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Quality of surgical care can impact survival in patients with bladder cancer after robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium

Youssef Ahmed¹, Ahmed A. Hussein^{1,2*}, Paul R. May¹, Basel Ahmad¹, Amir Khan¹, John Benkowski¹, Ayesha Durrani¹, Saira Khan¹, Justen Kozlowski¹, Matthias Saar³, Carl J. Wijburg⁴, Lee Richstone⁵, Andrew Wagner⁶, Bertram Yuh⁷, Joan Palou Redorta⁸, Prokar Dasgupta⁹, Mohammad Shamim Khan⁹, Mani Menon¹⁰, James O. Peabody¹⁰, Abolfazl Hosseini¹¹, Franco Gaboardi¹², Giovannalberto Pini¹², Francis Schanne¹³, Alexandre Mottrie¹⁴, Koon-ho Rha¹⁵, Ashok Hemal¹⁶, Michael Stockle³, John Kelly¹⁷, Wei Shen Tan¹⁷, Thomas J. Maatman¹⁸, Vassilis Poulakis¹⁹, Jihad Kaouk²⁰, Abdullah Erdem Canda²¹, Mevlana Derya Balbay²¹, Peter Wiklund¹¹ and Khurshid A. Guru^{1*}

Abstract

Background: Although pathological factors remain the main determinate of survival for patients with bladder cancer, quality of surgical care is crucial for satisfactory outcomes. Using a validated quality score, we investigated the impact of surgical factors on the overall survival (OS), recurrence-free survival (RFS) and disease-specific survival (DSS) in patients with locally advanced and organ-confined disease (OCD). Retrospective review of IRCC database includes 2460 patients from 29 institutions across 11 countries. The final cohort included 1343 patients who underwent RARCs between 2005 and 2016. Patients with locally advanced disease (LAD) (> pT2 and/or N+) were compared with OCD (\leq pT2/N0). Validated Quality Cystectomy Score (QCS) based on four sets of quality metrics was used to compare surgical performance. Kaplan–Meier method was used to compute RFS, CSS and OS rates. Multivariable stepwise logistic regression was used to evaluate variables associated with RFS, DSS and OS.

Results: 48% had LAD. When compared to patients with OCD, they received neobladders less frequently (17% vs. 28%, $p < 0.001$) and experienced higher estimated blood loss (513 vs. 376 ml, $p = 0.05$). Postoperatively, more patients in the LAD group received adjuvant chemotherapy (24% vs. 4%, $p < 0.001$) and positive surgical margins (14% vs. 2%, $p < 0.001$) and had higher 90-day mortality (6% vs. 2%, $p < 0.001$). On multivariable analysis, female gender, higher QCS score, intracorporeal diversion, pT stage, positive lymph node status and recurrence are considered as predictors of survival. Patients with OCD exhibited better RFS, DSS and OS than patients with LAD. For patients with OCD, higher QCS was associated with improved OS but not RFS or DSS. On the other hand, patients with LAD and higher QCS exhibited higher RFS, DSS and OS when compared to those with lower QCS.

*Correspondence: ahmedalyhussein@kasralainy.edu.eg; khurshid.guru@roswellpark.org

¹ Roswell Park Cancer Institute, Elm & Carlton St, Buffalo, NY 14263, USA
Full list of author information is available at the end of the article

Conclusion: Quality of surgical care can affect disease control and OS in patients with bladder cancer treated with robot-assisted radical cystectomy.

