

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL FACULDADE DE MEDICINA  
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

**BLADDER CANCER RECURRENCE PATTERNS AFTER ROBOTIC RADICAL CYSTECTOMY WITH  
COMPLETELY INTRACORPOREAL URINARY DIVERSION: A CONTEMPORARY COMPARISON  
WITH OPEN RADICAL CYSTECTOMY AT A HIGH-VOLUME ACADEMIC CENTER**

Aluno: Andre Berger

Porto Alegre 2021

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL FACULDADE DE MEDICINA  
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

**BLADDER CANCER RECURRENCE PATTERNS AFTER ROBOTIC RADICAL CYSTECTOMY WITH  
COMPLETELY INTRACORPOREAL URINARY DIVERSION: A CONTEMPORARY COMPARISON  
WITH OPEN RADICAL CYSTECTOMY AT A HIGH-VOLUME ACADEMIC CENTER**

Aluno: Andre Berger

Orientador: Prof. Dr. Gilberto Schwartzmann

Tese apresentada como requisito parcial para obtenção de Doutor em Medicina: Ciências Médicas, da Universidade Federal do Rio Grande do Sul, Programa de Pós- Graduação em Medicina: Ciências Médicas.

Porto Alegre 2021

## CIP - Catalogação na Publicação

Berger, Andre

BLADDER CANCER RECURRENCE PATTERNS AFTER ROBOTIC  
RADICAL CYSTECTOMY WITH COMPLETELY INTRACORPOREAL  
URINARY DIVERSION: A CONTEMPORARY COMPARISON WITH OPEN  
RADICAL CYSTECTOMY AT A HIGH-VOLUME ACADEMIC CENTER /  
Andre Berger. -- 2021.

14 f.

Orientador: Gilberto Schwartzmann.

Tese (Doutorado) -- Universidade Federal do Rio  
Grande do Sul, Faculdade de Medicina, Programa de  
Pós-Graduação em Medicina: Ciências Médicas, Porto  
Alegre, BR-RS, 2021.

1. cancer de bexiga. I. Schwartzmann, Gilberto,  
orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os  
dados fornecidos pelo(a) autor(a).

## RESUMO / ABSTRACT

**Background:** There is some debate about patterns of recurrence after robotic radical cystectomy (RARC) for bladder cancer compared to open radical cystectomy (ORC).

**Objective:** To compare rates and patterns of recurrence after RARC with completely intracorporeal urinary diversion (ICUD) and ORC.

**Design, Setting and Participants:** Between August 2009 and June 2016, 837 consecutive patients underwent RARC with ICUD or ORC for localized BC at a single high-volume academic cancer center.

**Intervention:** RARC and ICUD was performed in 237 patients, while ORC was performed in 598 patients.

**Outcome Measurements and Statistical Analysis:** The outcomes of interest were recurrence-free survival (RFS), overall survival (OS) and distribution of local and distant recurrence. The patterns of local and distant recurrences within 2 years were tabulated. Kaplan-Meier analysis, the log rank test, and Cox regression analyses were used to compare RFS and OS between the two groups. All data was collected prospectively within an IRB-approved database and analysed retrospectively. All statistical analyses were performed using SAS software.

**Results and limitations:** Both groups were comparable with respect to age, BMI, ASA, neoadjuvant chemotherapy status, CIS, LVI, positive soft-tissue margins and node-positive disease. RARC and ICUD patients were more likely to have an ileal conduit (64% vs 29%,  $p < 0.05$ ) and extravesical disease (38% vs 30%,  $p < 0.05$ ). There was no difference in recurrence-free survival for the entire cohort, and by pathological stage: organ-confined disease (pT0-pT2,  $n = 565$ ), extra-vesical disease (pT3-pT4,  $n = 270$ ) and node-positive disease (pN+,  $n = 183$ , all  $p > 0.05$ ). Median time to recurrence was 6.9 months in RARC arm and 7.7 months in the ORC

arm. On multivariable regression analysis, RARC was not an independent predictor of recurrence after adjusting for confounders (HR 1.05, 95%CI 0.75–1.48;  $p=0.8$ ). There were no differences in the number or patterns of recurrences, in particular, with respect to peritoneal carcinomatosis and extra-pelvic lymph node metastasis. The main limitation of this study is the retrospective analysis.

**Conclusions:** These contemporary data show no differences in the rates or patterns of local or distant bladder cancer recurrence between ORC and RARC with ICUD.

**Patient summary:** Radical cystectomy and urinary diversion for bladder cancer using the robotic platform is not associated with differences in the rates or patterns of recurrence compared to traditional open surgical techniques.

