Open vs. robot-assisted radical cystectomy with extracorporeal or intracorporeal urinary diversion for bladder cancer

A pairwise meta-analysis of outcomes and a network meta-analysis of complications

Carlos Riveros[1], Sanjana Ranganathan[1], Cole Nipper[1], Kelvin Lim[1], Michael Brooks[1], Furkan Dursun[2], Brian J. Miles[1], Alvin C. Goh[3], Mihir Desai[4], Zachary Klaassen[5], Girish S. Kulkarni[6,7], Christopher J.D. Wallis[6,7,8], Raj Satkunasivam[1]

[1]Department of Urology, Houston Methodist Hospital, Houston, TX, United States; [2]Department of Urology, University of Texas Health, San Antonio, TX, United States; [3]Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York City, NY, United States; [4]USC Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States; [5]Division of Urology, Medical College of Georgia, Augusta University, Augusta, GA, United States; [6]Division of Urology and Surgical Oncology, Department of Surgery, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [7]Division of Urology, University of Toronto, Toronto, ON, Canada; [8]Division of Urology, Mount Sinai Hospital, Toronto, ON, Canada

Cite as: Riveros C, Ranganathan S, Nipper C, et al. Open vs. robot-assisted radical cystectomy with extracorporeal or intracorporeal urinary diversion for bladder cancer: A pairwise meta-analysis of outcomes and a network meta-analysis of complications. Can Urol Assoc J 2023;17(3):E75-85. http://dx.doi.org/10.5489/cuaj.8096

Published online October 25, 2022

Appendix available at ***cuaj.ca***

ABSTRACT

INTRODUCTION: There are no meta-analyses of randomized controlled trials (RCTs) comparing open radical cystectomy (ORC) with robot-assisted radical cystectomy (RARC), inclusive of both intracorporeal (iRARC) and extracorporeal (hybrid RARC, hRARC) urinary reconstruction.

METHODS: MEDLINE, Embase, Scopus, the International Clinical Trials Registry Platform and ***ClinicalTrials.gov*** registries were searched in May 2022. Outcomes of interest included recurrence- or progression-free survival (RFS/PFS), margin status and lymph node yield, mean estimated blood loss (EBL) and operating room time (ORT), hospital length of stay (LOS), 90-day complications and readmissions, and quality of life (QoL). Pairwise meta-analyses and network meta-analyses were performed using random-effects models and Bayesian hierarchical random-effects models, respectively.

RESULTS: We found no significant differences between RARC and ORC for oncological and most perioperative outcomes: RFS/PFS (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.67–1.23); positive surgical margins (odds ratio [OR] 1.05, 95% CI 0.60–1.85); lymph node yield (mean difference [MD] -0.63, 95% CI -2.63–1.37); LOS (MD -0.22, 95% CI -1.10–0.65); overall complications (OR 0.81, 95% CI 0.61–1.07); major complications (OR 0.94, 95% CI 0.69–1.30); readmissions (OR 0.90, 95% CI 0.60–1.35); and QoL (standardized MD -0.02, 95% CI -0.17–0.14). We found significantly lower EBL for RARC compared to ORC (MD -312.61, 95% CI -447 to -178.22) at the expense of significantly prolonged ORT (MD 82.34 minutes, 95% CI 44.82–119.86). Network meta-analysis did not find significant differences in complications between hRARC and iRARC.

CONCLUSIONS: This meta-analysis confirms the equivalence of RARC and ORC with respect to oncological outcomes.

INTRODUCTION

Bladder cancer is the 10th most frequently diagnosed cancer worldwide, with roughly 573 000 new cases and 213 000 deaths in 2020.[1] Approximately 25% of patients have muscle-invasive bladder cancer (MIBC) at the time of diagnosis.[2] Radical cystectomy (RC) with bilateral pelvic lymphadenectomy remains the gold-standard treatment for MIBC;[3] however, RC is associated with a high postoperative morbidity. Overall complication rates within 30 and 90 days after RC range from 40–60%.[4] In an attempt to decrease surgical morbidity, robot-assisted radical cystectomy (RARC) was introduced in 2003.[5] Use of RARC continues to increase worldwide.[6,7]

Initially, the focus of RARC was on its extirpative component. Hybrid RARC (hRARC; i.e., RARC with extracorporeal urinary diversion [UD]) was initially the standard surgical technique.[5] Considering that the UD is the most technically demanding component of the procedure,[8] total intracorporeal RARC (iRARC) was introduced slowly afterwards.[9,10] Recent data from the International Robotic Cystectomy Consortium (IRCC) demonstrated the uptake of iRARC at centers focused on RARC.[11] The comparative effectiveness of hRARC and iRARC is controversial, based primarily on retrospective, non-randomized data.[12-14]

We previously performed a meta-analysis on randomized clinical trial (RCT) data comparing outcomes of patients treated with open radical cystectomy (ORC) vs.

KEY MESSAGES

- In comparing differences in 90-day complication rates, we found significantly lower EBL for RARC vs. ORC at the expense of significantly prolonged operating room time.
- Network meta-analysis did not find significant differences in 90-day complications between hybrid RARC and completely intracorporeal RARC.
- This contemporary meta-analysis confirms the equivalence of RARC and ORC with respect to oncological outcomes.

RARC. Our report found no differences in recurrence or progression-free survival (RFS/PFS), surgical margin rates, lymph node dissection yield, hospital length of stay (LOS), or complication rates; however, our previous meta-analysis was limited exclusively to data on hRARC.[15] Since then, results from RCTs comparing iRARC to ORC have been published. We sought to update the results from our previous meta-analysis, as well as indirectly compare differences in rates of 90-day complications between hRARC and iRARC through a network meta-analysis (NMA).

METHODS

We conducted the study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the extension for NMA.[16,17] The protocol has been pre-registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD341117).

Search strategy and selection criteria

We searched the MEDLINE, Embase, and Scopus databases, along with the International Clinical Trials Registry Platform (ICTRP) and ***ClinicalTrials.gov*** registries using the following search terms as medical subject headings and keywords: "cystectomy" AND "robotics" AND "randomized controlled trial." The searches were conducted without date restriction, from database inception to May 30, 2022. We limited our search to English-language RCTs in human adults. A full search strategy is presented in the Appendix (available at ***cuaj.ca***). Following the systematic search, duplicates were removed. The records were screened by two independent reviewers (CR and SR) and disagreements were resolved by a third reviewer (RS). Studies were selected if they compared ORC to either hRARC or iRARC for the treatment of MIBC. Non-randomized trials and retrospective studies were excluded.

