RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY **WILEY**

Outcomes of robotic-assisted versus open radical cystectomy in a large-scale, contemporary cohort of bladder cancer patients

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Abstract

Background and Objectives: To test for differences in perioperative outcomes and total hospital costs (THC) in nonmetastatic bladder cancer patients undergoing open (ORC) versus robotic-assisted radical cystectomy (RARC).

Methods: We relied on the National Inpatient Sample database (2016–2019). Statistics consisted of trend analyses, multivariable logistic, Poisson, and linear regression models.

Results: Of 5280 patients, 1876 (36%) versus 3200 (60%) underwent RARC versus ORC. RARC increased from 32% to 41% (estimated annual percentage

change [EAPC]: + 8.6%; $p = 0.02$). Rates of transfusion (8% vs. 16%), intraoperative (2% vs. 3%), wound (6% vs. 10%), and pulmonary (6% vs. 10%) complications were lower in RARC patients (all $p < 0.05$). Moreover, median length of stay (LOS) was shorter in RARC (6 vs. 7days; $p < 0.001$). Conversely, median THC (31,486 vs. 27,162\$; $p < 0.001$) were higher in RARC. Multivariable logistic regression-derived odds ratios addressing transfusion (0.49), intraoperative (0.53), wound (0.68), and pulmonary (0.71) complications favored RARC (all $p < 0.01$). In multivariable Poisson and linear regression models, RARC was associated with shorter LOS (Rate ratio:0.86; $p < 0.001$), yet higher THC (Coef.:5,859\$; $p < 0.001$). RARC in-hospital mortality was lower (1% vs. 2%; $p = 0.04$).

Conclusions: RARC complications, LOS, and mortality appear more favorable than ORC, but result in higher THC. The favorable RARC profile contributes to its increasing popularity throughout the United States.

KEYWORDS

bladder cancer, complication, open, outcomes, radical cystectomy, robotic-assisted

1 | INTRODUCTION

Uncertainty persists with respect to postoperative outcome differences between robotic-assisted radical cystectomy (RARC) versus open radical cystectomy (ORC) in the setting of bladder cancer treatment, despite the presence of five prospective, randomized trials (RARC: $n = 20-152$).[1–9] Specifically, these trials provided samples from highly select tertiary care centers and thus, results might not be generalizable to the urological community. In consequence, large-scale retrospective, population-based analyses are needed to examine RARC versus ORC differences, since outcome profiles recorded at tertiary care centers may not replicate those of population-based analyses. The existing population-based studies are of limited value, since they relied on historical populations, where RARC rates were low or even marginal (Leow et al.: 6%; Harb-De la Rosa et al.: 14%).[10–12] A National Cancer Database (NCDB) study relied on a more contemporary population (2010–2013) with a larger proportion of RARC (21%). However, its endpoint did not focus on postoperative outcomes.[13] We addressed the current knowledge gap and hypothesized that within a large-scale, contemporary data set, no differences will be identified and the previously described moderate benefits of RARC may not apply to large-scale epidemiological settings.[1–5,14] To test these hypotheses, we addressed four specific endpoints of interest: (a) complication rates, (b) in-hospital mortality, (c) length of stay (LOS), and (d) total hospital costs (THC). Additionally, trend analyses were performed to investigate the uptake of RARC rates in the most contemporary years. We relied on a contemporary North-American cohort of radical cystectomy (RC) patients from within the National Inpatient Sample (NIS) database between 2016 and 2019.[15]

2 | MATERIAL AND METHODS

2.1 | Data source

The NIS database represents a set of longitudinal hospital inpatient databases included in the Healthcare Cost and Utilization Project (HCUP), created by the Agency for Healthcare Research and Quality (AHRQ) through a Federal-state partnership.[15] The database includes approximately 20% of United States inpatient hospitalizations.[15]

2.2 | Study population

Within the NIS database (2016–2019), we selected patients (aged >18 years) with a primary diagnosis of bladder cancer (International Classification of Disease, Tenth Revision, Clinical Modification [ICD-10-CM] codes C67.0-C67.6, C67.8, C67.9). Of those, patients treated with radical cystectomy were selected relying on Procedure Coding System (ICD-10-PCS), as recently reported and validated by Lyon et al.[16,17] ICD-10-PCS codes were also used to distinguish between RARC versus ORC versus laparoscopic RC.[16] Additionally, patients with secondary ICD-10-CM codes indicating lymph-node invasion or metastatic stage were excluded from further analyses.