Keywords: bladder cancer; cystectomy; muscle-invasive; recurrence patterns; robotics

## LISTA DE TABELAS

### SUMÁRIO

1. INTRODUÇÃO .....	7
2. REVISÃO DA LITERATURA .....	8
2.1 Estratégias para localizar e selecionar as informações .....	8
3. MARCO CONCEITUAL .....	8
4. JUSTIFICATIVA.....	8
5. OBJETIVOS .....	15
1. 5.1 Objetivo primário.....	8
6. REFERÊNCIAS BIBLIOGRÁFICAS .....	9
7. ARTIGO.....	12
8. CONSIDERAÇÕES FINAIS.....	28
9. PERSPECTIVASFUTURAS.....	28
10. ANEXOS E/OU APÊNDICES.....	28

## 1. INTRODUÇÃO

## Introduction

Bladder cancer is ranked as the 9<sup>th</sup> most common cancer worldwide [1, 2]. It is estimated that there will be over 80,000 cases diagnosed and over 17,000 deaths from bladder cancer in the United States in 2019 [3]. Up to a third of patients with bladder cancer present with muscle-invasive bladder cancer (MIBC). Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) is the standard of care in clinically localized MIBC with neoadjuvant chemotherapy also recommended in eligible patients [4, 5]. Further, 'early' RC is recommended in patients with non-MIBC at high risk of progressing to MIBC or those failing a trial of intravesical chemotherapy.

Recurrence after RC is associated with poor prognosis. A significant portion of patients with MIBC develop recurrence after RC and subsequently death. The definitions and predictors of local and distant recurrence are not well-established in the literature. Robotic-assisted radical cystectomy (RARC), without the limitations of a purely laparoscopic technique, has had increasing popularity as a minimally invasive approach to RC over the last 15 years [6-8]. One of the criticisms raised about the robotic approach has been the potential for recurrence in unusual locations compared to open RC (ORC) [9] though two recent randomized trials have demonstrated no difference in recurrence-free survival between the two approaches at 2 and 5 years follow-up respectively [10, 11]. All of these comparative studies, however, used extracorporeal urinary diversion (ECUD) methods for both RARC and ORC procedures. Intracorporeal urinary diversion (ICUD) after RC was first described in the early 2000s [12, 13]. Evolution of surgical technique and increasing experience with the robotic platform have led to increased utilization of ICUD over the last decade [14]. To our knowledge, there is no Level 1 randomized data comparing RARC with ICUD and ORC. Our objective was to compare rates and patterns of recurrence after RARC with ICUD with ORC in a large contemporary cystectomy series.

## **2. REVISÃO DA LITERATURA**

### **2.1 Estratégias para localizar e selecionar as informações**

This literature search focused on patterns of bladder cancer recurrence.

Strategy included articles in the PubMed database from 1990 to 2019.

## **3. MARCO CONCEITUAL**

Does not apply

## **4. JUSTIFICATIVA**

To our knowledge, there is no Level 1 randomized data comparing RARC with ICUUD and ORC. Our objective was to compare rates and patterns of recurrence after RARC with ICUD with ORC in a large contemporary cystectomy series.

## **5. OBJETIVOS**

### **5.1 Objetivo primário**

Primary outcome was to assess the patterns of local and distant recurrences between RARC with ICUD and ORC. Secondary outcomes were recurrence-free survival (RFS) and overall survival (OS). Post-operative complications were graded according to the Clavien–Dindo classification system.

## 6. REFERÊNCIAS BIBLIOGRÁFICAS

### References

- [1] Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *Eur Urol.* 2018;74:784-95.
- [2] Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *European Urology.* 2017;71:96-108.
- [3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69:7-34.
- [4] Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. *J Urol.* 2017;198:552-9.
- [5] Alfred Witjes J, Lebet T, Comperat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. *Eur Urol.* 2017;71:462-75.
- [6] Liss MA, Kader AK. Robotic-assisted laparoscopic radical cystectomy: history, techniques and outcomes. *World J Urol.* 2013;31:489-97.
- [7] Johar RS, Hayn MH, Stegemann AP, Ahmed K, Agarwal P, Balbay MD, et al. Complications after robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. *Eur Urol.* 2013;64:52-7.
- [8] Leow JJ, Reese SW, Jiang W, Lipsitz SR, Bellmunt J, Trinh Q-D, et al. Propensity-Matched Comparison of Morbidity and Costs of Open and Robot-Assisted Radical Cystectomies: A

Contemporary Population-Based Analysis in the United States. *European Urology*. 2014;66:569-76.

[9] Nguyen DP, Al Hussein Al Awamih B, Wu X, O'Malley P, Inoyatov IM, Ayangbesan A, et al. Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. *Eur Urol*. 2015;68:399-405.

[10] Bochner BH, Dalbagni G, Marzouk KH, Sjoberg DD, Lee J, Donat SM, et al. Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: Oncologic Outcomes. *Eur Urol*. 2018.

[11] Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, 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;391:2525-36.

[12] Gill IS, Fergany A, Klein EA, Kaouk JH, Sung GT, Meraney AM, et al. Laparoscopic radical cystoprostatectomy with ileal conduit performed completely intracorporeally: the initial 2 cases. *Urology*. 2000;56:26-9; discussion 9-30.