Outcome measures and data extraction

Outcomes of interest included RFS/PFS, as well as surrogates of oncological efficacy (margin status and lymph node yield), perioperative outcomes (mean estimated blood loss [EBL], mean operating room time [ORT], hospital LOS, 90-day complications, and 90-day readmissions), and quality of life (QoL). We did not re-examine recurrence patterns due to inconsistent categorization among the studies. Data were extracted in duplicate using an a priori developed template. In cases of multiple publications on the same cohort, we extracted the most recent data for the outcome. For continuous variables, we extracted the mean and standard deviation (SD); median and interquartile ranges were converted using the approach described by Wan et. al.[18] We extracted the number of 90-day complications of any Clavien-Dindo (CD) grade, as well as major (CD grade ≥3) complications. On the basis of a previous meta-analysis,[19] we extracted the last recorded overall score for QoL 6–12 months after RC. Despite QoL questionnaire heterogeneity, higher global scores indicated a greater QoL. In cases where mean and 95% confidence interval (CI) were reported, we derived the SD using the method found in the Cochrane handbook.[20]

Risk of bias assessment

Risk of bias at the study level was assessed in duplicate using the Cochrane Collaboration tool. This qualitative assessment evaluates six domains: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition bias, and selective reporting. Each domain could be judged as having low, unclear, or high risk of bias.[21] Funnel plot asymmetry was not assessed due to the low number of eligible RCTs.[22]

Statistical analyses

Consistent with our original meta-analysis,[15] the pairwise meta-analysis was performed using random-effects models with RevMan software, version 5.4 (Review Manager 2020; The Cochrane Collaboration; Copenhagen, Denmark). We conducted pooled pairwise meta-analyses comparing ORC to RARC, regardless of the UD modality, as well as subgroup meta-analyses comparing ORC to either hRARC or iRARC.

The inverse variance and the Mantel-Haenszel methods were used for continuous and binary outcomes, respectively. For survival data and continuous outcomes, we report hazard ratio (HR) and mean difference (MD), respectively, along with 95% CI. Since the questionaries used to report QoL were different among the studies, we report standardized mean differences (SMD) with 95% CI. Binary outcomes were reported using odds ratio (OR) with 95% CI. Statistical heterogeneity was assessed using the I^2 statistic and the p-value of the Q statistic. P-values were two-sided and values <0.05 were deemed significant.

To indirectly compare 90-day complications between hRARC and iRARC, a NMA was performed under a Bayesian hierarchical random-effects model using MetaInsight (***https://crsu.shinyapps.io/MetaInsight_Beta/***).[23] Briefly, this application uses the 'gemtc' R package to simultaneously model all direct and indirect comparisons based on a Markov chain Monte Carlo simulation technique. We used pooled ORs with 95% credible interval (CrIs) to estimate the risk of 90-day complications across different RC surgical approaches. We generated league tables and rankograms based on surface under the cumulative ranking (SUCRA) values. League tables present the relative ORs with 95% CrIs for every possible pairwise (direct or indirect) combination. A treatment's SUCRA corresponds to its overall rank for efficacy; in this case, the highest value corresponds to the surgical approach associated with the lowest odds of 90-day complications (any CD grade and CD grade ≥3). An unrelated mean effects model was fitted to graphically assess for global inconsistency.[24]

RESULTS

Characteristics and risk of bias of the included studies

The initial literature search yielded 279 records; after the two screening stages, 14 publications were eligible for quantitative analysis (Figure 1). We identified five unique RCTs involving 541 participants comparing hRARC to ORC,[25-29] in addition to five related publications reporting updated QoL measures and RFS/PFS.[30-33] Three RCTs involving 483 participants comparing iRARC to ORC were identified,[34-36] along with one related publication reporting updated 90-day outcomes.[37] The trials comparing hRARC to ORC were conducted from 2008–2014, while the trials comparing iRARC to ORC were conducted from 2017–2020 (Table 1). The protocols and methods of all included studies were reviewed and generally considered to have an overall low risk of bias with adequate randomization (Supplementary Figure 1; available in the Appendix at ***cuaj.ca***). Due to the physical component of surgery, blinding was not attempted in all but one of the studies.[36] Thus, most studies were deemed at high risk of performance bias.

Pairwise meta-analysis

Recurrence/progression-free survival and oncological surrogates

Four studies (three comparing hRARC to ORC, and one comparing iRARC to ORC) (Figure 2A) were assessed for RFS/PFS. We found no difference between RARC (i.e., hRARC/iRARC) and ORC with respect to RFS/PFS (total HR 0.91, 95% CI 0.67–1.23, p=0.5, I^2= 0%). Subgroup meta-analysis comparing hRARC to ORC included five-year RFS/PFS data from Bochner et al,[33] as well as updated data from CORAL (five-year RFS/PFS) and RAZOR (three-year RFS/PFS).[31,32] We failed to find significant differences between hRARC and ORC in RFS/PFS (HR 0.83, 95% CI 0.58–1.19, p=0.3, I^2= 0%). Subgroup meta-analysis comparing iRARC to

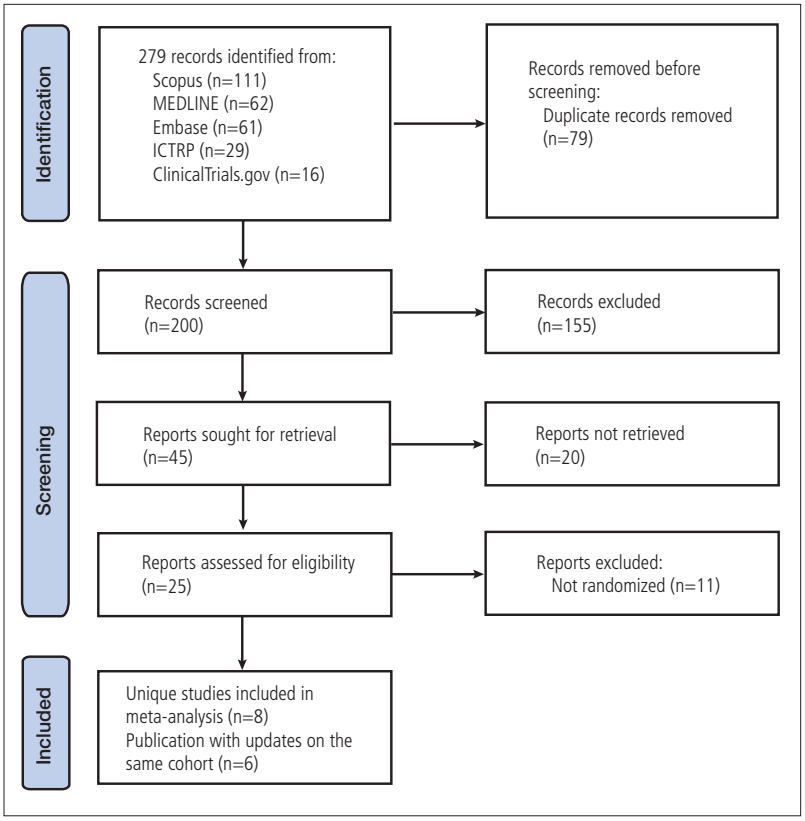


Figure 1. PRISMA flowchart of included studies. ICTRP: International Clinical Trials Registry Platform; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Clinical, demographic characteristics, and primary and secondary outcomes of the trials included in the meta-analysis of RARC and ORC