2.3 | Outcomes of interest

Primary outcome of interests consisted of: (a) in-hospital complication rates, (b) in-hospital mortality, (c) LOS, and (d) THC. Complication rates were defined using ICD-10-CM diagnostic codes, according to previously established methodology.[18–20] Overall complication rate

represented the sum of intraoperative and postoperative complications (bowel obstruction, transfusion, wound, cerebro-vascular, gastro-intestinal, cardiac, pulmonary, genitourinary, or other medical complication), as previously described.[18,21,22] Finally, total hospital charges, which are supplied by the NIS, were converted to THC using HCUP cost-to-charge ratios based on hospital accounting reports, in accordance to NIS methodological guidelines.[15] To facilitate comparison, all costs were additionally adjusted to 2016 dollars.

2.4 | Patient and hospital characteristics

Patient characteristics such as age, race/ethnicity (Caucasian, African American, Others), comorbidities, and insurance status (Medicare, Medicaid, private, Others) were ascertained from the NIS. A modified Charlson comorbidity index (CCI) was used according to the Deyo adaption for ICD-CM codes and patients were categorized as CCI 0-1 versus ≥2, as previously published and validated relying on ICD-10-CM codes.[18,23,24] Additional variables consisted of hospital region (Northeast, Midwest, South, West), income (1st, 2nd, 3rd, 4th income-quartile, unknown), hospital bed-size (small, medium, large), hospital annual volume and hospital teaching status (teaching vs. nonteaching). Hospital annual volume represents the number of RC performed at each participating institution during each study calendar year. To acquire teaching hospital status, institutions had to have either an American Medical Association-approved residency program, or needed to be a member of the Council of Teaching Hospitals, or had to have a ratio of 0.25 or higher of full-time equivalent interns and residents to nonnursing home beds.[15]

2.5 | Statistical analyses

Statistical analyses consisted of five steps. First, annual trends for each surgical approach of RC (RARC vs. ORC vs. laparoscopic RC) were illustrated by relying on estimated annual percentage change (EAPC) analyses according to the least squares linear regression methodology.[25,26] EAPC analyses were weighted in accordance with recommended NIS guidelines.[15] Due to limited sample size, patients treated with laporoscopic RC (n = 204) were excluded from all further, specific statistical analyses. Second, patient and surgery-related characteristics, as well as the outcome of interests were tabulated according to RARC versus ORC. Third, 12 separate multivariable logistic regression models specifically tested the effect of RARC versus ORC on in-hospital complications (overall-, intraoperative-, wound-, cerebro-vascular-, gastro-intestinal, cardiac, pulmonary, genito-urinary, other medical complications, bowel obstruction, transfusion) and in-hospital mortality. Fourth, since LOS is recorded as a day-count within the NIS, multivariable Poisson regression with log-link model tested the effect of RARC versus ORC on LOS.[18] Fifth, multivariable linear regression models tested the effect of RARC versus ORC on THC. All multivariable models were fitted after adjustment for clustering at hospital level using a

Generalized Estimating Equation (GEE) function and were weighted according to previously established NIS-specific weighing criteria.[15] Covariables for adjustment consisted of age (continuously coded), CCI (0-1 vs. ≥2), gender, history of chemotherapy, type of urinary diversion (incontinent vs. continent vs. Other/Unkown), year of surgery (per year), hospital bed size (small vs. medium vs. large), hospital annual volume (continuously coded), teaching status, insurance status (Medicare vs. Medicaid vs. private insurance vs. Others), and region (Northeast vs. Midwest vs. South vs. West). All tests were two-sided with a level of significance set at $p < 0.05$ and R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.[27]

