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Clinical-Bladder cancer

Robot Assisted Radical Cystectomy vs Open Radical Cystectomy: Over 10 years of the Mayo Clinic Experience

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Abstract

Objectives: There is scant information about intermediate / long-term comparative outcomes between robot assisted radical cystectomy (RARC) and open radical cystectomy (ORC). The purpose of this study is to present survival and oncological outcomes between bladder cancer patients who undergo RARC vs. ORC with an overall median follow-up of over 5 years.

Materials and Methods: A query of all patients who underwent radical cystectomy between January, 2007 and January, 2018 at Mayo Clinic Arizona yielded 595 patients. After excluding cystectomy performed for nonmalignant indication, cancer secondary to nonbladder primary, and cancers with grossly metastatic disease at the time of surgery, 481 patients remained. Data was collected on patient demographics, preoperative information, operative details, complications, and follow-up. Statistical analyses were generated using SPSS 22.0.

Results: In 481 total patients, 203 (42.2%) underwent RARC and 278 (57.8%) underwent ORC. The median follow-up for the entire cohort was 66 months. The 5-year recurrence-free survival (RFS) was 70.8% vs. 64.7% and the 10-year RFS was 69.6% vs. 62.7% for the RARC vs. ORC, respectively ($P = 0.135$). The 5-year overall survival (OS) was 58.9% vs. 57.7% and the 10-year OS was 39.9% vs. 45.6% for RARC vs. ORC patients, respectively ($P = 0.466$). There were no differences in any recurrence patterns, including the incidence of atypical recurrences (1.5% vs. 1.8% [$P = 0.786$], respectively). A Cox-proportional hazards model was fitted that included independent predictors of RFS and OS. The results revealed no difference in RFS (HR 1.235, 95% CI: 0.832−1.833, $P = 0.295$) or OS (HR 0.790, 95% CI: 0.550−1.135, $P = 0.202$) between the respectively.

Conclusions: Recurrence free survival, OS, and recurrence patterns are similar in bladder cancer patients who undergo either RARC or ORC. © 2019 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Cystectomy; Lymph node dissection; Robotics; Robot assisted

1. Introduction

Radical cystectomy (RC) is the gold standard treatment for optimal survival and oncological outcomes for patients with invasive bladder cancer requiring definitive treatment [1,2]. The use of robot assisted RC (RARC) for bladder cancer has increased significantly in recent years [3]. In addition, several recent randomized trials have described similar perioperative and short-term oncological outcomes between the 2 techniques [4,5].

Early concerns of the robot approach included the concern for higher positive margin rate [4,5,6], inferior oncological outcomes [7], cost effectiveness [6,8,9], longer operative times, and the possibility for more frequent local or atypical recurrences (i.e. port-site metastasis and

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carcinomatosis), due to theoretical seeding from the pneumoperitoneum, insufflation, and /or tumor spillage [10,11]. There have been many studies that have analyzed intermediate oncological outcomes of RARC [12−14], some of which are comparison studies to open RC (ORC) [15−17]. Results, in general, have suggested similar oncological outcomes mostly in retrospective settings. Randomised Open versus Robotic Cystectomy (RAZOR) was a multi-institutional, open label, randomized trial that compared the approaches and reported noninferiority with regards to progression-free survival between the 2 approaches at 2-years follow-up [4]. In addition, 1 recent trial demonstrated similar survival and cancer-free outcomes between the 2 approaches in 118 randomized patients who were followed for around 5 years [18]. Interestingly, in this trial, local/regional recurrences were statistically more common in the RARC cohort, whereas recurrence patterns in RAZOR were similar. As a result, it is important to further critically analyze the oncological differences between the 2 approaches.

Our institution is a high-volume cystectomy center that performs both RARC and ORC with no patient selection. We have extensively used the robotic approach for cystectomy since its infancy in the management of high-grade bladder cancer. In this context, we performed a comparative study to test whether the survival, recurrence-free survival (RFS), and recurrence patterns differ in patients with primary bladder malignancies who undergo either approach with a 5.5 years median follow-up. This study presents over 10 years of experience in a high-volume tertiary care cancer center, where surgeons are highly experienced in both RARC and ORC.