Study	Year of publication	Trial population	Design	Trial period	Sample size		Median/ mean age, yrs (range/ SD)	Median followup [IQR], months	Study endpoints	
					RARC	ORC			Primary	Secondary
Nix et al	2010	Single U.S. center	Randomized, non-inferiority study	Apr 2008 to Jan 2009	21	20	hRARC: 67.4 (33–81) ORC: 69.2 (51-80)	NR	Lymph node yield	Perioperative outcomes, pathologic results, narcotic use
Parekh et al	2013 2014 update	Single U.S. center	Pilot, randomized trial	July 2009 to June 2011	20	20	hRARC: 69.5 (62.3–74) ORC: 64.5 (59.8–72.3)	NR	Oncologic efficacy, perioperative outcomes	QoL outcomes, functional recovery
Bochner et al	2015 2018 update	Single U.S. center	Randomized trial	Mar 2010 to Mar 2013	60	58	hRARC: 66 (60–71) ORC: 65 (58–69)	58.8 [46.8 - 70.8]	Overall 90-day Clavien grade 2–5 complications Recurrence-free, cancer-specific, and overall survival	Clavien grade 3–5 complications, EBL, operative time, pathologic outcomes, 3- and 6-mo QoL outcomes, costs
Khan et al	2016 2020 update	Single U.K. center	Randomized trial	Mar 2009 to July 2012	20	20	hRARC: 68.6 (6.8) ORC: 66.6 (8.8)	60	30-d and 90-d Clavien complications	Perioperative clinical, pathologic, and oncological outcomes, QoL
Parekh et al	2018 2020 update	15 U.S. centers	Randomized, open-label, non-inferiority, phase 3 trial	July 2011 to Nov 2014	150	152	hRARC: 70 (40–90) ORC:67 (37–85)	36	2-year progression-free survival	EBL, transfusion rate, perioperative outcomes, pathologic results, operating time, length of hospital stay, 90-day complications, change in QoL
Maibom et al	2021 2022 update	Single Denmark center	Double-blinded, randomized feasibility trial	June 2019 to Oct 2020	25	25	iRARC: 70 (63–74) ORC: 67 (59–74)	3	Proportion of unblinded patients and success of blinding 90-d patient-reported QoL	Length of hospital stay, EBL, pain levels, opioid consumption Complication rates and days-alive-and-out-of-hospital
Mastroianni et al	2022	Single Italy center	Randomized trial	Jan 2018 to Oct 2020	58	58	iRARC: 64 (53–70) ORC: 66 (58–71)	6	Overall transfusion rate	Perioperative outcomes, global cost analysis, and 6-month functional, oncologic, and QoL outcomes
Catto et al	2022	9 U.K. centers	Randomized, unblinded, phase 3 trial	Mar 2017 to Mar 2020	161	156	iRARC: 69.3 (8.0) ORC: 68.7 (8.4)	18.4 [12.8-21.1]	Days alive and out of the hospital within 90 days of surgery (length of stay, readmissions, deaths)	Recovery, perioperative morbidity, oncological outcomes, surgeon fatigue

EBL: estimated blood loss; hRARC: hybrid robot-assisted radical cystectomy; iRARC: total intracorporeal robot-assisted radical cystectomy; IQR: interquartile range; NR: not reported; ORC: open radical cystectomy; QoL: quality of life; RARC: robot-assisted radical cystectomy.

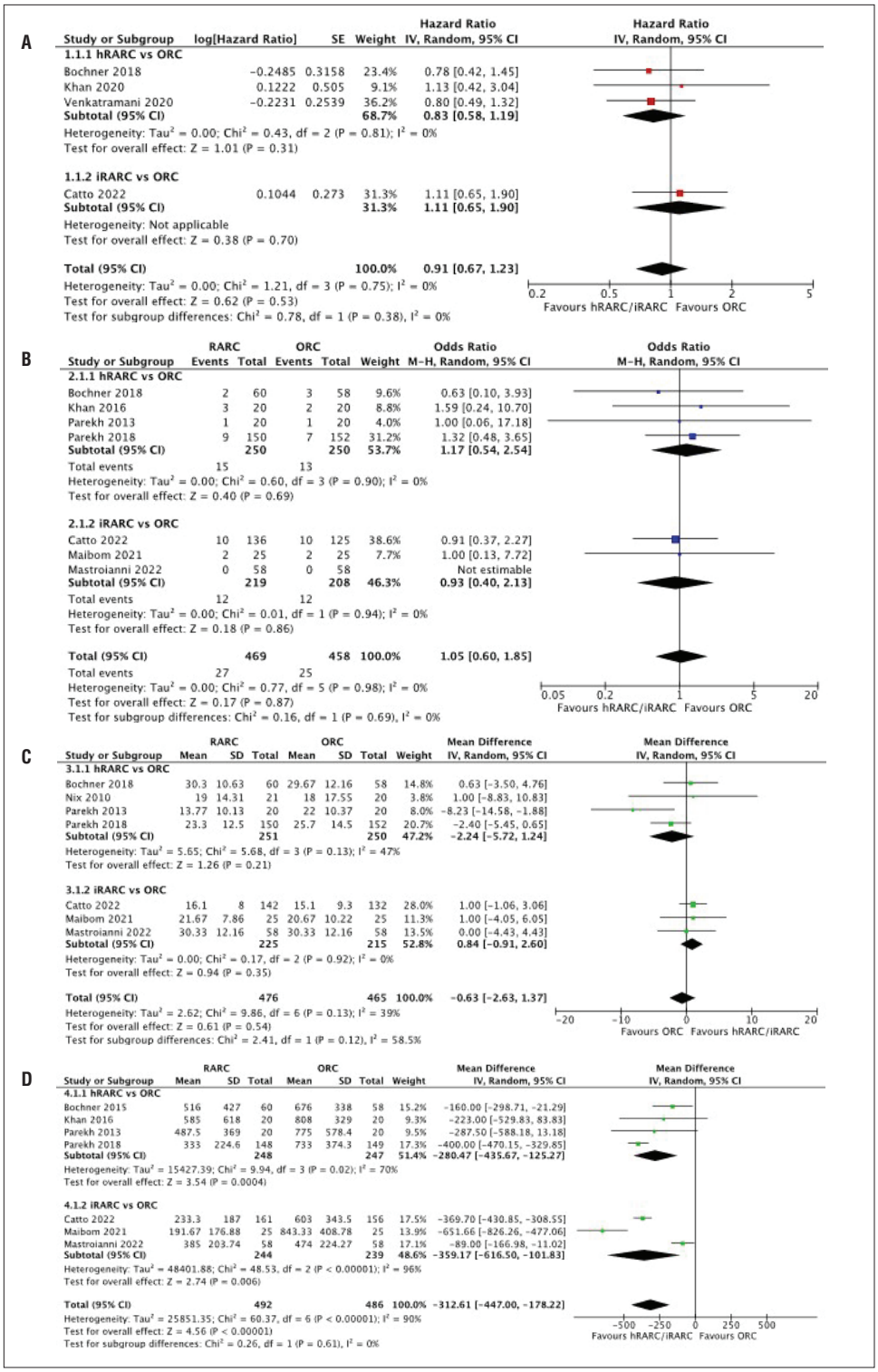


Figure 2 (A–D). Forest plots summarizing the meta-analyses between robot-assisted radical cystectomy (RARC) and open radical cystectomy (ORC) for: (A) recurrence-free or progression-free survival; (B) positive surgical margin; (C) lymph node dissection yield; (D) mean estimated blood loss (mL). *Since greater mean values were deemed desirable for this outcome, the X-axis was labeled accordingly. CI: confidence interval; df: degrees of freedom; hRARC: hybrid RARC; iRARC: completely intracorporeal RARC; IV: inverse variance; M-H: Mantel-Haenszel; SD: standard deviation; SE: standard error.