3 | RESULTS

3.1 | Patient characteristics and temporal trends

Between 2016 and 2019, 5280 nonmetastatic bladder cancer patients treated with RC were identified within the NIS. Of those, 1876 (36%), 3200 (60%), and 204 (4%) were treated with RARC, ORC, and laparoscopic RC, respectively. Annual rates of RARC increased from 32% to 41% (EAPC: +8.6%; 95% confidence interval [CI]: 6.4%–10.9%; $p = 0.02$) in the study period. Conversely, annual rates of ORC decreased from 66% to 55% (EAPC: −5.5%; 95% CI: −6.3% to −4.8%; $p = 0.005$). The annual rate of laparoscopic RC remained stable and ranged from 3% to 4% (EAPC: +14.4%; 95% CI: −0.3%–32.4%; $p = 0.2$) (Supporting Information: Figure 1). Due to limited sample size, patients treated with laporoscopic RC (n = 204) were excluded. Consequently, subsequent specific analyses focused on the comparison between RARC (n = 1876) versus ORC (n= 3200) (Table 1). Here, CCI 0-1 (87% vs. 84%; $p < 0.001$) was more frequent in RARC. RARC patients were more frequently treated at teaching hospitals (93% vs. 89%; $p < 0.001$). Moreover, lymph-node dissection was more frequently performed at RARC (94% vs. 88%; $p < 0.001$). Finally, no difference was recorded in median age, race/ethnicity distribution, type of urinary diversion, and obesity status (all $p \geq 0.1$; Table 1).

3.2 | Rates of outcomes of interest

Overall complication rates were 64% versus 68% in RARC versus ORC, respectively ($p = 0.009$). RARC patients exhibited lower rates of transfusions (8% vs. 16%; $p < 0.001$). Moreover, RARC patients exhibited differences in complication rates in six additional categories: Intraoperative (2% vs. 3%; $p = 0.003$), wound (6% vs. 10%; $p < 0.001$), gastro-intestinal (18% vs. 14%; $p = 0.002$), cardiac (16% vs. 19%; $p = 0.03$), pulmonary (6% vs. 10%; $p < 0.001$), and other medical complication (37% vs. 40%; $p = 0.03$) (Supporting Information: Table 1). In-hospital mortality rates were significantly lower in RARC patients (1% vs. 2%; $p = 0.04$). Similarly, median LOS was shorter in RARC patients (6 vs. 7 days; $p < 0.001$). Conversely, median THC were higher in RARC patients (31,486 vs. 27,162 $; $p < 0.001$).

TABLE 1 Descriptive characteristics of 5067 nonmetastatic bladder cancer patients stratified according to robotic-assisted versus open radical cystectomy within the National Inpatient Sample database (2016–2019)