[13] Hubert J, Feuillu B, Beis JM, Coissard A, Mangin P, Andre JM. Laparoscopic robotic-assisted ileal conduit urinary diversion in a quadriplegic woman. *Urology*. 2003;62:1121.

[14] Hussein AA, May PR, Jing Z, Ahmed YE, Wijburg CJ, Canda AE, et al. Outcomes of Intracorporeal Urinary Diversion after Robot-Assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *J Urol*. 2018;199:1302-11.

[15] Stein JP, Skinner DG. Surgical atlas. Radical cystectomy. *BJU Int*. 2004;94:197-221.

[16] Desai MM, de Abreu AL, Goh AC, Fairey A, Berger A, Leslie S, et al. Robotic intracorporeal urinary diversion: technical details to improve time efficiency. *J Endourol*. 2014;28:1320-7.

[17] Hussein AA, Saar M, May PR, Wijburg CJ, Richstone L, Wagner A, et al. Early Oncologic Failure after Robot-Assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *The Journal of Urology*. 2017;197:1427-36.

[18] Mari A, Campi R, Tellini R, Gandaglia G, Albisinni S, Abufaraj M, et al. Patterns and predictors of recurrence after open radical cystectomy for bladder cancer: a comprehensive review of the literature. *World J Urol*. 2018;36:157-70.

- [19] Dotan ZA, Kavanagh K, Yossepowitch O, Kaag M, Olgac S, Donat M, et al. Positive Surgical Margins in Soft Tissue Following Radical Cystectomy for Bladder Cancer and Cancer Specific Survival. *The Journal of Urology*. 2007;178:2308-13.
- [20] Herr HW, Faulkner JR, Grossman HB, Natale RB, deVere White R, Sarosdy MF, et al. Surgical Factors Influence Bladder Cancer Outcomes: A Cooperative Group Report. *Journal of Clinical Oncology*. 2004;22:2781-9.
- [21] Hong X, Li T, Ling F, Yang D, Hou L, Li F, et al. Impact of surgical margin status on the outcome of bladder cancer treated by radical cystectomy: a meta-analysis. *Oncotarget*. 2017;8:17258-69.
- [22] Pak JS, Lee JJ, Bilal K, Finkelstein M, Palese MA. Utilization trends and outcomes up to 3 months of open, laparoscopic, and robotic partial nephrectomy. *J Robot Surg*. 2017;11:223-9.
- [23] Khan MS, Gan C, Ahmed K, Ismail AF, Watkins J, Summers JA, et al. A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). *Eur Urol*. 2016;69:613-21.
- [24] Nix J, Smith A, Kurpad R, Nielsen ME, Wallen EM, Pruthi RS. Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: perioperative and pathologic results. *Eur Urol*. 2010;57:196-201.
- [25] Messer J, Parekh DJ. Perioperative outcomes and Oncologic Efficacy from a Pilot Prospective Randomized Clinical Trial of Open Versus Robotic Assisted Radical Cystectomy. *J Urol*. 2013.
- [26] Messer JC, Punnen S, Fitzgerald J, Svatek R, Parekh DJ. Health-related quality of life from a prospective randomised clinical trial of robot-assisted laparoscopic vs open radical cystectomy. *BJU International*. 2014;114:896-902.
- [27] Parekh DJ, Messer J, Fitzgerald J, Ercole B, Svatek R. Perioperative outcomes and oncologic efficacy from a pilot prospective randomized clinical trial of open versus robotic assisted radical cystectomy. *J Urol*. 2013;189:474-9.
- [28] Bochner BH, Sjoberg DD, Laudone VP, Memorial Sloan Kettering Cancer Center Bladder Cancer Surgical Trials G. A randomized trial of robot-assisted laparoscopic radical cystectomy. *N Engl J Med*. 2014;371:389-90.

- [29] Sathianathen NJ, Kalapara A, Frydenberg M, Lawrentschuk N, Weight CJ, Parekh D, et al. Robotic Assisted Radical Cystectomy vs Open Radical Cystectomy: Systematic Review and Meta-Analysis. *J Urol*. 2019;201:715-20.
- [30] Tan WS, Khetrpal P, Tan WP, Rodney S, Chau M, Kelly JD. Robotic Assisted Radical Cystectomy with Extracorporeal Urinary Diversion Does Not Show a Benefit over Open Radical Cystectomy: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *PLoS One*. 2016;11:e0166221.
- [31] Tang JQ, Zhao Z, Liang Y, Liao G. Robotic-assisted versus open radical cystectomy in bladder cancer: A meta-analysis of four randomized controlled trails. *Int J Med Robot*. 2018;14.
- [32] Novara G, Catto JWF, Wilson T, Annerstedt M, Chan K, Murphy DG, et al. Systematic Review and Cumulative Analysis of Perioperative Outcomes and Complications After Robot-assisted Radical Cystectomy. *European Urology*. 2015;67:376-401.
- [33] Attalla K, Kent M, Waingankar N, Mehrazin R. Robotic-assisted radical cystectomy versus open radical cystectomy for management of bladder cancer: review of literature and randomized trials. *Future Oncol*. 2017;13:1195-204.
- [34] Rai BP, Bondad J, Vasdev N, Adshead J, Lane T, Ahmed K, et al. Robotic versus open radical cystectomy for bladder cancer in adults. *Cochrane Database Syst Rev*. 2019;4:CD011903.