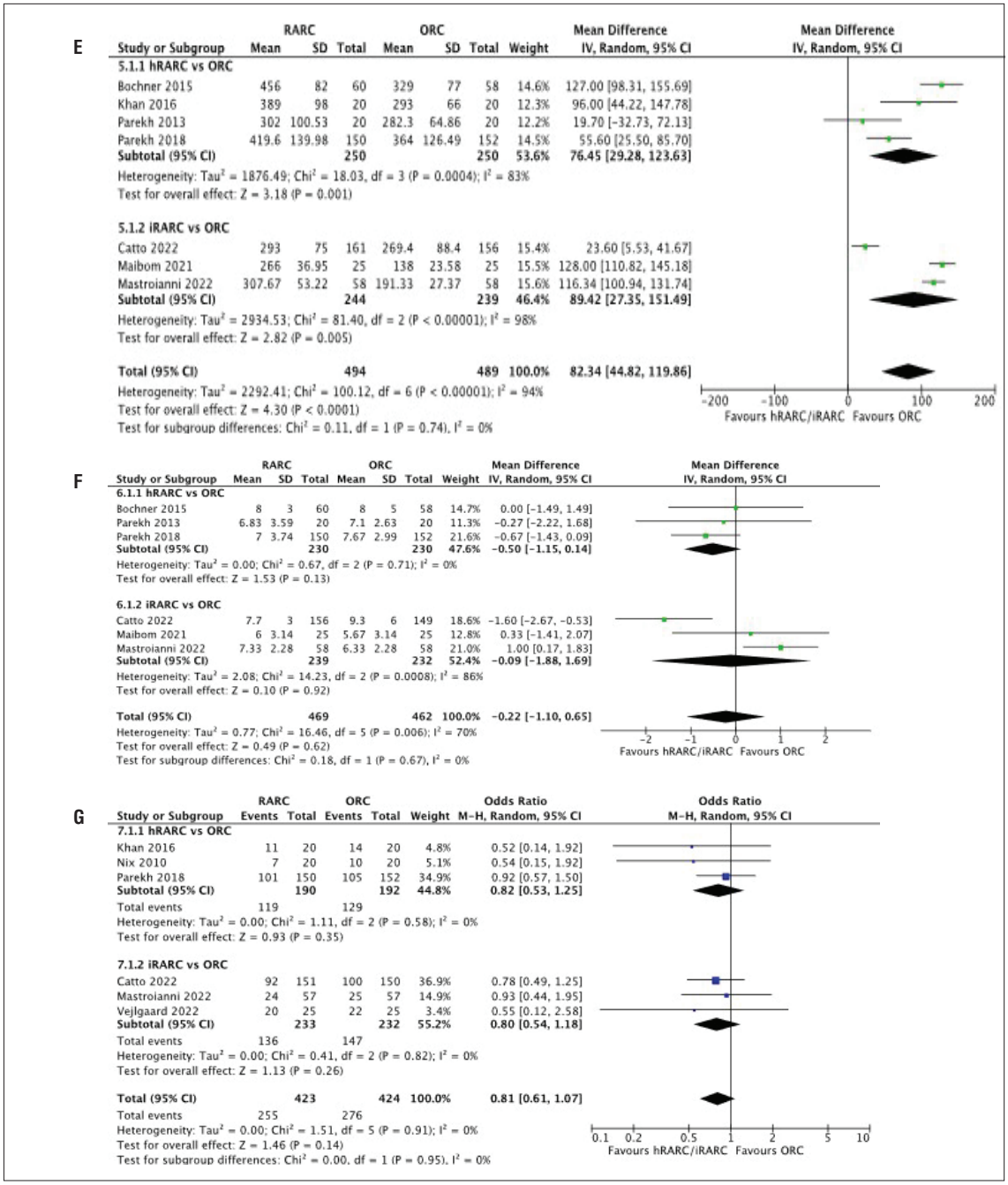


Figure 2 (E–G). Forest plots summarizing the meta-analyses between robot-assisted radical cystectomy (RARC) and open radical cystectomy (ORC) for: (E) mean operating room time (min); (F) hospital length of stay (days); (G) 90-day complications of any Clavien-Dindo grade. *Since greater mean values were deemed desirable for this outcome, the X-axis was labeled accordingly. CI: confidence interval; df: degrees of freedom; hRARC: hybrid RARC; iRARC: completely intracorporeal RARC; IV: inverse variance; M-H: Mantel-Haenszel; SD: standard deviation; SE: standard error.

ORC was not possible, given that only one study had data on RFS/PFS.[35]

The pooled meta-analysis for oncological surrogates (surgical margin rates and lymph node yield) was based on seven studies (four comparing hRARC to ORC, and three comparing iRARC to ORC) (Figures 2B, 2C). We found no difference between RARC and ORC with respect to positive surgical margins (total OR 1.05, 95% CI 0.60–1.85, p=0.9, I^2=0%) and lymph node yield (total MD -0.63, 95% CI -2.63–1.37, p=0.5, I^2=39%).