Keywords: Bladder cancer, Robotic, Cystectomy, Locally advanced, Organ confined, Quality

1 Background

Robot-assisted radical cystectomy (RARC) has been increasingly utilized for muscle-invasive bladder cancer, as it provides similar oncological efficacy to open radical cystectomy (RC) and is superior in terms of perioperative outcomes and recovery [1]. Approximately 37% of patients have locally advanced disease (LAD) (extravesical disease ($>pT2$) and/or positive lymph nodes) at surgery [2]. The negative impact of tumor stage (pT stage) and lymph node stage (pN stage) on oncological outcomes following RC has been reported by several open and robot-assisted series [3–5]. Surgery in the setting of LAD may invariably become inevitable to alleviate adverse urinary symptoms and poor quality of life that may occur [6]. Additionally, similar to ovarian cancer and renal cell carcinoma, surgery offers good local control, decreases tumor burden and therefore may be associated with survival benefit [7]. Moreover, adjuvant chemotherapy (NAC) have been associated with significant pathologic downstaging and improved survival, and surgery may be done even with curative intent in this setting [8].

Controversy remains with regards to the best approach for locally advanced bladder cancer, with concerns regarding poor oncological outcomes, higher morbidity and mortality, cost-effectiveness and the economic impact [9]. In addition to patient comorbidities and extent of the disease, it has been shown that quality of surgical performance can largely contribute to outcomes of RC independent of the extent of the disease [10, 11]. However, the role RARC in the setting of LAD is yet to be defined. The lack of tactile feedback and the potential higher risk of positive surgical margins may advocate against the use of RARC [12]. Additionally, there have been concerns about possible higher incidence of extrapelvic lymph node (LN) metastasis, local recurrence and peritoneal carcinomatosis with RARC when compared to open surgery [13].

In this context, we sought to describe the outcomes of our patients who underwent RARC for LAD and investigate the impact of quality of surgical performance on perioperative outcomes and survival.

2 Methods

A retrospective review of the International Robotic Cystectomy Consortium (IRCC) database was performed (I-79606) which includes 2460 patients who underwent

RARC between 2005 and 2016, from 29 institutions across 11 countries.

Patients were divided into two groups: patients with LAD ($>pT2$ and/or $N+$) and those with organ-confined disease (OCD) ($\leq pT2/N0$). Patients were reviewed for demographics (age, sex, body mass index [BMI] and American Society of Anesthesiologists [ASA] score), preoperative characteristics (prior abdominal or pelvic surgery, prior irradiation, neoadjuvant chemotherapy [NAC] and clinical staging), operative (type and technique of diversion, operative time, blood loss and transfusion), postoperative variables (hospital and intensive care unit stay, complications, readmissions, pathological staging, lymph node yield) and oncological outcomes (disease recurrence and survival). Patients were again grouped according to the quality of surgical care they received, measured by the validated Quality Cystectomy Score (QCS) for RARC into high and low QCS [10]. The score comprises four domains that measure surgical quality of RARC independent of patient and disease characteristics and then assigned a star score depending on the number of quality metrics fulfilled (Additional file 1: Fig. S1). Oncological outcomes were then compared between the different groups.

2.1 Statistical analysis

Data were described in terms of means and standard deviations. Univariable associations were statistically assessed using the Wilcoxon rank sum test or Kruskal–Wallis test for ordinal data, and Pearson chi-square test for categorical variables. Kaplan–Meier curves were used to describe recurrence-free (RFS), disease-specific (DSS) and overall (OS) survival. Multivariable stepwise logistic regression models were fit to evaluate preoperative, operative and postoperative predictors of RFS, DSS and OS, excluding factors included in the QCS to avoid collinearity. All tests were two-sided, with statistical significance defined as $p < 0.05$. All statistical analyses were performed using SAS software (version 9.3, SAS Institute Inc., Cary, NC).