2. Materials and methods

2.1. Data source

This is a retrospective study that reviewed the medical records of patients who underwent a RC for a primary bladder malignancy at our institution from January, 2007 to January, 2018. A prospectively maintained cancer registry and database were utilized for the analysis.

2.2. Patient selection and surgical experience

After institutional board review approval, a query of all RCs performed in adult patients (>18 years of age) between January, 2007 and January, 2018 yielded 585 patients. Patients who underwent cystectomy for primary bladder malignancy were included. After excluding ineligible patients (Fig. 1), 481 total patients remained for analysis. Most RARC cases were performed by 1 surgeon who always begins with a robotic approach except for a period of 2 years during which 50 cases of ORC and RARC were
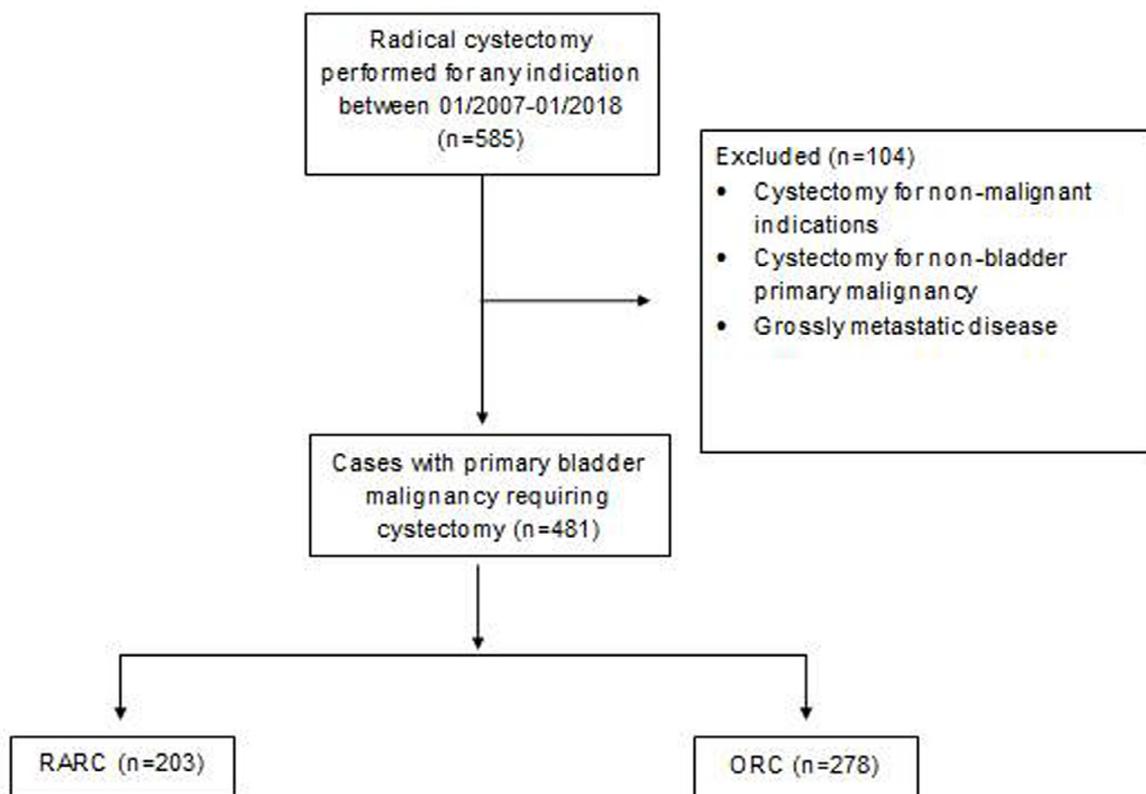

Fig. 1. Consort diagram for patient inclusion criteria.

randomized as participation in the RAZOR trial [4]. Our technique for RARC has been described in detail previously in peer-reviewed articles and instructional book chapters [19]. The robotic surgeon had trained in open surgery and transitioned exclusively to robotics for bladder cancer in 2005. The open surgeons in this comparison had over 20 years of experience with ORC each individually.

2.3. Variables measured

Data was collected on patient demographics, comorbidities, clinical data, perioperative data, and surveillance. A positive soft tissue margin (PSTM) was defined as the presence of tumor at the inked margin of the cystectomy specimen. Open conversions were included in the RARC cohort in the analysis.