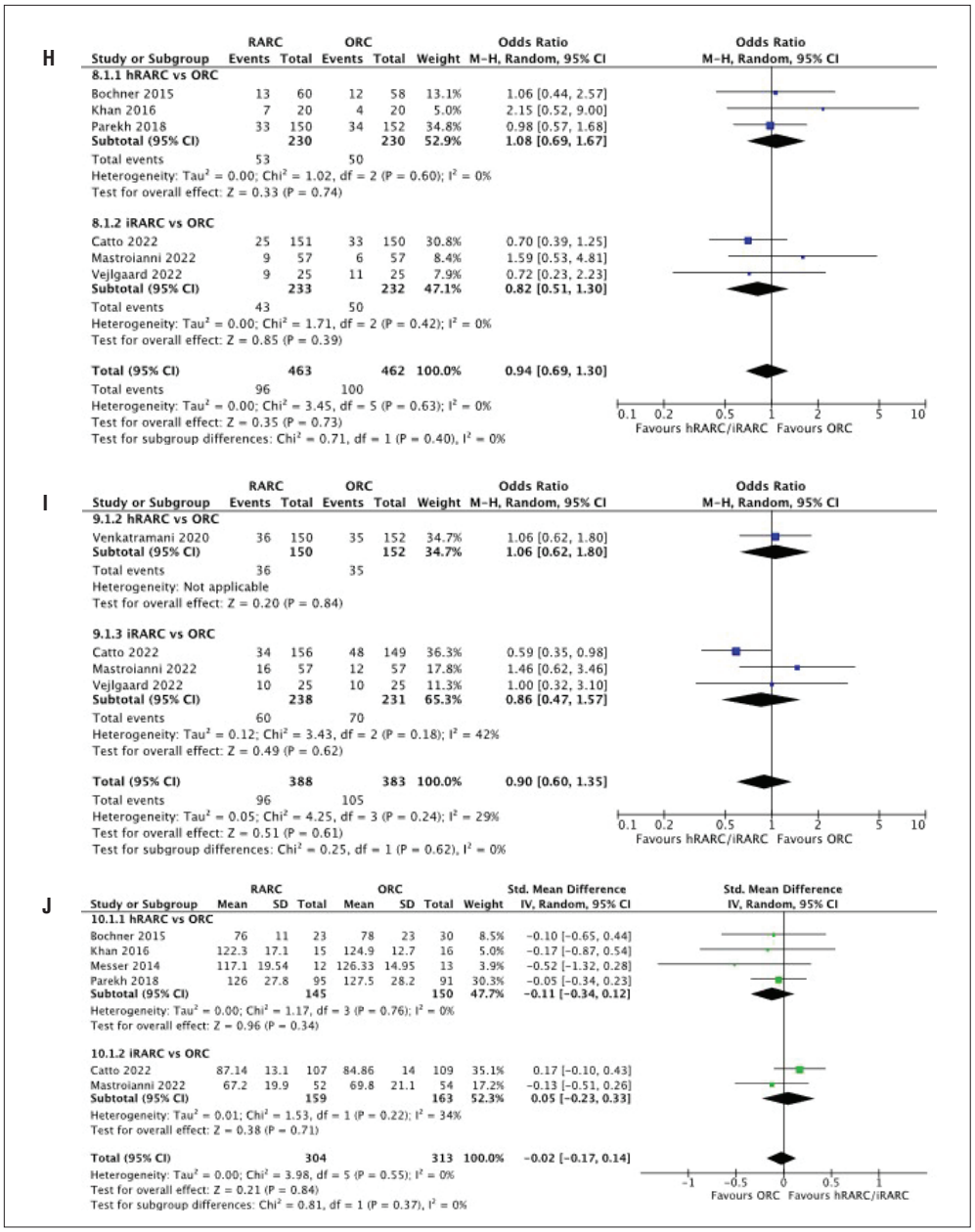
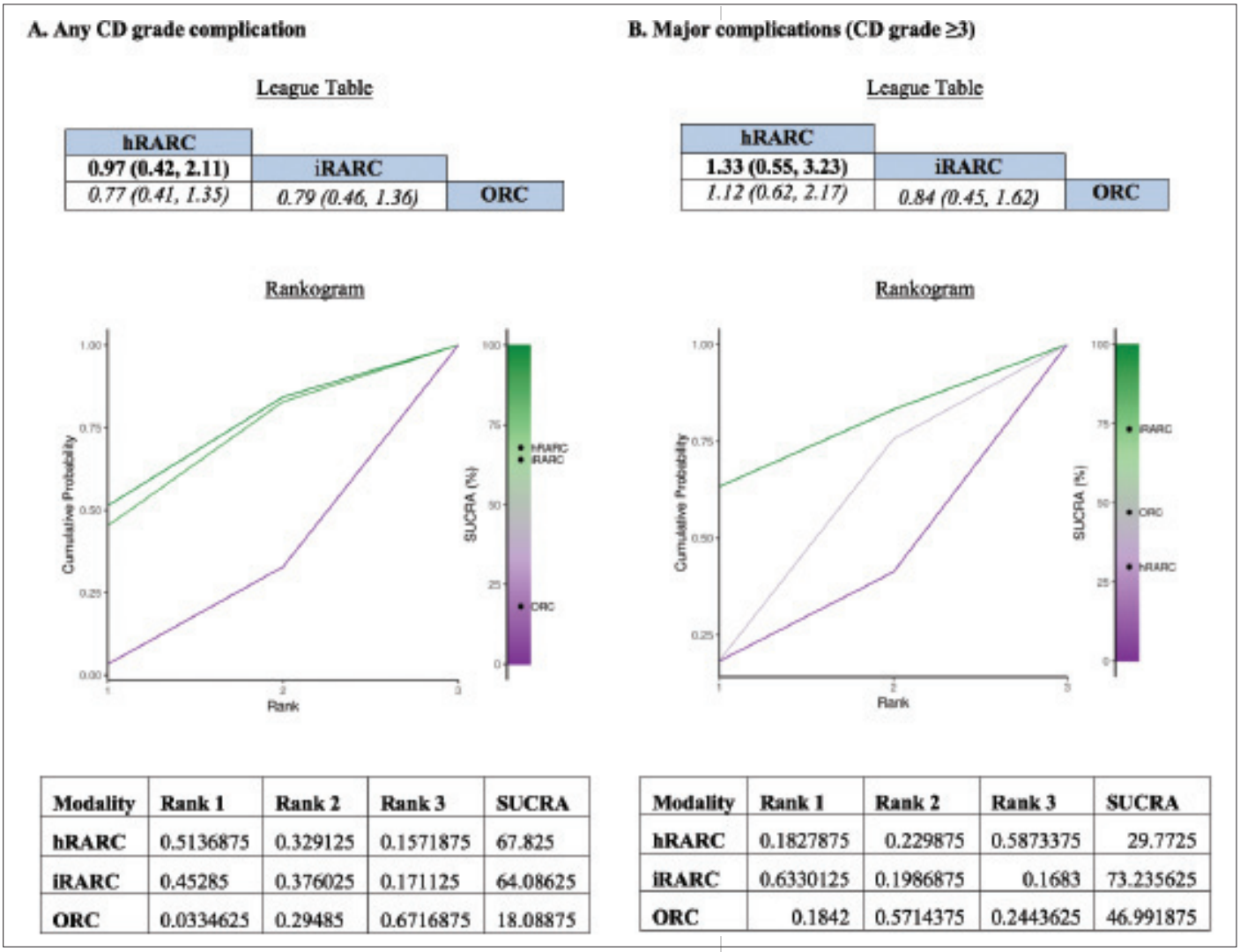


Figure 2 (H–J). Forest plots summarizing the meta-analyses between robot-assisted radical cystectomy (RARC) and open radical cystectomy (ORC) for: (H) Clavien-Dindo high-grade (≥3) complications; (I) 90-day readmissions; (J) wuality of life. *Since greater mean values were deemed desirable for this outcome, the X-axis was labeled accordingly. CI: confidence interval; df: degrees of freedom; hRARC: hybrid RARC; iRARC: completely intracorporeal RARC; IV: inverse variance; M-H: Mantel-Haenszel; SD: standard deviation; SE: standard error.