3 Results

The final cohort comprised 1343 patients, 41 surgeons from 24 institutions in 10 countries. Mean age was 67 years, 74% were men and 20% received NAC. A total of 640 (48%) patients had LAD (86% had extravesical disease, 47% had positive lymph nodes and 33% had

both). Patients with LAD received ileal conduits more often (83% vs. 72%, $p < 0.001$), experienced higher estimated blood loss (444 vs. 376 ml, $p = 0.05$) and received adjuvant chemotherapy more often (24% vs. 4%, $p < 0.001$). Both groups exhibited a similar lymph node yield (median 18, standard deviation [SD] 11). There was no significant difference in terms of operative

times, complications or readmissions up to 3 months after RARC. LAD patients had more positive soft tissue surgical margins (14% vs. 2%, $p < 0.001$). They had higher incidence of both local (19% vs. 4%, $p < 0.001$) and distant (31% vs. 8%, $p < 0.001$) recurrences. They also exhibited higher mortality at 90 days (6% vs. 2%, $p < 0.001$) (Table 1).

Table 1 Perioperative characteristics of patients who underwent RARC between 2005 and 2016 (OC vs. LAD)

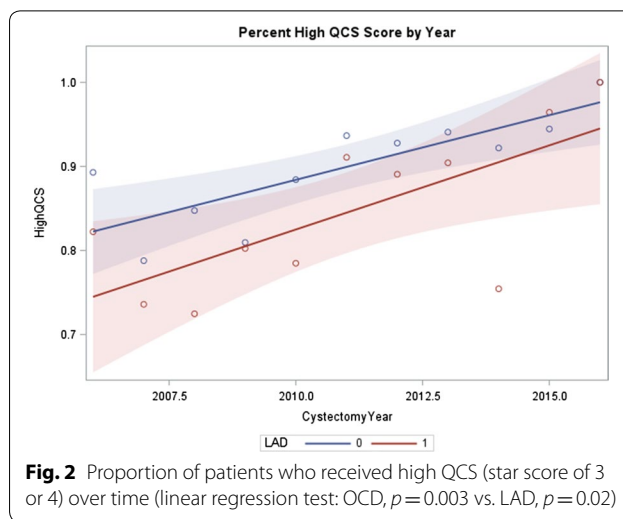
| Variable | OCD | LAD | <i>p</i> value |
|---|---------------|---------------|------------------|
| <i>N</i> (%) | 703 (52) | 640 (48) | – |
| Preoperative | | | |
| Age, mean (SD), years | 67 (10) | 68 (10) | 0.04 |
| Sex, males, <i>n</i> (%) | 528 (75) | 461 (72) | 0.24 |
| BMI, kg/m², mean (SD) | 28 (5) | 27 (5) | 0.01 |
| ASA score, median (IQR) | 2 (2–3) | 3 (2–3) | 0.06 |
| Prior surgery, <i>n</i> (%) | 221 (31) | 209 (33) | 0.63 |
| NAC, <i>n</i> (%) | 139 (20) | 126 (20) | 0.97 |
| Operative | | | |
| Ileal conduit, <i>n</i> (%) | 503 (72) | 529 (83) | <0.001 |