Patients were followed at intervals in accordance to the National Comprehensive Cancer Network (NCCN) guidelines. Surveillance data were reviewed through chart reviews up to the most recent clinical visit and accessible via the Mayo Clinic Cancer Registry. Recurrence was recorded by location and time from cystectomy. A local recurrence was defined as a recurrence that developed within the surgical field (i.e. pelvis, pelvic lymph nodes), while distant recurrences were any recurrences outside of the pelvis [2]. Atypical recurrences were defined as one or a combination of the following: port-site metastasis, peritoneal carcinomatosis [10,20]. Recurrences were diagnosed by imaging and underwent secondary central radiological review by an experienced genitourinary radiologist. Similarly, if patients died, the date and cause of death was noted per the medical record and formal cancer registry, while those who did not die were censored at their last clinical follow-up.

2.4. Statistical analysis

Continuous variables were described using medians and interquartile ranges, while categorical variables were described using frequencies and percentages. Bivariate analysis was performed using Pearson's chi-square test or Fisher's Exact test. Continuous variables were examined using a Mann-Whitney U test. Kaplan−Meier survival plots were generated to evaluate both survival and recurrence outcomes. Univariate and multivariate Cox regression analyses were performed to identify predictive variables of both overall survival (OS) and RFS. All statistical analyses were performed using SPSS 25.0 (IBM Corp 2017).

3. Results

In a total of 481 patients, 203 underwent RARC and 278 underwent ORC. Table 1 illustrates patient characteristics. There were no statistically significant differences between the cohorts with respect to demographics or disease stage

(Supplementary Fig. 1). The median follow-up for the entire cohort was 66 months.

Supplementary Table 1 summarizes surgical outcomes. There were no differences observed with respect to diversion type, disease stage (Supplementary Fig. 2), or PSTM rate, regardless of the pathological stage (Supplementary Table 2). There were statistically less complications in the RARC group (61.6% vs. 75.9%, $P = 0.001$), a large part of this likely attributed to the lower transfusion rates in the RARC cohort (33.5% vs. 55.8%, $P < 0.001$). There was no difference in Clavien >2 complications (23.2% vs. 23.4%, $P = 0.953$). There was a greater median IQR node count in the RARC group (18 [14−24, range 0−53] vs. 12 [9−18, range 0−39], $P < 0.001$). Nodal positivity was more common in the RARC group ($P = 0.050$). The median follow-up time was greater for the RARC group (81 vs. 56 months, $P < 0.001$). There were 2 out of 203 (1.0%) conversions in the RARC group, both in patients with significant adhesions secondary to a previously operated field in 1 patient and a prior large bladder perforation in another patient.

The 5-year RFS (Fig. 2A) was 70.8% vs. 64.7% and the 10-year RFS was 69.6% vs. 62.7% for the RARC vs. ORC, respectively ($P = 0.135$). The 5-year OS (Fig. 2B) was 58.9% vs. 57.7% and the 10-year OS was 39.9% vs. 45.6% for RARC vs. ORC patients, respectively ($P = 0.466$). There were no differences in recurrence patterns (Fig. 3) or incidence of atypical recurrences (3 out of 203 [1.5%] vs. 5 out of 278 [1.8%], $P = 0.786$). There were 12 out of 203 (5.9%) and 19 out of 278 (6.8%) local recurrences ($P = 0.683$) and 29 (14.3%) and 53 (19.1%) distant recurrences ($P = 0.17$) in the RARC and ORC groups, respectively.

Fig. 4 illustrates the univariate and multivariate models for RFS. Univariate statistical predictors of recurrence included adjuvant chemotherapy, pathologic stage ≥T2, node positivity, PSTM, variant histology, lymphovascular invasion (LVI). These variables were fitted in a multivariate model that also included other possible clinically significant variables. The results of the multivariate model indicated that there was no significant association between surgical approach and RFS in the ORC vs. RARC cohorts, respectively (HR 1.235, 95% CI: 0.832−1.833, $P = 0.0295$).