Perioperative outcomes: Estimated blood loss, operating room time, and hospital length of stay

The pooled meta-analysis for mean EBL and ORT was based on seven studies (four comparing hRARC to ORC, and three comparing iRARC to ORC) (Figures 2D, 2E). Mean EBL favored RARC over ORC (total MD -312.61, 95% CI -447.00 to -178.22 mL, p<0.001, I^2=90%). In subgroup meta-analyses, mean EBL favored hRARC alone over ORC (MD -280.47, 95% CI -435.67 to -125.57 mL, p<0.001, I^2=70%) and iRARC alone over ORC (MD -359.17, 95% CI -616.50 to -101.83 mL, p=0.006, I^2=96%). Mean ORT favored ORC over RARC (total MD 82.34, 95% CI 44.82–119.86 minutes, p<0.001, I^2=94%). In subgroup meta-analyses, mean



Modality	Rank 1	Rank 2	Rank 3	SUCRA
hRARC	0.5136875	0.329125	0.1571875	67.825
iRARC	0.45285	0.376025	0.171125	64.08625
ORC	0.0334625	0.29485	0.6716875	18.08875

Modality	Rank 1	Rank 2	Rank 3	SUCRA
hRARC	0.1827875	0.229875	0.5873375	29.7725
iRARC	0.6330125	0.1986875	0.1683	73.235625
ORC	0.1842	0.5714375	0.2443625	46.991875

Figure 3. League tables and Rankograms for: (A) any Clavien-Dindo grade; and (B) Clavien-Dindo high-grade (≥3) complications among the three different surgical approaches for radical cystectomy. For league tables, direct comparisons are represented in italics, and indirect comparisons are represented in bold. Outcomes are shown as odds ratios (OR) with corresponding 95% CrIs (credible intervals). Rankograms demonstrate the probabilities of the rank order for each surgical approach; table below shows the actual values plotted in the rankogram. A surgical approach's surface under the cumulative ranking (SUCRA) value corresponds to its overall rank for safety (higher values corresponding to greater safety). hRARC: hybrid robot-assisted radical cystectomy; iRARC: completely intracorporeal robot-assisted radical cystectomy; ORC: open radical cystectomy.

ORT favored ORC over hRARC alone (MD 76.45, 95% CI 29.28–123.63 minutes, p=0.001, I^2=83%) and ORC over iRARC alone (MD 89.42, 95% CI 27.35–151.49 minutes, p=0.005, I^2=98%).

The pooled meta-analysis for hospital LOS was based on six studies (three comparing hRARC to ORC, and three comparing iRARC to ORC) (Figure 2F). We found no difference between RARC and ORC in hospital LOS (total MD -0.22, 95% CI -1.10–0.65 days, p=0.6, I^2=70%). Likewise, we did not find differences in subgroup meta-analyses: hRARC vs. ORC (MD -0.50, 95% CI -1.15–0.14 days, p=0.13, I^2=0%) and iRARC vs. ORC (MD -0.09, 95% CI -1.88–1.69, p=0.9, I^2=86%).

90-day postoperative complications, readmissions, and quality of life

The pooled meta-analysis for any and major complications was based on six studies (three comparing hRARC to ORC, and three comparing iRARC to ORC) (Figures 2G, 2H). We found no difference between RARC and ORC in complications of any CD grade (total OR 0.81, 95% CI 0.61–1.07, p=0.14, I^2=0%), as well as major complications (total OR 0.94, 95% CI 0.69–1.30, p=0.7, I^2=0%). Likewise, we did not find differences in subgroup meta-analyses: hRARC vs. ORC (any complications: OR 0.82, 95% CI 0.53–1.25, p=0.4, I^2=0%; major complications: OR 1.08, 95% CI

0.69–1.67, p=0.7, I^2=0%), and iRARC vs. ORC (any complications: OR 0.80, 95% CI 0.54–1.18, p=0.3, I^2 =0%; major complications: OR 0.82, 95% CI 0.51–1.30, p=0.4, I^2=0%).

The pooled meta-analysis for 90-day readmissions was based on four studies (one comparing hRARC to ORC, and three comparing iRARC to ORC) (Figure 2I). We found no difference between RARC and ORC in 90-day readmissions (total OR 0.90, 95% CI 0.60–1.35, p=0.6, I^2=29%). Likewise, we did not find differences in subgroup meta-analysis of iRARC vs. ORC (OR 0.86, 95% CI 0.47–1.57, p=0.6, I^2=42%). Subgroup meta-analysis comparing hRARC to ORC was not possible, given that only one study had data on 90-day readmissions.

The pooled meta-analysis for QoL was based on six studies (four comparing hRARC to ORC, and two comparing iRARC to ORC) (Figure 2J). We found no difference between RARC and ORC in QoL (total SMD -0.02, 95% CI -0.17–0.14, p=0.8, I^2=0%). Likewise, we did not find differences in subgroup meta-analyses: hRARC vs. ORC (SMD -0.11, 95% CI -0.34–0.12, p=0.3, I^2=0%) and iRARC vs. ORC (SMD 0.05, 95% CI -0.23–0.33, p=0.7, I^2=34%).

Network meta-analyses

Six studies were included in the NMAs for any and major 90-day postoperative complications (network geometry plot is shown in Supplementary Figure 2; available in the Appendix at ***cuaj.ca***). Our analysis indicated that there were no significant differences in the odds of any CD grade complication (OR 0.97, 95% CrI 0.42–2.11) or major complications (OR 1.33, 95% CrI 0.55–3.23) between hRARC and iRARC (Figures 3A, 3B). Among the surgical modalities, both hRARC and iRARC had similar probabilities for any CD grade complications, with SUCRA scores of 67.8 and 64.1 respectively (Figure 3A). Regarding major complications, iRARC was associated with the highest probability of having the lowest complications (SUCRA 73.2), followed by ORC (SUCRA 47.0) and hRARC (SUCRA 29.8) (Figure 3B). Lastly, the deviance contribution plots showed no evidence of global inconsistency (Supplementary Figure 3; available in the Appendix at ***cuaj.ca***).

DISCUSSION

This study presents an up-to-date, pairwise meta-analysis comparing RARC to ORC, as well as a novel NMA indirectly comparing hRARC to iRARC with respect to 90-day complications. After the inclusion of three recently published RCTs comparing iRARC to ORC,[34-36] RARC and ORC remain equivalent with respect to all oncological outcomes of interest. Further, we did not find significant differences in perioperative outcomes between RARC and ORC, except for lower EBL in the case of RARC at the expense of prolonged ORT. Indirect comparisons of overall and major 90-day complications between hRARC and iRARC failed to show any significant differences.

The increased use of RARC has been accompanied by concerns regarding its oncological equivalence to ORC.[38] This has been a topic of exploration within other surgical specialties as well, specifically laparoscopic surgery for cervical cancer.[39] Although these factors were of concern in the adoption of RARC, the summative and consistent safety profile, as measured by RFS/PFS, between RARC and ORC has been reassuring. The iROC study was the only RCT that compared RFS/PFS between iRARC and ORC. It did not find significant differences in cancer recurrence between the two groups after a median followup of 18.4 months.[35] While encouraging, we await long-term, prospective data for RFS/PFS, particularly from RCTs comparing iRARC to ORC. We did not compare recurrence site patterns, given the irreconcilable categorization among the RCTs;[29,33,35] however, our previous meta-analysis showed that neither RARC nor ORC was associated with a significantly higher likelihood of locoregional or distant recurrence.[15]

Complication rate has been a topic of close investigation for RARC since the sentinel RCTs. In this updated meta-analysis, we did not find significant differences between RARC and ORC with respect to any or major complications. One of the motivations for a completely intracorporeal robotic approach has been to potentially decrease perioperative complications. The three recent RCTs comparing iRARC to ORC failed to show significant differences between these two surgical approaches (any complications: OR 0.80, 95% CI 0.54–1.18, p=0.26; major complications: OR 0.82, 95% CI 0.51–1.30, p=0.39). In the iROC study, iRARC was associated with lower rates of thromboembolic and wound complications compared to ORC.[35] The other two studies did not have granular data regarding complication types.[34,36] Fundamentally, these results might indicate that enhanced recovery after surgery (ERAS) protocols have equalized safety profiles between RARC and ORC,[40] and/or we have reached a plateau in terms of morbidity despite the introduction of RARC.