## 7. ARTIGO

### **BLADDER CANCER RECURRENCE PATTERNS AFTER ROBOTIC RADICAL CYSTECTOMY WITH COMPLETELY INTRACORPOREAL URINARY DIVERSION: A CONTEMPORARY COMPARISON WITH OPEN RADICAL CYSTECTOMY AT A HIGH-VOLUME ACADEMIC CENTER**

Akbar N. Ashrafi, Pierre-Alain Hueber, Giovanni E. Cacciamani, Nieroshan Rajarubendra, Michael Lin-Brandt, Jie Cai, Gus Miranda, Hooman Djaladat, Anne Schuckman, Monish Aron, Siamak Daneshmand, Inderbir S. Gill, Mihir M. Desai, Andre K. Berger.

USC Institute of Urology  
Keck School of Medicine  
University of Southern California  
Los Angeles, CA

**\*Corresponding author:**

Akbar N. Ashrafi, MD

USC Institute of Urology

University of Southern California

1441 Eastlake Ave, Suite 7416; Los Angeles, CA 90089

Ph: (323) 865 3749

Fax: (323) 865 0120

Email: [dr.akbarashrafi@gmail.com](mailto:dr.akbarashrafi@gmail.com)

Word count:

Tables: 0, Figures: 0

References:

Keywords: bladder cancer; cystectomy; muscle-invasive; recurrence patterns; robotics

## CIP - Catalogação na Publicação

Berger, Andre

BLADDER CANCER RECURRENCE PATTERNS AFTER ROBOTIC  
RADICAL CYSTECTOMY WITH COMPLETELY INTRACORPOREAL  
URINARY DIVERSION: A CONTEMPORARY COMPARISON WITH OPEN  
RADICAL CYSTECTOMY AT A HIGH-VOLUME ACADEMIC CENTER /  
Andre Berger. -- 2021.

14 f.

Orientador: Gilberto Schwartzmann.

Tese (Doutorado) -- Universidade Federal do Rio  
Grande do Sul, Faculdade de Medicina, Programa de  
Pós-Graduação em Medicina: Ciências Médicas, Porto  
Alegre, BR-RS, 2021.

1. cancer de bexiga. I. Schwartzmann, Gilberto,  
orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os  
dados fornecidos pelo(a) autor(a).

## Abstract

**Background:** There is some debate about patterns of recurrence after robotic radical cystectomy (RARC) for bladder cancer compared to open radical cystectomy (ORC).

**Objective:** To compare rates and patterns of recurrence after RARC with completely intracorporeal urinary diversion (ICUD) and ORC.

**Design, Setting and Participants:** Between August 2009 and June 2016, 837 consecutive patients underwent RARC with ICUD or ORC for localized BC at a single high-volume academic cancer center.

**Intervention:** RARC and ICUD was performed in 237 patients, while ORC was performed in 598 patients.

**Outcome Measurements and Statistical Analysis:** The outcomes of interest were recurrence-free survival (RFS), overall survival (OS) and distribution of local and distant recurrence. The patterns of local and distant recurrences within 2 years were tabulated. Kaplan-Meier analysis, the log rank test, and Cox regression analyses were used to compare RFS and OS between the two groups. All data was collected prospectively within an IRB-approved database and analysed retrospectively. All statistical analyses were performed using SAS software.

**Results and limitations:** Both groups were comparable with respect to age, BMI, ASA, neoadjuvant chemotherapy status, CIS, LVI, positive soft-tissue margins and node-positive disease. RARC and ICUD patients were more likely to have an ileal conduit (64% vs 29%,  $p < 0.05$ ) and extravesical disease (38% vs 30%,  $p < 0.05$ ). There was no difference in recurrence-free survival for the entire cohort, and by pathological stage: organ-confined disease (pT0-pT2,  $n=565$ ), extra-vesical disease (pT3-pT4,  $n=270$ ) and node-positive disease (pN+,  $n=183$ , all  $p > 0.05$ ). Median time to recurrence was 6.9 months in RARC arm and 7.7 months in the ORC

arm. On multivariable regression analysis, RARC was not an independent predictor of recurrence after adjusting for confounders (HR 1.05, 95%CI 0.75–1.48;  $p=0.8$ ). There were no differences in the number or patterns of recurrences, in particular, with respect to peritoneal carcinomatosis and extra-pelvic lymph node metastasis. The main limitation of this study is the retrospective analysis.