Fig. 5 illustrates the univariate and multivariate models for OS. Univariate statistical predictors of mortality included age, Charlson Comorbidity Index (CCI), Eastern Cooperative Oncology Group (ECOG) ≥2, node positivity, PSTM, variant histology, LVI, pathologic stage ≥T2, perioperative complications (need for perioperative blood transfusion), local recurrence, and distant recurrence. These variables were fitted in a multivariate model that also included other possible clinically significant variables. The results of the multivariate model indicated that there was no significant associations between surgical approach and OS in the ORC vs. RARC cohorts, respectively (HR 0.790, 95% CI: 0.550−1.135, $P = 0.202$).

Neoadjuvant chemotherapy (NAC) was not associated with a survival benefit on either univariate or multivariate

Table 1
Patient characteristics

	Robotic (*n* = 203)	Open (*n* = 278)	*P* value
Median age (IQR)	73.0 (67.0−78.0)	71 (65.0−77.0)	0.120
Median BMI (IQR)	27.4 (25.0−30.6)	28.1 (24.3−31.8)	0.374
ECOG status			0.405
>2	14 (6.9)	25 (9.0)	
≤2	189 (93.1)	253 (91.0)	
Median ASA (IQR)	3 (2−3)	3 (2−3)	0.524
CCI (IQR)	3 (2−4)	3 (2−4)	0.292
ECOG status (IQR)	1 (1−2)	1 (1−2)	0.902
No. Male (%)	167 (82.3)	228 (82.0)	0.943
Race (%)			
White	190 (93.6)	268 (96.4)	0.169
Nonwhite	13 (6.4)	10 (3.4)	
History of smoking (%)	134 (76.6)	177 (75.6)	0.827
CIS (%)	132 (65.0)	157 (56.5)	0.059
LVI (%)			
Yes	31 (15.3)	39 (14.0)	0.146
Histological grade (%)			0.863
G1	2 (1.0)	3 (1.1)	
G2	35 (17.2)	40 (14.4)	
G3	152 (74.9)	216 (77.7)	
Not specified	14 (6.9)	19 (6.8)	
Clinical T stage			0.736
Tis	21 (10.3)	22 (7.9)	
Ta	5 (2.5)	11 (4.0)	
T1	44 (21.7)	69 (24.8)	
T2	106 (52.2)	143 (51.4)	
T3	21 (10.3)	23 (8.3)	
T4	6 (3.0)	10 (3.6)	
Clinical N stage			0.487
N0	190 (93.6)	263 (94.6)	
Nx	7 (3.4)	5 (1.8)	
N1	6 (3.0)	10 (3.6)	
Neoadjuvant chemo in cT2+ patients(%)	75/133 (56.4)	81/176 (46.0)	0.070
History of abdominal surgery (%)	119 (58.6)	168 (60.4)	0.689
Preoperative abdominal radiation (%)	17 (8.4)	20 (7.2)	0.631

LVI = lymphovascular invasion

analyses, likely due to the inclusion of lower risk patients who would not have been eligible for NAC (e.g. cTa, cTis, cT1). However, when evaluating patients with cT2-cT4 disease, though not statistically significant, those who received NAC had a 24 month greater median survival than those who did not (81.0 vs. 57.0 respectively months, *P* = 0.123). In addition, patients who received NAC more commonly experienced any downstage (38.9% vs. 24.2%, *P* = 0.001) and downstage to T0 (20.6% vs. 9.8%, *P* = 0.001), when compared to those who did not NAC.

4. Discussion

In this review of our greater than 10-year experience of 481 patients who underwent RC, we found no difference in 5- and 10-year OS or RFS and no difference in recurrence patterns between patients who underwent RARC and ORC at a median follow-up of 81 and 56 months, respectively. This study is the first to describe up to 10-year comparison data between the cohorts.

When evaluating intermediate/long-term outcomes after ORC for bladder cancer, there are several series useful in understanding the natural history of this entity [2,21]. In a report by Stein et al. of 1,054 patients who underwent RC with bilateral pelvic iliac lymphadenectomy who had a median of 10.2 years of follow-up, the overall RFS at 5 and 10 years was 68% and 66%, respectively and the overall 5- and 10-year OS was 60% and 43%, respectively [2]. Most importantly, cancer specific recurrences and survival rates plateaued at 3−5 years supporting that 5 year outcomes are adequate when evaluating oncological outcomes following RC. Of course, OS may be impacted by other factors may require longer-term follow-up.