This meta-analysis indicates equivalence between RARC and ORC, except for lower EBL in exchange for longer ORT in RARC. We did not find differences in hospital LOS between RARC and ORC. Two RCTs

comparing iRARC and ORC examined days alive and out of the hospital (DAOH) within 90 days of surgery. The BORARC feasibility trial did not find differences in DAOH, while the iROC study found a statistically significant increase of 2.2 days in DAOH for iRARC over ORC.[35,37] DAOH reflects a composite of recovery and major complications. The increase of 2.2 days in DAOH for iRARC was largely driven by lower rates of readmission in this group (21.8%) compared to ORC (32.2%).[35] Nonetheless, our meta-analysis did not find significant differences in 90-day readmissions between RARC and ORC.

While oncological outcomes and 90-day complications are equivalent between RARC and ORC, patient-reported outcome measures may ultimately be the tiebreaker. We did not find significant differences between RARC and ORC regarding QoL 6–12 months after RC. The results must be interpreted with caution, given the differences in questionnaires used. As pointed out by the authors of the iROC study, qualitative/quantitative recovery measures seem to give RARC an advantage over ORC. They found that differences in QoL, disability scores, and stamina tests were greatest at five weeks after RC, with ORC patients having a significantly worse recovery than iRARC patients. These differences persisted up to three months for disability and stamina but not for QoL,[35] which could explain our results. Analysis of QALYs for iROC was not reported,[41] but it might be what ultimately supports a higher cost-effectiveness for RARC.

Limitations

To our knowledge, this is the first meta-analysis that includes data on iRARC, as well as the first NMA indirectly comparing the odds of 90-day complications between hRARC and iRARC. Nonetheless, the present study is not without limitations.

First, our analysis included a small number of studies. We limited our inclusion criteria to RCTs because they are more likely to provide unbiased information.[20]

Second, there was a high level of performance bias given the inherent characteristics of a surgical intervention.

Third, there was a high degree of heterogeneity for some of our analyzed outcomes, such as EBL and ORT. For EBL, the high heterogeneity might be due to the subjectivity of this measure.

Fourth, although iROC argues in favor of an earlier assessment of QoL (i.e., less than three months after RC),[35] we did not have enough data to compare earlier QoL differences between RARC and ORC.

Fifth, given the lack of granular data, we were not able to perform analyses in subgroups of interest, such as type of UD.

Sixth, the generalizability of our findings might be limited to high-volume centers. Nonetheless, current guidelines recommend RARC to be performed in centers with yearly RC volumes >10.[42]

Finally, the data included in this meta-analysis span over 12 years, during which much has evolved within the field of robotic surgery.

CONCLUSIONS

This updated, pairwise meta-analysis with inclusion of data on iRARC affirms the oncological equivalence of RARC. An indirect comparison between hRARC and iRARC failed to show differences in overall and major complication rates between these two robotic approaches.

COMPETING INTERESTS: Dr. Miles is a consultant for EDAP Technomed. Dr. Kulkarni has been an advisory board member for Astellas, AAA/Novartis, BMS, EMD Serono, Ferring, Janssen, Merck, Roche, Theralase, and Verity; has received grant and/or honoraria from AbbVie, Astra Zeneca, Ferring, Sanofi, and TerSera; has participated in clinical trials supported by Astra Zeneca, BMS, Janssen, Merck, Pfizer, Seagen, Theralase, and Verity; and is the vice-Chair Research of Bladder Cancer Canada. Dr. Wallis has been an advisory board member for Knight Therapeutics; as received payment and grants/honoraria from Bayer, EMD Serono, Haymarket Media, Healing and Cancer Foundation, Janssen Oncology, Knight Therapeutics, Precision Point Specialty LLC, SESEN Bio, TerSera, and Tolmar. The remaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209. https://doi.org/10.3322/caac.21660
2. Chang SS, Bochner BH, Chou R, et al. Treatment of nonmetastatic muscle-invasive bladder cancer: American Urological Association/American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Urologic Oncology clinical practice guideline summary. *J Oncol Pract* 2017;13:621. https://doi.org/10.1200/JOP.2017.024919
3. Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2020 guidelines. *Eur Urol* 2021;79:82. https://doi.org/10.1016/j.eururo.2020.03.055
4. Maibom SL, Joensen UN, Poulsen AM, et al. Short-term morbidity and mortality following radical cystectomy: A systematic review. *BMJ Open* 2021;11:e043266. https://doi.org/10.1136/bmjopen-2020-043266
5. Menon M, Hemal A, Tewari A, et al. Nerve–sparing robot–assisted radical cystoprostatectomy and urinary diversion. *BJU Int* 2003;92:232. https://doi.org/10.1046/j.1464-410X.2003.04329.x
6. Mitra AP, Cai J, Miranda G, et al. Management trends and outcomes of patients undergoing radical cystectomy for urothelial carcinoma of the bladder: Evolution of the University of Southern California Experience over 3347 cases. *J Urol* 2022;207:302. https://doi.org/10.1097/JU.0000000000002242
7. Tamhankar AS, Thurtle D, Hampson A, et al. Radical cystectomy in England from 2013 to 2019 on 12 644 patients: An analysis of national trends and comparison of surgical approaches using hospital episode statistics data. *BJUI Compass* 2021;2:338. https://doi.org/10.1002/bco2.79
8. Satkunasivam R, Wallis CJ, Nam RK, et al. Contemporary evidence for robot-assisted radical cystectomy for treating bladder cancer. *Nat Rev Urol* 2016;13:533. https://doi.org/10.1038/nrurol.2016.139