| Intracorporeal diversion, <i>n</i> (%) | 435 (76) | 347 (72) | 0.12 |
| Operative time, median (IQR), min | 371 (310–450) | 369 (310–442) | 0.80 |
| EBL, mean (SD), ml | 376 (339) | 444 (513) | 0.05 |
| Perioperative | | | |
| Hospital stay, median (IQR), days | 9 (7–13) | 9 (7–13) | 0.42 |
| ICU stay, median (IQR), days | 1 (0–1) | 1 (0–1) | 0.73 |
| Adjuvant treatment, <i>n</i> (%) | 26 (4) | 154 (24) | <0.001 |
| 30-d complications, <i>n</i> (%) | 224 (32) | 205 (32) | 0.95 |
| 90-d complications, <i>n</i> (%) | 261 (37) | 249 (39) | 0.50 |
| 30-d high-grade complications, <i>n</i> (%) | 63 (9) | 72 (11) | 0.16 |
| 90-d high-grade complications, <i>n</i> (%) | 74 (11) | 88 (14) | 0.07 |
| 30-d readmission, <i>n</i> (%) | 48 (7) | 50 (8) | 0.49 |
| 90-d readmission, <i>n</i> (%) | 85 (12) | 91 (14) | 0.25 |
| 30-d mortality, <i>n</i> (%) | 4 (0.6) | 7 (1) | 0.29 |
| 90-d mortality, <i>n</i> (%) | 12 (1.9) | 33 (6) | <0.001 |
| Pathologic | | | |
| LNY, mean (SD) | 18 (11) | 18 (11) | 0.86 |
| Positive LN, <i>n</i> (%) | 0 (0) | 301 (47) | NA |
| Pathologic T stage > 2 | 0 (0) | 544 (86) | NA |
| PSM, <i>n</i> (%) | 16 (2) | 89 (14) | <0.001 |
| Any recurrence, <i>n</i> (%) | 73 (10) | 252 (39) | <0.001 |
| Local recurrence, <i>n</i> (%) | 31 (4) | 123 (19) | <0.001 |
| Distant recurrence (<i>n</i>) | 56 (8) | 198 (31) | <0.001 |
| Median time to any recurrence (months) | 12 (6–21) | 6 (3–11) | <0.001 |
| Non-TCC histology, <i>n</i> (%) | 163 (30) | 171 (30) | 0.76 |
| QCS domains | | | |
| Preoperative | 139 (20) | 126 (20) | 0.97 |
| Operative | 359 (51) | 318 (50) | 0.61 |
| Postoperative | 603 (86) | 529 (83) | 0.12 |
| Pathologic | 266 (38) | 209 (33) | 0.05 |