The widespread adoption of robot assisted surgery for genitourinary malignancies has led to the development of several studies that assess the oncological efficacy when using this tool. The RAZOR trial was a multicenter randomized, noninferiority trial that looked to provide data on intermediate-term oncological outcomes. This study compared outcomes between 176 and 174 patients undergoing
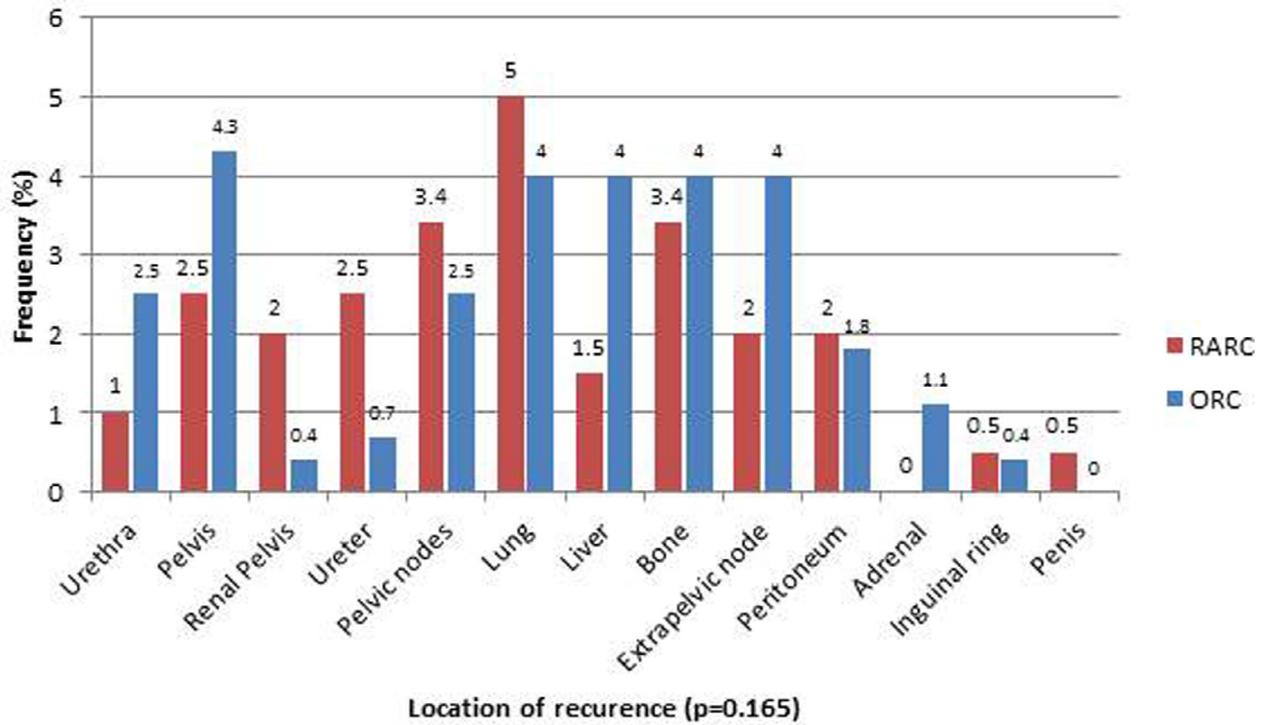
Fig. 2. Recurrence patterns. Illustrates the distribution of recurrence location between the cohorts. There were no statistical differences between the surgical approaches with respect to recurrence location.

RARC and ORC, respectively [4]. Patients were followed for a minimum of 2 years to evaluate a primary outcome of progression-free survival. In this intention-to-treat model, the 2-year RFS was 72.3% in the RARC and 71.6% in the ORC groups, respectively, showing noninferiority of the robotic-approach. In addition, there were no port-site recurrences recorded and no difference in bladder cancer-related deaths at the data cut-off of 3 years (19% vs. 21%, respectively). In a randomized trial by Bochner et al. that included 118 patients who were randomized to RARC ($n = 60$) vs.