**Conclusions:** These contemporary data show no differences in the rates or patterns of local or distant bladder cancer recurrence between ORC and RARC with ICUD.

**Patient summary:** Radical cystectomy and urinary diversion for bladder cancer using the robotic platform is not associated with differences in the rates or patterns of recurrence compared to traditional open surgical techniques.

## Introduction

Bladder cancer is ranked as the 9<sup>th</sup> most common cancer worldwide [1, 2]. It is estimated that there will be over 80,000 cases diagnosed and over 17,000 deaths from bladder cancer in the United States in 2019 [3]. Up to a third of patients with bladder cancer present with muscle-invasive bladder cancer (MIBC). Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) is the standard of care in clinically localized MIBC with neoadjuvant chemotherapy also recommended in eligible patients [4, 5]. Further, 'early' RC is recommended in patients with non-MIBC at high risk of progressing to MIBC or those failing a trial of intravesical chemotherapy.

Recurrence after RC is associated with poor prognosis. A significant portion of patients with MIBC develop recurrence after RC and subsequently death. The definitions and predictors of local and distant recurrence are not well-established in the literature. Robotic-assisted radical cystectomy (RARC), without the limitations of a purely laparoscopic technique, has had increasing popularity as a minimally invasive approach to RC over the last 15 years [6-8]. One of the criticisms raised about the robotic approach has been the potential for recurrence in unusual locations compared to open RC (ORC) [9] though two recent randomized trials have demonstrated no difference in recurrence-free survival between the two approaches at 2 and 5 years follow-up respectively [10, 11]. All of these comparative studies, however, used extracorporeal urinary diversion (ECUD) methods for both RARC and ORC procedures. Intracorporeal urinary diversion (ICUD) after RC was first described in the early 2000s [12, 13]. Evolution of surgical technique and increasing experience with the robotic platform have led to increased utilization of ICUD over the last decade [14]. To our knowledge, there is no Level 1 randomized data comparing RARC with ICUD and ORC. Our objective was to compare rates and patterns of recurrence after RARC with ICUD with ORC in a large contemporary cystectomy series.

## **Patients and Methods**

### ***Patients***

We identified 837 consecutive patients undergoing RARC with ICUD or ORC for localized BC an institutional review board-approved radical cystectomy database at a high-volume, academic cancer center from August 2009 to June 2016. Patients undergoing surgery for palliation or patients with metastatic disease were excluded. Both ORC and RARC with ICUD were performed in the usual manner as previously described [15, 16]. Patient follow-up included routine history and physical examination, blood profiles, and interval radiological imaging. Baseline clinical and pathological data were collated including age, gender, American Society of Anesthesiologists (ASA) status, Charlson comorbidity index (CCI), clinical stage, pathological stage, tumor multifocality, lymphovascular invasion (LVI), carcinoma-in-situ, soft tissue margin status, and chemotherapy status. All data were collected prospectively. Data up to the most recent follow-up was used at the time of analysis.

### ***Primary Outcomes***

Primary outcome was to assess the patterns of local and distant recurrences between RARC with ICUD and ORC. Secondary outcomes were recurrence-free survival (RFS) and overall survival (OS). Post-operative complications were graded according to the Clavien–Dindo classification system.

### ***Statistical Analysis***

Demographic, pathological, perioperative and early oncological outcomes were compared between two groups. Continuous variables were summarized using median and interquartile range and compared using the Kruskal-Wallis test. Nominal variables were analyzed using the chi-square or Fisher exact test. The distribution of local and distant recurrences within 2 years were tabulated. The Kaplan-Meier method and log-rank analysis was used to estimate and compare the probability of RFS and OS by surgical approach. Subgroup survival analyses were

performed based on pathological stage. Cox proportional hazards were used to estimate the impact of surgical approach on RFS and OS with hazard ratios (HR) and 95% confidence intervals. Data was collated prospectively within an institutional review board-approved database and analysed retrospectively. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA). A two-tailed p-value of less than 0.05 for was considered statistically significant.

## Results

### ***Baseline Characteristics and Pathological Outcomes***

A total of 837 patients were treated with RC and PLND, of which 598 had ORC and 137 underwent RARC with ICUD. Baseline demographic and clinical characteristics were equivalent between the two groups including age, sex, BMI, history of smoking, history of previous abdominal surgery, CCI, ASA score and number of transurethral resections prior to cystectomy (**Table 1**). The rate of neoadjuvant and adjuvant chemotherapy were similar between groups. In the RARC, all RCs and UDs were completed completely robotically and intracorporeally. RARC patients were more likely to have an ileal conduit for urinary diversion (93.7% vs 28.9%;  $p < 0.01$ ). The pathological extent of tumor was different between the two groups with the RARC patients more likely to have extravesical (pT3 or pT4) disease (38.0% vs 31.0%,  $p = 0.03$ ) compared to the ORC group. Otherwise, there was no significant difference in pathologic lymph node positivity, lymphovascular invasion, carcinoma-in-situ, multifocal disease or positive soft tissue margins (**Table 1**).