Bold indicates statistically significant difference

In terms of quality of surgical care provided, both groups received comparable surgical care, where 83% of LAD patients were assigned a high QCS (3–4 stars) compared to 90% of OCD patients (Fig. 1). The proportion of patients who received high QCS score significantly increased with time, irrespective of their disease extent (linear regression test: OCD: $p=0.003$; LAD $p=0.02$) (Fig. 2).

Patients with high QCS significantly demonstrated better 5-year OS irrespective of their disease stage (LAD: 29% vs. 23%, $p=0.02$) and (OCD: 70% vs. 55%, $p=0.03$). When compared to patients who had LAD and low QCS, patients with LAD and high QCS demonstrated better 5-year RFS (41% vs. 29%, $p=0.05$) and DSS (55% vs. 37%, $p=0.01$). This benefit was not demonstrated for patients with OCD (Fig. 3).

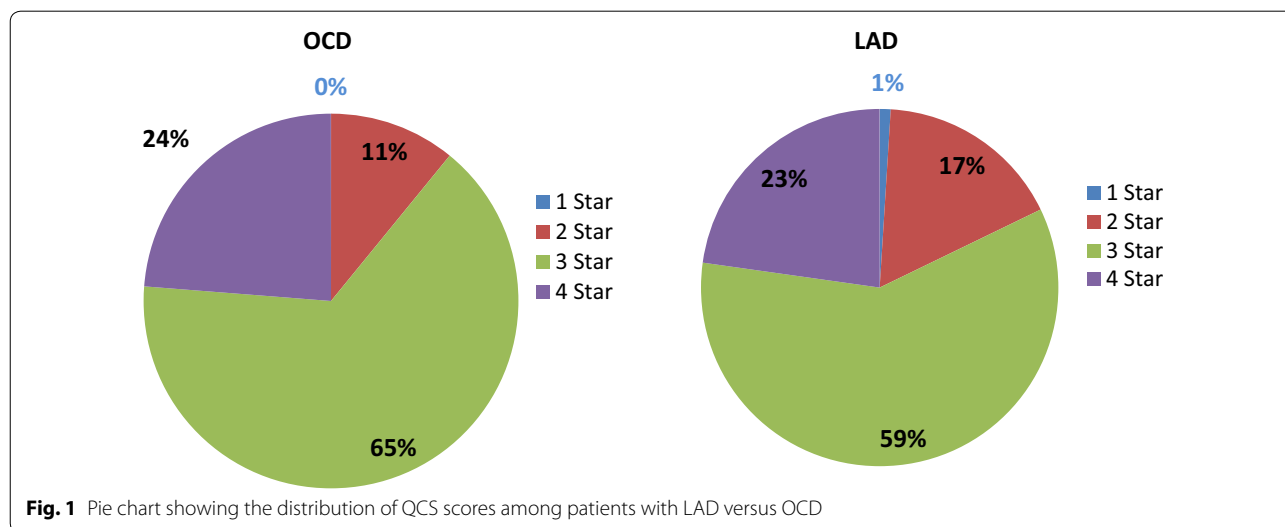
Looking at predictors of survival, >pT3 stage and N+ status at RARC were associated with worse RFS (hazards ratio [HR] 1.60, 95% confidence interval [CI] 1.15–2.22, $p=0.006$; HR 1.63, 95% CI 1.19–2.24, $p=0.003$), DSS (HR 5.12, 95% CI 3.23–8.12, $p<0.0001$; HR 2.05, 95% CI 1.39–3.04, $p=0.0003$) and OS (HR 3.66, 95% CI 2.76–4.84, $p<0.0001$; HR 1.83, 95% CI 1.4–2.40, $p<0.0001$), respectively. Patients who received neobladders and high QCS score exhibited better DSS (HR 0.30, 95% CI 0.12–0.74, $p=0.009$; HR 0.53, 95% CI 0.34–0.84, $p=0.007$) and OS (HR 0.366, 95% CI 0.21–0.65, $p=0.0005$; HR 0.63, 95% CI 0.46–0.86, $p=0.004$). BMI had a modest effect on DSS and OS. Male patients (HR 0.69, 95% CI 0.49–0.95, $p=0.02$) and those who received extracorporeal diversion (HR 0.67, 95% CI 0.49–0.91, $p=0.01$) demonstrated better RFS. Higher ASA score was associated with worse OS (HR 1.41, 95% CI 1.13–1.75, $p=0.002$) (Table 2).



4 Discussion

For decades, RC has been the gold standard for treatment of muscle-invasive bladder cancer and refractory non-muscle-invasive disease. However, even with the advents in surgical techniques and perioperative care, it remains with considerable morbidity and mortality, especially for LAD (pT3–T4 and/or lymph node-positive) [14]. We aimed to explore the outcomes of RARC in the setting of locally advanced bladder cancer and whether the quality of surgical care affected survival in this setting or not (Additional file 2: Table S1).

Although RC in LAD (alone or as part of multimodal-ity approach) may be of considerable risks, other alternatives, as bladder preservation modalities, which usually entail radiation and chemotherapy combined with transurethral resection (TUR) of the primary tumor, do not