ORC ($n = 58$), data was reported on oncological outcomes at a median follow-up of 4.9 years after surgery [18]. The study demonstrated similar recurrence-free, bladder cancer-specific, and OS between the RARC and ORC groups. Similarly, in our study we were able to demonstrate equivalent unadjusted and adjusted long-term outcomes between the 2 cohorts that compare favorably to both to short and intermediate comparison series, as well as modern ORC series.

There are well-established predictors for disease recurrence in patients with high-grade bladder cancer undergoing
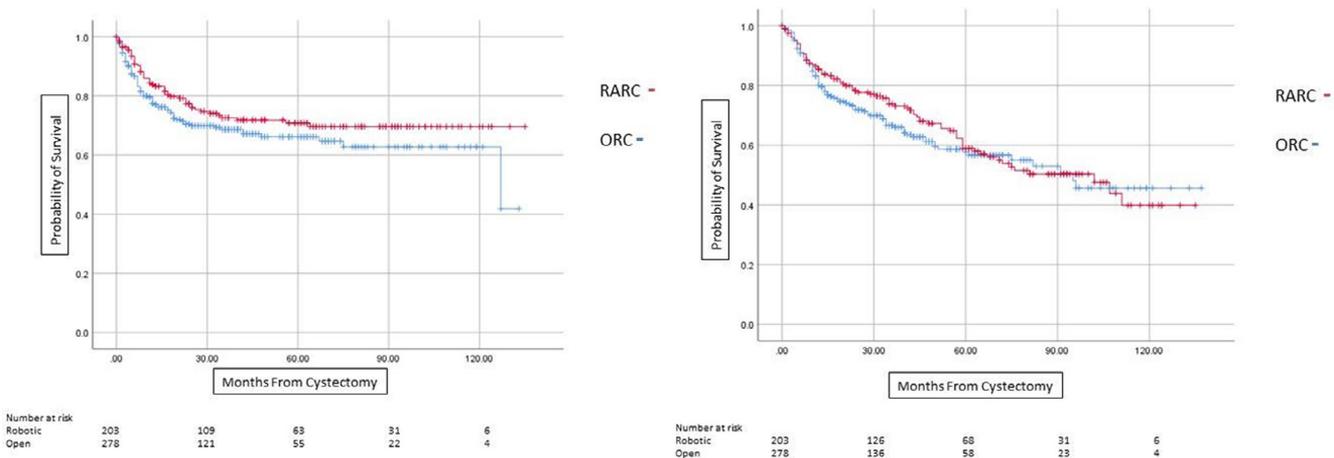

Fig. 3. Kaplan−Meier Survival Curves. Recurrence-free survival (left) and overall survival (right) are both depicted. There was no statistical difference between the cohorts with respect to both recurrence-free survival ($P = 0.135$) or overall survival ($P = 0.466$).
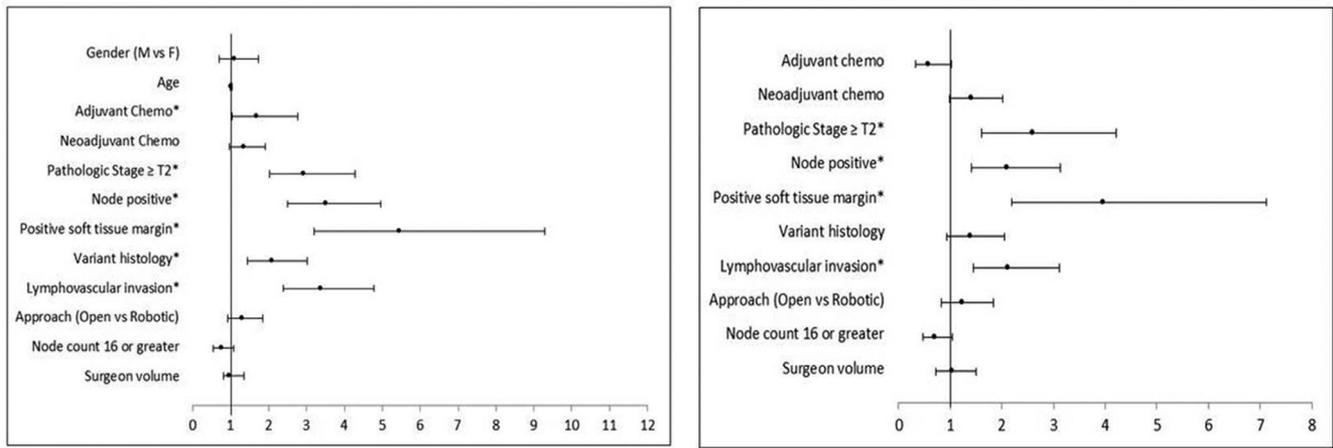
Fig. 4. Cox Proportional Hazards Model for Recurrence-free Survival. (Left) Illustrates a univariate model for recurrence-free survival. (Right) Shows a multivariate analysis for recurrence free survival. Each point represents the hazard ratio for that variable. The 95% confidence intervals are represented by associated horizontal error bars. *indicates statistically significant predictors.