### ***Oncological Outcomes***

Median follow up was 14 months.

Kaplan-Meier survival curves demonstrated similar RFS and OS probability for RARC with ICUD and ORC in all patients (**Figure 1**). Further, Kaplan-Meier analysis showed no difference in RFS probability when stratified into groups as follow: organ-confined disease (pTa/pTis/pT1/pT2), extra-vesical disease (pT3/T4) and node-positive disease (pN+). Multivariable Cox regression analysis demonstrated that RARC with ICUD was not an

independent predictor of any recurrence after adjusting for patient age, gender, neoadjuvant chemotherapy, pathological tumor and nodal stage stage, lymphovascular invasion, and PSM (Table 3)

### **Patterns of Recurrence**

There were no significant differences in the patterns of recurrence in patients with a minimum of two years follow-up.

### **Discussion**

Recurrence of bladder cancer after RC is associated with poor prognosis[17]. The exact pathogenesis of the timing and sites of recurrence is not well-understood. Recurrences at the urethral or ureteral margins have been referred to as secondary urothelial carcinoma [9]. Recurrences outside the RC resection bed or area of PLND is considered to be distant recurrence. Local recurrence is commonly defined as soft-tissue recurrence in the RC resection bed or nodal recurrence in the area of pelvic lymph node dissection but has also variably included recurrences anywhere in the urinary tract[14] or recurrences in the abdominal wall or port sites [11]. The exact mechanisms of recurrent bladder cancer recurrence are not well understood. Several factors have been associated with bladder cancer recurrence after RC [18]. Positive soft-tissue surgical margins at the time RC is a particularly poor prognostic marker, predicting high rates of local tumor recurrence and inferior recurrence-free and overall survival [19-21]. However, even with negative surgical margins, the recurrent rates after RC remain high.

Open surgery has been the traditional standard for RC. Over the last decade, there has been an increasing uptake of minimally-invasive robotic approach to RC [6, 8, 22] leading to numerous comparative analyses to demonstrate non-inferiority with RARC. Several randomized trials, systematic reviews and meta-analyses comparing RARC and ORC have reported the potential for improved perioperative outcomes with RARC including reduced blood loss, perioperative blood transfusions and shorter length of hospital stay [23-33]. These

perioperative outcomes have been achieved without equivalence with regards to major complications and quality of life [29].

In 2015, Nguyen et al reported that RARC may be associated with altered patterns of recurrence although there was no difference in overall local or distant recurrence rates between the two groups [9]. They reported increased peritoneal carcinomatosis and extra-pelvic lymph node metastases with RARC; however, these differences did not reach statistical significance [9]. It has been speculated that these potential differences may have been due to seeding of malignant urothelial cells, prolonged pneumoperitoneum, as well as specimen bag failure and excessive manipulation of the cystectomy specimen leading to cell spillage. Inferior anatomic lymph node dissection with RARC has also been proposed as a reason for any altered patterns of recurrence. From a pathological standpoint, there is now Level 1 data to show that lymph node yield and positive soft-tissue margin rates are equivalent between RARC and ORC [27, 31]. More recently, oncological endpoints have been published for two of the landmark randomized trials. The RAZOR trial was a multi-center, randomized, phase 3 trial of 302 patients across 15 centers in the U.S comparing RARC vs ORC with a primary endpoint of 2-year progression-free survival. The initial publication reported equivalent pathological outcomes including positive surgical margins and lymph node yield between RARC and ORC [27]. The updated report incorporating the primary endpoint demonstrated that RARC was non-inferior to ORC with regards to 2-year progression-free survival [11]. Similarly, Bochner et al. published updated data from the randomized trial of 118 patients undergoing RARC vs ORC at the Memorial Sloan Kettering Cancer Center[10]. After a median follow-up of 4.9 years, there was no difference in recurrence, cancer-specific or overall survival. Further, a recent Cochrane review demonstrated non-inferiority of the robotic approach compared to ORC with regards to major complications, positive surgical margins and overall survival [34].

With regards to patterns of recurrence, a contemporary summary of single-arm series and comparative RARC vs ORC series is shown in **Table 3**. Importantly, the RAZOR trial reported no differences in local or distant recurrent patterns and no cases of port recurrences [11]. Local recurrences were defined as recurrences in the cystectomy bed, nodal template or those occurring in the abdominal wall while bowel recurrences and peritoneal carcinomatosis were

considered distant recurrences. Bochner et al's trial considered bowel recurrence and peritoneal carcinomatosis as a separate entity termed as "abdominal recurrences" rather than distant recurrences. Interestingly, this trial showed that patients undergoing ORC had a trend towards higher rates of distant recurrences, although this difference was not statistically significant ( $p=0.06$ ). With regards to local recurrences, there was a trend towards increased recurrences in the RARC arm which again did not reach statistical significance ( $p=0.08$ ). There were no differences in abdominal recurrences ( $p=0.2$ ) including no difference in the rate of peritoneal carcinomatosis (3.3% vs 3.4%). Different trends in patterns of recurrences were noted. RARC was associated with increased rectal (5% vs 0%), abdominal wall (8.3% vs 0%) and bowel recurrences (8.3% vs 1.7%). ORC had increased extra-pelvic nodal recurrences (17.2% vs 8.3%) and lung metastasis (15.5% vs 1.7%).