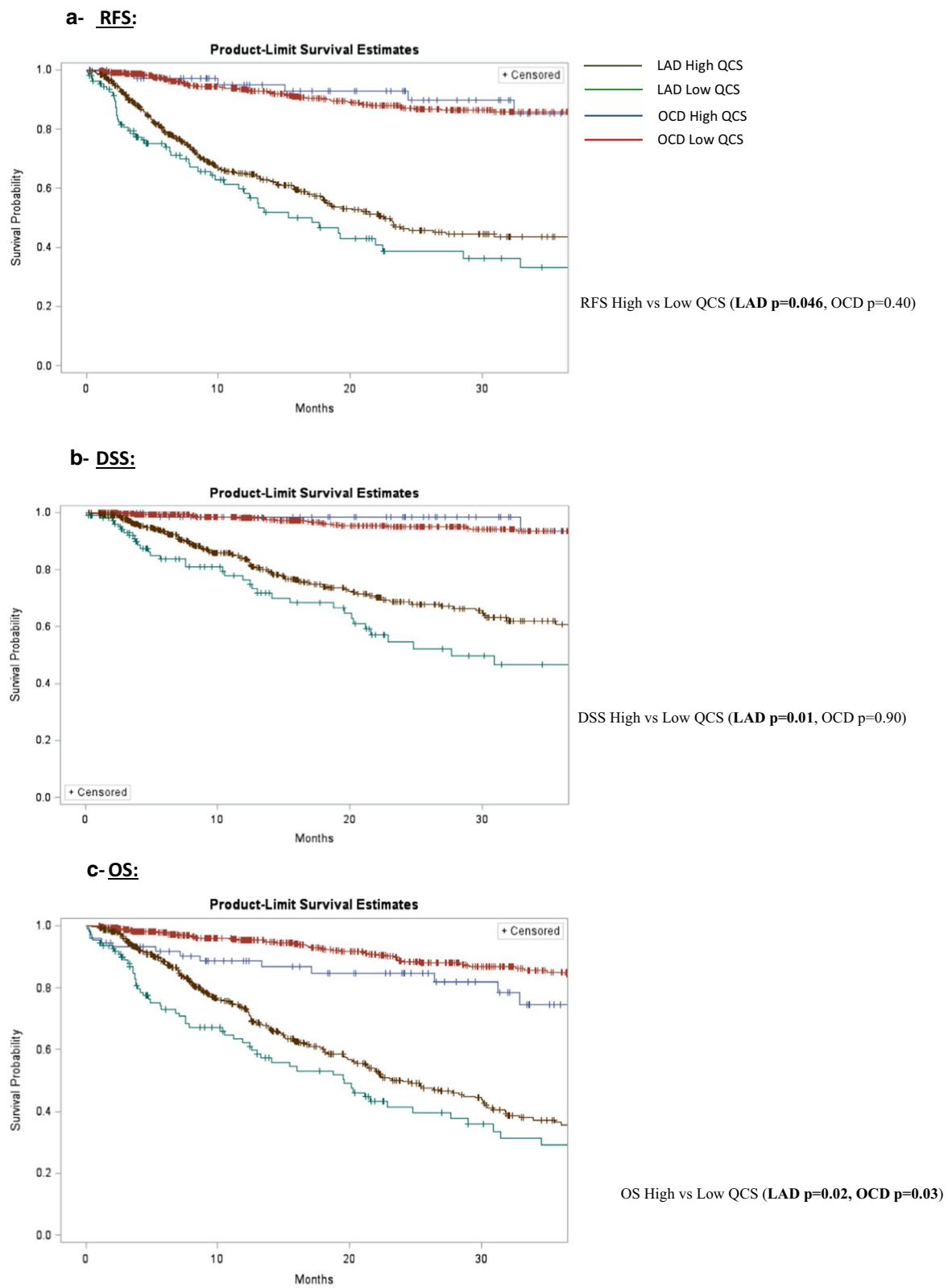


Fig. 3 Kaplan–Meier curves for RFS, DSS and OS for patients with OCD versus LAD stratified by QCS score (high QCS vs. low QCS)

Table 2 Multivariable stepwise Cox proportional hazards regression modeling predictors of RFS, DSS and OS

| Variables | RFS | | | DSS | | | OS | | |
|-------------------------------------|-------|-------------|----------|-------|-------------|----------|-------|-------------|----------|
| | HR | CI | <i>p</i> | HR | CI | <i>p</i> | HR | CI | <i>p</i> |
| Gender (females) | 0.685 | 0.493–0.952 | 0.02 | | | | | | |
| BMI | | | | 0.956 | 0.924–0.99 | 0.01 | 0.964 | 0.943–0.986 | 0.002 |
| ASA | | | | | | | 1.409 | 1.133–1.751 | 0.002 |
| Diversion type (ileal conduit) | | | | 0.297 | 0.12–0.736 | 0.009 | 0.366 | 0.208–0.645 | 0.0005 |
| Diversion approach (intracorporeal) | 0.67 | 0.49–0.91 | 0.01 | | | | | | |
| pT (\leq pT2) | 1.595 | 1.146–2.218 | 0.006 | 5.119 | 3.225–8.124 | <0.0001 | 3.656 | 2.762–4.837 | <0.0001 |
| pN (N–) | 1.629 | 1.185–2.239 | 0.003 | 2.053 | 1.385–3.043 | 0.0003 | 1.833 | 1.4–2.399 | <0.0001 |
| QCS (low QCS) | | | | 0.533 | 0.338–0.84 | 0.007 | 0.629 | 0.457–0.864 | 0.004 |