9. Beecken W-D, Wolfram M, Engl T, et al. Robotic-assisted laparoscopic radical cystectomy and intra-abdominal formation of an orthotopic ileal neobladder. *Eur Urol* 2003;44:337. https://doi.org/10.1016/S0302-2838(03)00301-4
10. Hussein AA, May PR, Jing Z, et al. Outcomes of intracorporeal urinary diversion after robot-assisted radical cystectomy: Results from the International Robotic Cystectomy Consortium. *J Urol* 2018;199:1302. https://doi.org/10.1016/j.juro.2017.12.045
11. Hussein AA, Elsayed AS, Aldhaam NA, et al. A comparative propensity score-matched analysis of perioperative outcomes of intracorporeal vs. extracorporeal urinary diversion after robot-assisted radical cystectomy: Results from the International Robotic Cystectomy Consortium. *BJU Int* 2020;126:265. https://doi.org/10.1111/bju.15083
12. Ahmed K, Khan SA, Hayn MH, et al. Analysis of intracorporeal compared with extracorporeal urinary diversion after robot-assisted radical cystectomy: Results from the International Robotic Cystectomy Consortium. *Eur Urol* 2014;65:340. https://doi.org/10.1016/j.eururo.2013.09.042
13. Lenfant L, Verhoest G, Campi R, et al. Perioperative outcomes and complications of intracorporeal vs. extracorporeal urinary diversion after robot-assisted radical cystectomy for bladder cancer: A real-life, multi-institutional French study. *World J Urol* 2018;36:1711. https://doi.org/10.1007/s00345-018-2313-8
14. Shim JS, Kwon TG, Rha KH, et al. Do patients benefit from total intracorporeal robotic radical cystectomy?: A comparative analysis with extracorporeal robotic radical cystectomy from a Korean multicenter study. *Invest Clin Urol* 2020;61:11. https://doi.org/10.4111/icu.2020.61.1.11
15. Satkunasivam R, Tallman CT, Taylor JM, et al. Robot-assisted radical cystectomy vs. open radical cystectomy: A meta-analysis of oncologic, perioperative, and complication-related outcomes. *Eur Urol Oncol* 2019;2:443. https://doi.org/10.1016/j.euo.2018.10.008
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *Ann Intern Med* 2009;151:W65. https://doi.org/10.7326/0003-4819-151-4-200908180-00136
17. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions: Checklist and explanations. *Ann Intern Med* 2015;162:777. https://doi.org/10.7326/M14-2385
18. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. https://doi.org/10.1186/1471-2288-14-135
19. Rai BP, Bondad J, Vasdev N, et al. Robotic vs. open radical cystectomy for bladder cancer in adults. *Cochrane Database Syst Rev* 2019;4:CD011903. https://doi.org/10.1002/14651858.CD011903.pub2
20. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, ed. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 Updated February 2022. Cochrane; 2022. Available at: www.training.cochrane.org/handbook. Accessed October 25, 2022.
21. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ* 2011;343:d5928. https://doi.org/10.1136/bmj.d5928
22. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002. https://doi.org/10.1136/bmj.d4002
23. Owen RK, Bradbury N, Xin Y, et al. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Res Synth Methods* 2019;10:569. https://doi.org/10.1002/jrsm.1373
24. Daly C, Downing BC, Welton NJ. A practical guide to inconsistency checks in Bayesian network meta-analysis. Available at: https://www.bristol.ac.uk/media-library/sites/social-community-medicine/documents/mpes/Guide%20to%20Checking%20for%20Inconsistency%20in%20NMA_TSU.pdf. Accessed October 25, 2022.
25. Bochner BH, Dalbagni G, Sjoberg DD, et al. Comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: A randomized clinical trial. *Eur Urol* 2015;67:1042. https://doi.org/10.1016/j.eururo.2014.11.043
26. Khan MS, Gan C, Ahmed K, 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. https://doi.org/10.1016/j.eururo.2015.07.038
27. Nix J, Smith A, Kurpad R, et al. Prospective randomized controlled trial of robotic vs. open radical cystectomy for bladder cancer: Perioperative and pathologic results. *Eur Urol* 2010;57:196. https://doi.org/10.1016/j.eururo.2009.10.024
28. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *Eur Urol* 2015;68:464. https://doi.org/10.1016/j.eururo.2014.10.021
29. Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): An open-label, randomized, phase 3, non-inferiority trial. *Lancet* 2018;391:2525. https://doi.org/10.1016/S0140-6736(18)30996-6
30. Messer JC, Punnen S, Fitzgerald J, et al. Health-related quality of life from a prospective randomised clinical trial of robot-assisted laparoscopic vs. open radical cystectomy. *BJU Int* 2014;114:896. https://doi.org/10.1111/bju.12818
31. Khan MS, Omar K, Ahmed K, et al. Long-term oncological outcomes from an early phase randomised controlled three-arm trial of open, robotic, and laparoscopic radical cystectomy (CORAL). *Eur Urol* 2020;77:110. https://doi.org/10.1016/j.eururo.2019.10.027
32. Venkatramani V, Reis IM, Castle EP, et al. Predictors of recurrence, and progression-free and overall survival following open vs. robotic radical cystectomy: Analysis from the RAZOR trial with a 3-year followup. *J Urol* 2020;203:522. https://doi.org/10.1097/JU.0000000000000565
33. Bochner BH, Dalbagni G, Marzouk KH, et al. Randomized trial comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: Oncological outcomes. *Eur Urol* 2018;74:465. https://doi.org/10.1016/j.eururo.2018.04.030
34. Mastroianni R, Tuderti G, Anceschi U, et al. Comparison of patient-reported health-related quality of life between open radical cystectomy and robot-assisted radical cystectomy with intracorporeal urinary diversion: Interim analysis of a randomized controlled trial. *Eur Urol Focus* 2022;8:465. https://doi.org/10.1016/j.euf.2021.03.002
35. Catto JWF, Khetrapal P, Ricciardi F, et al. Effect of robot-assisted radical cystectomy with intracorporeal urinary diversion vs. open radical cystectomy on 90-day morbidity and mortality among patients with bladder cancer: A randomized clinical trial. *JAMA* 2022;327:2092-2103. https://doi.org/10.1001/jama.2022.7393
36. Maibom SL, Roder MA, Aasvang EK, et al. Open vs robot-assisted radical cystectomy (BORARC): A double-blinded, randomized, feasibility study. *BJU Int* 2022;130:102-13. https://doi.org/10.1111/bju.15619
37. Vejlgaard M, Maibom SL, Joensen UN, et al. Quality of life and secondary outcomes for open versus robot-assisted radical cystectomy: A double-blinded, randomized, feasibility trial. *World J Urol* 2022;40:1669-77. https://doi.org/10.1007/s00345-022-04029-9
38. Nguyen DP, Al Hussein Al Awamlh B, Wu X, et al. Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. *Eur Urol* 2015;68:399. https://doi.org/10.1016/j.eururo.2015.02.003
39. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive vs. abdominal radical hysterectomy for cervical cancer. *N Engl J Med* 2018;379:1895. https://doi.org/10.1056/NEJMoa1806395
40. Williams SB, Cumberbatch MGK, Kamat AM, et al. Reporting radical cystectomy outcomes following implementation of enhanced recovery after surgery protocols: A systematic review and individual patient data meta-analysis. *Eur Urol* 2020;78:719. https://doi.org/10.1016/j.eururo.2020.06.039
41. Catto JWF, Khetrapal P, Ambler G, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy (iROC): Protocol for a randomized, controlled trial with internal feasibility study. *BMJ Open* 2018;8:e020500. https://doi.org/10.1136/bmjopen-2017-020500
42. Bruins HM, Veskimae E, Hernandez V, et al. The importance of hospital and surgeon volume as major determinants of morbidity and mortality after radical cystectomy for bladder cancer: A systematic review and recommendations by the European Association of Urology Muscle-Invasive and Metastatic Bladder Cancer Guideline Panel. *Eur Urol Oncol* 2020;3:131. https://doi.org/10.1016/j.euo.2019.11.005

CORRESPONDENCE: Dr. Raj Satkunasivam, Department of Urology, Houston Methodist Hospital, Houston, TX, United States; raj.satkunasivam@gmail.com