cystectomy including PSTM, higher cancer stage, presence of LVI, and nodal positivity [6,22]. Acceptable PSTM rates are generally thought to be around 5% [18,21−23]. One of the early criticisms about the robotic approach included the concern to obtain negative soft tissue margins, especially in higher stage disease. RARC studies that reported higher PSTM rates were typically smaller series and/or involved patients with higher stage disease [6,24]. There were also concerns that it would be difficult to obtain negative margins using the robotic approach in nonorgan confined disease, it has been reported that higher PSTM rates are not unexpected with pT3-pT4 disease [6]. For instance, in a review of 4,410 patients treated with RC at 12 academic centers, Novara et al. reported a PSTM of 7.6% for pT3 and 24% for pT4 disease [23]. Similarly, the PSTM rates for pT3 and pT4 disease for the RARC and ORC cohorts in our study were 8.6% vs. 8.2% and 18.2% vs. 27.3%, respectively.

Another factor that was a perceived drawback of the robotic approach in the early days of RARC was the concern of obtaining sufficient lymph node counts during lymphadenectomy. Sufficient lymph node dissections, defined variably in the literature [21,25,26] (a minimum between 9 and 16 lymph nodes), have been associated with greater cancer-free and OS benefits in patients undergoing RC for bladder cancer [27−29]. Despite this initial concern, many studies have demonstrated the feasibility of pursuing and obtaining large lymph node counts using the robotic approach [4,5,16]. Similarly, in our study the median lymph nodes obtained for the RARC and ORC group were 18 (range 0−53) and 12 (range 0−39).

An additional concern of RARC has been the potential for more frequent atypical and local recurrences compared to ORC [10,20]. Reports of atypical recurrences after minimally invasive surgery for malignancy have been described in various cancers [30−32], including in an early series for
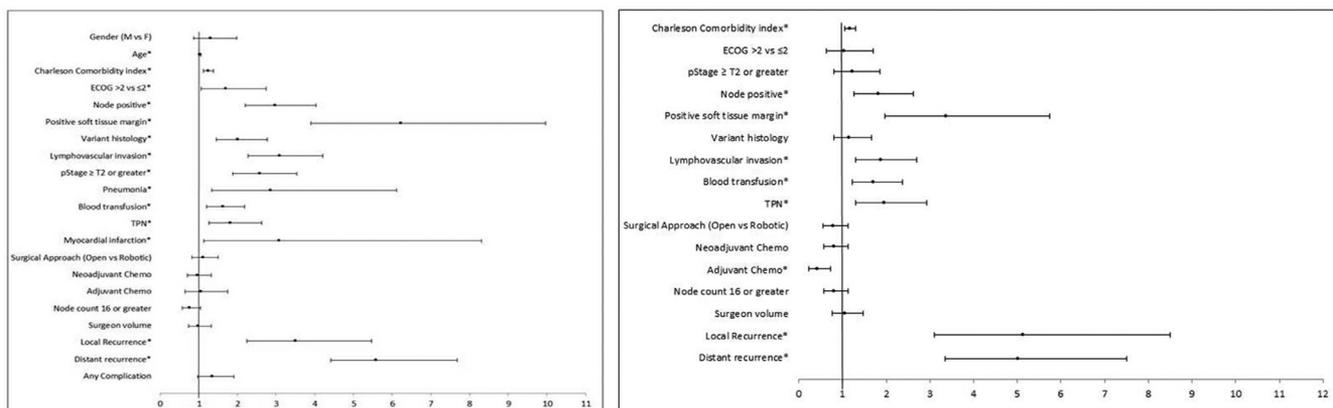

Fig. 5. Cox Proportional Hazards Model for Overall Survival. (Left) Illustrates a univariate model for overall survival. (Right) Shows a multivariate analysis for overall survival. Each point represents the hazard ratio for that variable. The 95% confidence intervals are represented by associated horizontal error bars. *indicates statistically significant predictors.