provide adequate primary tumor control. Additionally, they may be associated with worse voiding symptoms, uncontrollable bleeding, repeated hospital readmissions and poor quality of life [15]. Inadequate local tumor control may also cause fistulation, ureteral obstruction and symptomatic distant metastasis [6]. Consequently, approximately one-quarter of the patients will undergo salvage cystectomy for symptom relief [16]. RC following extensive chemo-irradiation and multiple TURs has very limited clinical efficacy and usually associated with even higher morbidity and mortality [17]. Therefore, resection of the bladder with an adequate safety margin and extended lymph node dissection may offer symptomatic relief and offer some oncological benefits especially when combined with chemotherapy for control of micrometastatic disease [6].

The present outcomes showed similar perioperative outcomes between LAD and OCD, with only modest difference in the estimated blood loss (444 vs. 376). More patients in the LAD showed PSM (14% vs. 2%, $p < 0.001$) and experienced recurrence more often (39% vs. 10%, $p < 0.001$). This can be explained by disease aggressiveness. Even with adequate surgical techniques, LAD cohort may still experience more positive soft tissue surgical margins, which is associated with disease relapse [18, 19].

Survival following RARC depends on several key factors: stage of disease at presentation, patient age and comorbidities, and the quality of operative management [5, 20, 21]. Deal management should include multidisciplinary consultation regarding NAC, a procedure that respects oncological principles, optimized perioperative care and the availability of adequate institutional resources [22]. Disease factors mainly drive survival outcomes for bladder cancer. The adverse impact of advanced pT stage and nodal status has been shown, and long-term survival is dismal when bladder cancer invades the pelvic sidewall or adjacent structures [3, 4, 12, 23,

24]. Nodal involvement had a clear negative prognostic impact independent of pT stage [24].

While disease and patient characteristics are less controllable, disease management and perioperative care are “modifiable” and should be optimized. It has been previously shown that independent of patient and disease characteristics, high-quality surgical care is associated with RFS, DSS and OS [22]. In the current study, more patients in the OCD received higher quality of care when compared to LAD (90% vs. 83%), which is attributed primarily to the pathologic criteria that include positive soft tissue surgical margins (Table 1). The improvement in surgical care provided for patients with time corresponds to increased trends of utilization of NAC and is in agreement with data from National Medicare, which shows a 37% decline in mortality [22, 25]. Our findings confirm that quality of surgical care is mandatory to optimize OS for all patients, irrespective of their disease status. Among patients with OCD, those who received a higher quality of surgical care demonstrated better OS at 5 years (70% vs. 55%, $p = 0.03$). Among patients with LAD, disease control benefit (in terms of RFS and DSS) has been additionally demonstrated. This reflects that a quality surgery that involves thorough lymphadenectomy is worthwhile and can provide recurrence-free and disease-free survival benefit even in patients with the locally advanced and micrometastatic disease. However, controversies do exist with respect to the required extent of lymphadenectomy and the number of nodes that should be retrieved. It has been concluded that bilateral and meticulous lymphadenectomy up to the common iliac artery is adequate and that such a dissection would provide a yield of approximately 20 lymph nodes [22]. The introduction of NAC has been associated with improved survival in these patients, especially in patients with complete pathological response [8]. Meticulous surgical clearance and extended lymph node dissection are crucial for achievement of optimal survival following RARC.