	Overall, N = 5076	Robotic-assisted radical cystectomy, N = 1876 (37%)	Open radical cystectomy, N = 3200 (63%)	p value
Age in years, Median (IQR)	70 (63, 76)	69 (63, 76)	70 (63, 76)	0.1
Gender, n (%)				0.04
Female	1112 (22%)	382 (20%)	730 (23%)	
Male	3964 (78%)	1494 (80%)	2470 (77%)	
Charlson-Comorbidity Index, n (%)				<0.001
0–1	4306 (85%)	1633 (87%)	2673 (84%)	
≥2	770 (15%)	243 (13%)	527 (16%)	
Hospital annual volume, Median (IQR)	5 (2, 11)	5 (2, 10)	5 (2, 12)	0.5
History of smoking, n (%)	2016 (40%)	778 (41%)	1238 (39%)	0.051
History of malignancy, n (%)	913 (18%)	335 (18%)	578 (18%)	0.9
History of chemotherapy, n (%)	1011 (20%)	383 (20%)	628 (20%)	0.5
Obesity, n (%)	850 (17%)	324 (17%)	526 (16%)	0.4
Race/Ethnicity, n (%)				0.3
Caucasian	4116 (81%)	1540 (82%)	2576 (80%)	
African American	292 (6%)	96 (5%)	196 (6%)	
Others	668 (13%)	240 (13%)	428 (13%)	
Lymph-node dissection, n (%)	4582 (90%)	1763 (94%)	2819 (88%)	<0.001
Type of urinary diversion, n (%)				0.2
Incontinent	4771 (94%)	1772 (94%)	2999 (94%)	
Continent	≤268 (5%)	≤96 (5%)[a]	≤172 (5%)[a]	
Other/Unkown	40 (1%)	10 (1%)[a]	≤30 (1%)[a]	
Hospital bed size, n (%)				0.14
Small	558 (11%)	209 (11%)	349 (11%)	
Medium	1070 (21%)	387 (21%)	683 (21%)	
Large	3448 (68%)	1280 (68%)	2168 (68%)	
Teaching hospital, n (%)	4587 (90%)	1740 (93%)	2847 (89%)	<0.001
Region, n (%)				<0.001
Midwest	1414 (28%)	562 (30%)	852 (27%)	
Northeast	973 (19%)	383 (20%)	590 (18%)	
South	1761 (35%)	560 (30%)	1201 (38%)	
West	928 (18%)	371 (20%)	557 (17%)	
Income, n (%)				0.1
0–25 percentile	1127 (22%)	368 (20%)	759 (24%)	
26–50 percentile	1318 (26%)	461 (25%)	857 (27%)	
51–75 percentile	1354 (27%)	538 (29%)	816 (26%)	
76–100 percentile	1201 (24%)	488 (26%)	713 (22%)	
Other/Unknown	76 (2%)	21 (1%)	55 (2%)	

(Continues)

TABLE 1 (Continued)

	Overall, N = 5076	Robotic-assisted radical cystectomy, N = 1876 (37%)	Open radical cystectomy, N = 3200 (63%)	p value
Insurance provider, n (%)				0.03
Medicare	3314 (65%)	1187 (63%)	2127 (66%)	
Private	1306 (26%)	527 (28%)	779 (24%)	
Medicaid	271 (5%)	98 (5%)	173 (5%)	
Others	185 (4%)	64 (3%)	121 (4%)	

Note: All values either represent means (Interquartile range) or frequencies (%).

[a]Values censored in line with National Inpatient Sample (NIS) reporting guidelines.
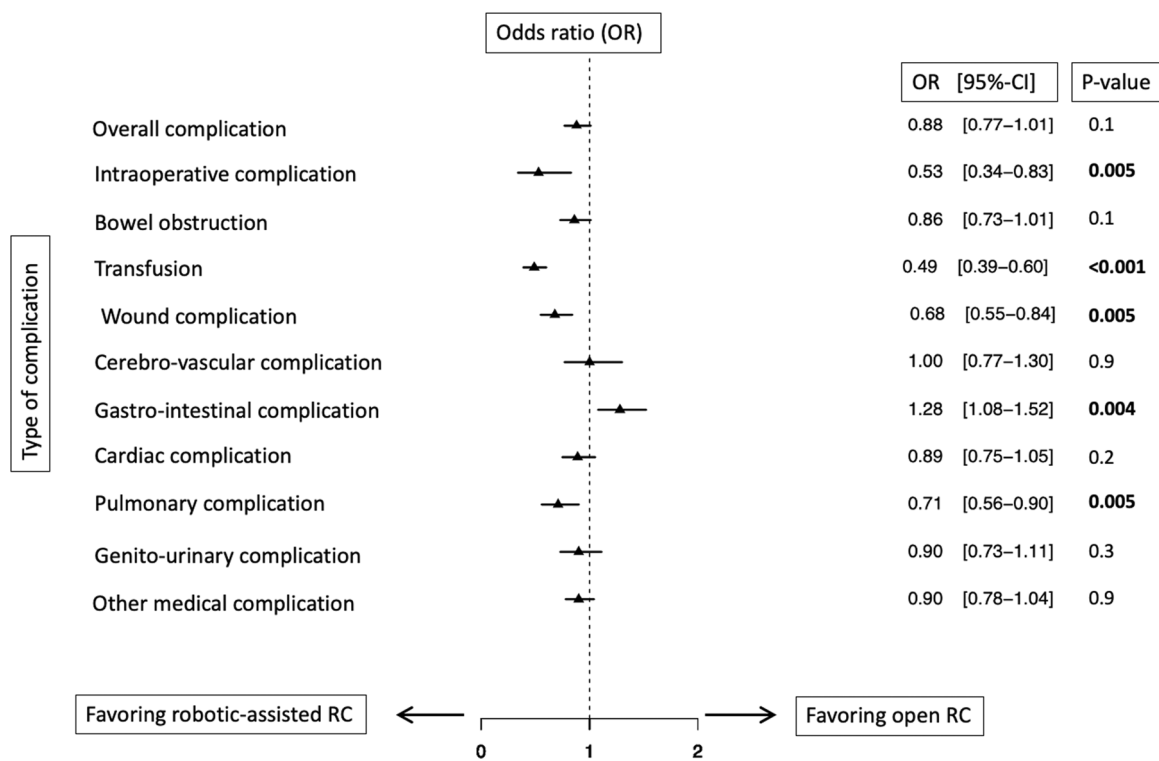