RARC [33]. The mechanism behind this risk arises from the idea that peritoneal seeding can potentially be facilitated by minimally invasive surgery and pneumoperitoneum [34,35]. With regards to the local recurrence rate, in the study by Bochner et al., local/regional recurrences were significantly lower in the patients undergoing ORC (HR = 0.34, $P = 0.035$) [18]. In contrast, the randomized RAZOR trial found no difference in atypical or local recurrence, where the local recurrence rates between RARC and ORC (4% vs. 3%) were similar to the figures in our study (5.9% for RARC and 6.8% in ORC) and atypical recurrences were uncommon (1.5% for RARC vs. 1.8% for ORC) [4]. While our study was not randomized, the large number of patients in our analysis and longer follow-up is reassuring that there is no difference in local and atypical recurrences.

This study is not without its limitations. This is a retrospective study with variable follow-up between patients, where some patients were lost to follow-up. In addition, though all the primary surgeons involved in this study were experienced in cystectomy, there was a difference in distribution between cases and surgeon. For instance, a vast majority of RARC cases were done by 1 experienced surgeon (EPC), whereas multiple surgeons were included in the open cohort. Despite these limitations, this is the largest intermediate/long-term comparison study between RARC and ORC. We report that the RARC cohort was able to achieve lower PSTM rates, statistically greater lymph node yields than the ORC group and there was no difference in the cohorts when assessing recurrence patterns. The RARC cohort was also able to appreciate some of the objective benefits of RARC, with lower estimated blood loss (200 vs. 500 ml, $P < 0.01$), lower rates of transfusion (33.5% vs. 55.8%, $P < 0.001$), and less wound complications (5.9% vs. 13.3%, $P = 0.008$), as well as shorter median hospital LOS (5 vs. 7 days, $P < 0.01$) [4,5,36]. However, the difference in LOS has been less evident in recent years since the introduction of alvimopan in our practice in 2014 (5 vs. 6 days, $P < 0.01$). In addition, this study is unique in that we present comparison data from a high-volume academic center that offers both surgical approaches. The RARC cases were mostly performed by a surgeon that utilizes this approach exclusively and as a consequence, there was no patient selection. Though some patients may have requested a specific approach be performed, the retrospective nature of this study limits our ability to quantify how many patients fit this criteria, but a vast majority of patients proceeded with surgery with the surgeon they saw in initial consultation. This allowed for the patient populations and stage groupings to be more reflective of a real world cystectomy cohort. As a result, we were able to include a similar number of nonorgan confined cases in this study reflective of what has been seen in other series in the literature [2,4,21]. This is significant, as it was higher stage patients that were thought to experience inferior outcomes with a robotic approach. This study can provide a valuable

benchmark of what survival and oncological outcomes should be for patients undergoing RARC for bladder cancer at median follow-up of around 5 years. Additional topics of interest that would be useful in the long-term comparison between these surgical approaches include differences in long-term quality of life outcomes, patient reported outcomes, and a modern comparison of a cost analyses. Though the RAZOR trial described similar short-term quality of life outcomes between the approaches, long-term data should be pursued to confirm this [4]. In addition, several studies comparing costs between the approaches have been described, but it would be useful to have a modern comparison, given the increased implementation of enhanced recovery protocols, which have contributed to a decrease in certain complications (i.e. gastrointestinal) and as a result, length of stay [37−39].

5. Conclusions

We report favorable oncological outcomes for RARC similar to ORC in the largest long-term comparison study with median follow-up of over 5 years. Recurrence free survival, OS, recurrence patterns were similar in both groups. These oncological outcomes should serve as a benchmark for surgeons that will be performing robot assisted RC.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.07.019.

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