To our knowledge, there have been no comparative studies of recurrence patterns for RARC vs ORC in patients undergoing completely intracorporeal urinary diversion. If malignant cell seeding from specimen bag failure or excessive specimen handling is at all a factor, then the increased duration of pneumoperitoneum from a totally intracorporeal urinary diversion would exacerbate any true differences in recurrence or recurrence patterns. In this study, we demonstrate no difference in patterns of local and distant recurrences in 837 consecutive patients undergoing ORC or RARC with intracorporeal urinary diversion. Our study further supports the safety of the robotic approach to RC with BC recurrence.

Our study is not without limitations. Assessment of the patterns of recurrence required more granular data than overall recurrence statistics. Patients may have multiple sites of recurrence detected concurrently during radiological surveillance or may present with metachronous recurrences adding further complexity to robust data collection and presentation.

## **Conclusions**

Radical cystectomy and urinary diversion for bladder cancer using the robotic platform is not associated with differences in the rates or patterns of recurrence compared to traditional open surgical techniques

## References

- [1] Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *Eur Urol.* 2018;74:784-95.
- [2] Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *European Urology.* 2017;71:96-108.
- [3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69:7-34.
- [4] Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. *J Urol.* 2017;198:552-9.
- [5] Alfred Witjes J, Lebet T, Comperat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. *Eur Urol.* 2017;71:462-75.
- [6] Liss MA, Kader AK. Robotic-assisted laparoscopic radical cystectomy: history, techniques and outcomes. *World J Urol.* 2013;31:489-97.
- [7] Johar RS, Hayn MH, Stegemann AP, Ahmed K, Agarwal P, Balbay MD, et al. Complications after robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. *Eur Urol.* 2013;64:52-7.
- [8] Leow JJ, Reese SW, Jiang W, Lipsitz SR, Bellmunt J, Trinh Q-D, et al. Propensity-Matched Comparison of Morbidity and Costs of Open and Robot-Assisted Radical Cystectomies: A Contemporary Population-Based Analysis in the United States. *European Urology.* 2014;66:569-76.
- [9] Nguyen DP, Al Hussein Al Awamih B, Wu X, O'Malley P, Inoyatov IM, Ayangbesan A, et al. Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. *Eur Urol.* 2015;68:399-405.
- [10] Bochner BH, Dalbagni G, Marzouk KH, Sjoberg DD, Lee J, Donat SM, et al. Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: Oncologic Outcomes. *Eur Urol.* 2018.

- [11] Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, 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;391:2525-36.
- [12] Gill IS, Fergany A, Klein EA, Kaouk JH, Sung GT, Meraney AM, et al. Laparoscopic radical cystoprostatectomy with ileal conduit performed completely intracorporeally: the initial 2 cases. *Urology*. 2000;56:26-9; discussion 9-30.
- [13] Hubert J, Feuillu B, Beis JM, Coissard A, Mangin P, Andre JM. Laparoscopic robotic-assisted ileal conduit urinary diversion in a quadriplegic woman. *Urology*. 2003;62:1121.
- [14] Hussein AA, May PR, Jing Z, Ahmed YE, Wijburg CJ, Canda AE, et al. Outcomes of Intracorporeal Urinary Diversion after Robot-Assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *J Urol*. 2018;199:1302-11.
- [15] Stein JP, Skinner DG. Surgical atlas. Radical cystectomy. *BJU Int*. 2004;94:197-221.
- [16] Desai MM, de Abreu AL, Goh AC, Fairey A, Berger A, Leslie S, et al. Robotic intracorporeal urinary diversion: technical details to improve time efficiency. *J Endourol*. 2014;28:1320-7.
- [17] Hussein AA, Saar M, May PR, Wijburg CJ, Richstone L, Wagner A, et al. Early Oncologic Failure after Robot-Assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *The Journal of Urology*. 2017;197:1427-36.
- [18] Mari A, Campi R, Tellini R, Gandaglia G, Albisinni S, Abufaraj M, et al. Patterns and predictors of recurrence after open radical cystectomy for bladder cancer: a comprehensive review of the literature. *World J Urol*. 2018;36:157-70.
- [19] Dotan ZA, Kavanagh K, Yossepowitch O, Kaag M, Olgac S, Donat M, et al. Positive Surgical Margins in Soft Tissue Following Radical Cystectomy for Bladder Cancer and Cancer Specific Survival. *The Journal of Urology*. 2007;178:2308-13.
- [20] Herr HW, Faulkner JR, Grossman HB, Natale RB, deVere White R, Sarosdy MF, et al. Surgical Factors Influence Bladder Cancer Outcomes: A Cooperative Group Report. *Journal of Clinical Oncology*. 2004;22:2781-9.
- [21] Hong X, Li T, Ling F, Yang D, Hou L, Li F, et al. Impact of surgical margin status on the outcome of bladder cancer treated by radical cystectomy: a meta-analysis. *Oncotarget*. 2017;8:17258-69.