FIGURE 1 Forrest plot displaying odds ratios of multivariable logistic regression analyses predicting in-hospital postoperative complications of radical cystectomy (RC), according to surgical approach (*ref.*: open RC), after adjustment for clustering. All models were weighted relying on a Generalized Estimation Equation function and were adjusted for clustering. Additional adjustment variables consisted of age, CCI, obesity, gender, surgical approach, type of urinary diversion, year of surgery, hospital bed size, hospital annual volume, teaching status, insurance status, and region. CCI, Charlson comorbidity index.

3.3 | Multivariable analyses

In multivariable logistic regression models predicting overall complications, RARC approach failed to achieve statistical significance (odds ratio [OR]: 0.88; 95% CI: 0.77–1.01; $p = 0.1$). However, in separate multivariable logistic regression models addressing specific complication types (Figure 1), RARC surgical approach was an independent predictor of lower rates of transfusion (OR: 0.49; 95% CI: 0.39–0.60; $p < 0.001$) as well as of four additional specific complication categories: intraoperative

(OR: 0.53; 95% CI: 0.34–0.83; $p = 0.005$), wound (OR: 0.68; 95% CI: 0.55–0.84; $p = 0.005$), and pulmonary (OR: 0.71; 95% CI: 0.56–0.90; $p = 0.005$). Conversely, RARC exhibited independent predictor status for higher gastro-intestinal complications (OR: 1.28; 95% CI: 1.08–1.52; $p = 0.004$). In sensitivity analyses, where lymph node status was additionally incorporated as adjustment variable, results remained virtually unchanged (data not shown).

In multivariable Poisson regression models, RARC was an independent predictor of shorter LOS (rate ratio: 0.86; 95% CI: 0.83–0.90;

$p < 0.001$). Additionally, in multivariable linear regression models predicting THCs, RARC approach was an independent predictor for higher THCs (Coef.: 5,859$; 95% CI: 4613–7106 $; $p < 0.001$). Finally, independent predictor status for in hospital-mortality was not recorded (OR: 0.67; 95% CI: 0.39–1.16; $p = 0.2$) in multivariable logistic regression models, when mortality rates between RARC and ORC were analyzed (Supporting Information: Table 2).

