancer Center; CI: confidence intervals; CT: chemotherapy; FCCC: Fox Chase Cancer Center; ORC: open radical cystectomy; OS: overall survival; RARC: robot-assisted radical cystectomy; RFS: relapse-free survival.