- [22] Pak JS, Lee JJ, Bilal K, Finkelstein M, Palese MA. Utilization trends and outcomes up to 3 months of open, laparoscopic, and robotic partial nephrectomy. *J Robot Surg.* 2017;11:223-9.
- [23] Khan MS, Gan C, Ahmed K, Ismail AF, Watkins J, Summers JA, et al. A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). *Eur Urol.* 2016;69:613-21.
- [24] Nix J, Smith A, Kurpad R, Nielsen ME, Wallen EM, Pruthi RS. Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: perioperative and pathologic results. *Eur Urol.* 2010;57:196-201.
- [25] Messer J, Parekh DJ. Perioperative outcomes and Oncologic Efficacy from a Pilot Prospective Randomized Clinical Trial of Open Versus Robotic Assisted Radical Cystectomy. *J Urol.* 2013.
- [26] Messer JC, Punnen S, Fitzgerald J, Svatek R, Parekh DJ. Health-related quality of life from a prospective randomised clinical trial of robot-assisted laparoscopic vs open radical cystectomy. *BJU International.* 2014;114:896-902.
- [27] Parekh DJ, Messer J, Fitzgerald J, Ercole B, Svatek R. Perioperative outcomes and oncologic efficacy from a pilot prospective randomized clinical trial of open versus robotic assisted radical cystectomy. *J Urol.* 2013;189:474-9.
- [28] Bochner BH, Sjoberg DD, Laudone VP, Memorial Sloan Kettering Cancer Center Bladder Cancer Surgical Trials G. A randomized trial of robot-assisted laparoscopic radical cystectomy. *N Engl J Med.* 2014;371:389-90.
- [29] Sathianathen NJ, Kalapara A, Frydenberg M, Lawrentschuk N, Weight CJ, Parekh D, et al. Robotic Assisted Radical Cystectomy vs Open Radical Cystectomy: Systematic Review and Meta-Analysis. *J Urol.* 2019;201:715-20.
- [30] Tan WS, Khetrupal P, Tan WP, Rodney S, Chau M, Kelly JD. Robotic Assisted Radical Cystectomy with Extracorporeal Urinary Diversion Does Not Show a Benefit over Open Radical Cystectomy: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *PLoS One.* 2016;11:e0166221.
- [31] Tang JQ, Zhao Z, Liang Y, Liao G. Robotic-assisted versus open radical cystectomy in bladder cancer: A meta-analysis of four randomized controlled trials. *Int J Med Robot.* 2018;14.

[32] Novara G, Catto JWF, Wilson T, Annerstedt M, Chan K, Murphy DG, et al. Systematic Review and Cumulative Analysis of Perioperative Outcomes and Complications After Robot-assisted Radical Cystectomy. *European Urology*. 2015;67:376-401.

[33] Attalla K, Kent M, Waingankar N, Mehrazin R. Robotic-assisted radical cystectomy versus open radical cystectomy for management of bladder cancer: review of literature and randomized trials. *Future Oncol*. 2017;13:1195-204.

[34] Rai BP, Bondad J, Vasdev N, Adshead J, Lane T, Ahmed K, et al. Robotic versus open radical cystectomy for bladder cancer in adults. *Cochrane Database Syst Rev*. 2019;4:CD011903.

## **8. CONSIDERAÇÕES FINAIS**

To our knowledge, there have been no comparative studies of recurrence patterns for RARC vs ORC in patients undergoing completely intracorporeal urinary diversion. If malignant cell seeding from specimen bag failure or excessive specimen handling is at all a factor, then the increased duration of pneumoperitoneum from a totally intracorporeal urinary diversion would exacerbate any true differences in recurrence or recurrence patterns. In this study, we demonstrate no difference in patterns of local and distant recurrences in 837 consecutive patients undergoing ORC or RARC with intracorporeal urinary diversion. Our study further supports the safety of the robotic approach to RC with BC recurrence. These contemporary data show no differences in the rates or patterns of local or distant bladder cancer recurrence between ORC and RARC with ICUD.

## **9. PERSPECTIVAS FUTURAS**

Randomized trials comparing intra and extracorporeal diversions should be able to more certainly answer the recurrence question.

## **10. ANEXOS E/OU APÊNDICES**

Does not apply