4 | DISCUSSION

We hypothesized that within a large-scale, contemporary data repository, no differences in perioperative outcomes will be identified between RARC versus ORC perioperative outcomes, unlike in previously reported reports from select tertiary care centers and/or from prospectively, randomized trials.[1–5,14] We addressed four specific endpoints of interest: (a) complication rates, (b) in-hospital mortality, (c) length of stay (LOS), and (d) THC. To test these hypotheses, we relied on a contemporary North-American cohort of RC patients from within the NIS (2016–2019) and made several noteworthy findings.[15]

First, we identified clinically meaningful differences in patient and clinical characteristics between RARC versus ORC patients. Specifically, rates of CCI 0-1 were higher in RARC patients (87% vs. 84%; $p < 0.001$) and the proportion of males was higher at RARC (80% vs. 77%; $p = 0.04$). Moreover, RARC patients more frequently underwent lymph node-dissection (94% vs. 88%; $p < 0.001$) and were more frequently treated at teaching hospitals (Table 1). Taken together, RARC patients differed from ORC patients within the current study. It is noteworthy that RARC patients from within the current study also differed from RARC patients, described in previous studies from select tertiary care centers. For example, RARC patients enrolled in the second largest, randomized prospective trial of Bochner et al. exhibited a median age of 66 years, compared with a median age of 69 years for RARC patients in the current study.[1] Similarly, it is also noteworthy that ORC patients enrolled in previous randomized prospective trials were younger compared with ORC patients in the current study. For example, ORC patients enrolled in the Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR) trial of Parekh et al. exhibited a median age of 67 versus 70 years in the current study.[1,3–5] These evident differences in patients and clinical characteristics distinguish the current population from more homogenous populations enrolled in previously reported trials.

Second, RARC rates observed in the current study increased from 32% to 41% between 2016 and 2019 (EAPC: + 8.6%; $p = 0.02$). Conversely, ORC rates decreased from 66% to 55% (EAPC: −5.5%; $p = 0.005$) in the same period. These temporal trends are comparable to other population-based studies. For example, Hanna et al. relied on the NCDB and reported increasing RARC rates (17%–25%) of RARC rates during their study period between 2010 and 2013.[13] It is noteworthy that these historical trends reported by Hanna et al. appear to be ongoing, according to the current results.

Third, we also observed several advantages, when RARC was compared to ORC with respect to perioperative outcomes. Specifically,

lower overall complication rates for RARC were recorded (64% vs. 68%; $p = 0.009$). Within those, RARC exhibited lower rates of transfusions, intraoperative-, wound- and pulmonary complications in addition to shorter LOS. In multivariable regression analyses, majority of the former rates also resulted in statistically significantly lower odds rates for transfusion, intraoperative-, wound- and pulmonary complications, and lower rate ratio for LOS. Moreover, lower rates of in-hospital mortality were recorded for RARC, albeit critical sample size limitations undermined testing in multivariable logistic regression models. Our findings agree with transfusion rates recorded in the largest prospective randomized trial (Parekh et al.) comparing RARC to ORC.[2] However, we also identified RARC advantages over ORC in several other complication endpoints. Interestingly, RARC disadvantages specifically surfaced regarding gastrointestine complications. These differences between RARC versus ORC were not identified in prospective randomized trials or studies originated from tertiary care centers.[1–9] Discrepancies between the current study and prospective randomized trials may relate to different complication assessments, in addition to patient and clinical characteristics as well as methodological differences.[1,3–5,28] For example, prospective randomized trials rely on prospectively assessed Clavien–Dindo classification.[28] Conversely, epidemiological studies that rely on large-scale databases, rely on diagnostic codes to quantify complication rates. In consequence, direct comparisons between retrospective versus prospective studies examining RARC versus ORC differences should be interpreted with caution.