Other factors that have been shown in this study to affect survival included female gender, ASA score, intracorporeal diversion and continent diversion. Females in general have worse outcomes of bladder cancer. The effects of the diversion technique and type may be related to patient selection bias, where sicker patients usually receive conduits that are mostly performed intracorporeally, or may be related to longer operative times associated with intracorporeal diversion.

The present study has its limitations. First, the limitations inherent to retrospective analysis are well recognized. Second, the study includes 24 different institutions which may vary in their management protocols. Still, our study reflects real practice patterns and may be used for better patient counseling. Regarding QCS score, an equal weight was assigned for each of the parameters used, which may not reflect their actual importance. Also, the pathologic criteria of QCS may still be affected by disease stage, which can affect the assessment of the quality of surgical care.

5 Conclusion

Disease-related factors remain the main determinant of survival for bladder cancer. Quality of surgical care can affect disease control and overall survival in patients with bladder cancer treated with robot-assisted radical cystectomy. In patients with locally advanced disease, quality surgical care is mandatory to achieve acceptable cancer control.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12301-020-00031-y>.

Additional file 1: Figure S1. Criteria included in QCS ²².

Additional file 2: Table S1. Life tables for RFS, DSS and OS for LAD (high vs low QCS) vs OCD (high vs low QCS).

Abbreviations

RARC: Robot-assisted radical cystectomy; RC: Radical cystectomy; LAD: Locally advanced disease; NAC: Neoadjuvant chemotherapy; LN: Lymph node; IRCC: International Robotic Cystectomy Consortium; OCD: Organ-confined disease; BMI: Body mass index; ASA: American Society of Anesthesiologists; QCS: Quality cystectomy score; RFS: Recurrence-free; DSS: Disease-specific; OS: Overall survival; TUR: Transurethral resection.

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Authors' contributions

YA, AAH and KAG conceived and designed the study. YA, AAH, BA, AK, JB, AD, SK, JK, MS, CW, LR, AW, BY, JPR, PD, MSK, MM, JOP, ABH, FG, GP, FS, AM, KR, AH, MS, JK, JST, TJM, VP, JK, AEC, MDB and PW collected the data and revised the final manuscript. YA, AAH and PRM contributed to statistical analysis. YA and AAH drafted the manuscript. AAH and KAG supervised the study. All authors have read and approved the manuscript.

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Availability of data and material

Available upon request.

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Roswell Park Cancer Institute, Elm & Carlton St, Buffalo, NY 14263, USA. ² Cairo University, Giza, Egypt. ³ University of the Saarland, Homburg Saar, Germany. ⁴ Rijnstate Hospital, Arnhem, The Netherlands. ⁵ The Arthur Smith Institute for Urology, New York, NY, USA. ⁶ Beth Israel Deaconess Medical Center, Boston, MA, USA. ⁷ City of Hope and Beckman Research Institute, Duarte, CA, USA. ⁸ Fundacio Puigvert, Barcelona, Spain. ⁹ Guy's Hospital and King's College London School of Medicine, London, UK. ¹⁰ Henry Ford Health System, Detroit, MI, USA. ¹¹ Karolinska University Hospital, Stockholm, Sweden. ¹² San Raffaele Turro Hospital, Milan, Italy. ¹³ Urological Surgical Associates of Delaware, Wilmington, DE, USA. ¹⁴ Onze-Lieve-Vrouw Ziekenhuis, Aalst, Belgium. ¹⁵ Yonsei University Health System Severance Hospital, Seoul, Korea. ¹⁶ Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA. ¹⁷ Division of Surgery and Interventional Science, Department of Urology, University College London, London, UK. ¹⁸ Michigan Urological Clinic, Grand Rapids, MI, USA. ¹⁹ Doctor's Hospital of Athens, Athens, Greece. ²⁰ Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA. ²¹ School of Medicine, Ankara Atatürk Training and Research Hospital, Yildirim Beyazit University, Ankara, Turkey.

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