Fourth, in the final part of the analyses, we focused on LOS and THC. Here, we recorded a small, albeit statistically significant LOS benefit favoring RARC. Conversely, we also recorded a clinically important, highly statistically significant RARC THC disadvantage. In that context, shorter LOS is a clear and undisputable benefit of RARC. However, higher THC is a clear and undisputable RARC disadvantage. Our findings are in agreement with several historical analyses, where a similar dichotomy was observed: robotic versus open surgery for prostate and kidney cancers.[25,29] In the current analysis, RARC THC disadvantage resulted in an estimated addition of 5859 $ for each robotic surgery relative to open surgery. In consequence, if all RARCs were replaced with ORCs, a potential THC saving of 10,991,484 $ would have been recorded. It is noteworthy that the recorded RARC-specific THC increase applies despite more favorable CCI and shorter median LOS in RARC patients (Table 1). In consequence, it also may be postulated that universal or more generalized use of RARC in patients with higher CCI may result in higher median THC increase than that recorded in the current model.

Taken together, this study demonstrated a RARC benefit, when complication rates and LOS were examined. However, THC were higher at RARC. In consequence, a trade-off needs to be made between RARC patient benefits versus its THC disadvantages.

This study is not devoid of limitations. First, relying on administrative databases, such as the NIS, do not provide disease-specific grade and stage characteristics. In consequence, stage and grade-adjusted comparisons between RARC and ORC could not be made. Administrative databases also do not provide longitudinal cancer-control outcomes and vital status. Although the NIS does provide details regarding robotic versus open surgery type, no reliable information is available if urinary

diversion was performed extracorporeally or intracorporeally in RARC patients.[30,31] Moreover, the conceptualization and reporting guidelines of the NIS strongly prohibits reporting low numbers of events to preserve the nonidentifiable nature of its population. As a consequence, marginal differences may have not been captured within the current manuscript.[15] Ideally, other large-scale, data repositories should be queried to confirm the current results and their clinical meaningfulness, especially focusing on less pronounced complication rate differences which were recorded in the current manuscript. Finally, additional specific information that is included in prospective randomized trials such as operation room time, intraoperative blood-loss, or specific postoperative recovery programs, such as enhanced recovery after surgery protocols, are not provided and consequently could not be adjusted for.[32]

5 | CONCLUSION

RARC complications, LOS, and mortality appear more favorable than ORC, but invariably result in higher THC. A favorable RARC profile together with increasing familiarity with robotics undoubtedly contributes to its increasing popularity throughout the United States in recent years.

AUTHOR CONTRIBUTIONS

Benedikt Hoeh: Concept and design; draft of manuscript; statistical analysis; analysis and interpretation of the data; R**occo Simone Flammia**: Acquisition of data; statistical analysis. **Lukas Hohenhorst**: Acquisition of data; analysis and interpretation of the data. **Gabriele Sorce**: Acquisition of data; analysis and interpretation of the data. **Francesco Chierigo**: Analysis and interpretation of the data. **Andrea Panunzio**: Analysis and interpretation of the data. **Zhe Tian**: Concept and design; acquisition of data; statistical analysis. **Fred Saad**: Acquisition of data; supervision. **Michele Gallucci**: Critical revision of the manuscript; important intellectual content. **Alberto Briganti**: Critical revision of the manuscript; important intellectual content. **Carlo Terrone**: Critical revision of the manuscript; important intellectual content. **Shahrokh F. Shariat**: Critical revision of the manuscript; important intellectual content. **Markus Graefen**: Critical revision of the manuscript; important intellectual content. **Derya Tilki**: Critical revision of the manuscript; important intellectual content. **Alessandro Antonelli**: Critical revision of the manuscript; important intellectual content. **Luis A. Kluth**: Concept and design; critical revision of the manuscript; important intellectual content. **Andreas Becker**: Supervision; analysis and interpretation of the data. **Felix K.H. Chun**: Concept and design; supervision; analysis and interpretation of the data. **Pierre I. Karakiewicz**: Concept and design; acquisition of data; draft of manuscript; statistical analysis; supervision; critical revision of the manuscript; important intellectual content.

ACKNOWLEDGEMENT

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated for this study were from the National Inpatient Sample (NIS) database. The code for the analyses will be made available upon request.

ETHICS STATEMENT

All analyses and their reporting followed the NIS reporting guidelines. Due to the anonymously coded design of the NIS database, study-specific Institutional Review Board ethics approval was not required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.