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Review – Bladder Cancer

# Robot-assisted Radical Cystectomy Versus Open Radical Cystectomy: A Systematic Review and Meta-analysis of Perioperative, Oncological, and Quality of Life Outcomes Using Randomized Controlled Trials

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**Abstract**

***Context:*** Differences in recovery, oncological, and quality of life (QoL) outcomes between open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) for patients with bladder cancer are unclear.
***Objective:*** This review aims to compare these outcomes within randomized trials of ORC and RARC in this context. The primary outcome was the rate of 90-d perioperative events. The secondary outcomes included operative, pathological, survival, and health-related QoL (HRQoL) measures.
***Evidence acquisition:*** Systematic literature searches of MEDLINE, Embase, Web of Science, and clinicaltrials.gov were performed up to May 31, 2022.
***Evidence synthesis:*** Eight trials, reporting 1024 participants, were included. RARC was associated with a shorter hospital length of stay (LOS; mean difference [MD] 0.21, 95% confidence interval [CI] 0.03–0.39, $p$ = 0.02) than and similar complication rates to ORC. ORC was associated with higher thromboembolic events (odds ratio [OR] 1.84, 95% CI 1.02–3.31, $p$ = 0.04). ORC was associated with more blood loss (MD 322 ml, 95% CI 193–450, $p$ < 0.001) and transfusions (OR 2.35, 95% CI 1.65–3.36, $p$ < 0.001), but shorter operative time (MD 76 min, 95% CI 39–112, $p$ < 0.001) than RARC. No

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Open radical cystectomy
Complications
Survival
Quality of life

differences in lymph node yield (MD 1.07, 95% CI –1.73 to 3.86, $p$ = 0.5) or positive surgical margin rates (OR 0.95, 95% CI 0.54–1.67, $p$ = 0.9) were present. RARC was associated with better physical functioning or well-being (standardized MD 0.47, 95% CI 0.29–0.65, $p$ < 0.001) and role functioning (MD 8.8, 95% CI 2.4–15.1, $p$ = 0.007), but no improvement in overall HRQoL. No differences in progression-free survival or overall survival were seen. Limitations may include a lack of generalization given trial patients.

***Conclusions:*** RARC offers various perioperative benefits over ORC. It may be more suitable in patients wishing to avoid blood transfusion, those wanting a shorter LOS, or those at a high risk of thromboembolic events.

***Patient summary:*** This study compares robot-assisted keyhole surgery with open surgery for bladder cancer. The robot-assisted approach offered less blood loss, shorter hospital stays, and fewer blood clots. No other differences were seen.



## 1. Introduction

Radical cystectomy (RC) is recommended for the management of bladder cancer (BC) [1]. The robotic platform has become popular because of its potential to offer quicker recovery, while replicating the oncological principles of open RC (ORC). Indeed, analyses of national databases, such as the National Cancer Database in USA [2] and Health Episode Statistics from England [3], have shown a rapid increase in the uptake of robot-assisted RC (RARC) for BC. Interestingly, this adoption preceded high-quality randomized data supporting benefits of RARC over ORC.

Previously, meta-analyses have compared RARC and ORC [4,5] using small randomized controlled trials (RCTs) and case series [6–9]. A 2019 Cochrane review [5] concluded that RARC may offer similar oncological outcomes, quality of life (QoL), and positive surgical margin (PSM) rates. Since the initial meta-analyses, several larger RCTs comparing ORC and RARC have been published [10–12]. In addition, studies included within the Cochrane review have published updated reports with longer oncological outcomes and new health-related quality of life (HRQoL) findings [13–15].

Therefore, we aimed to undertake a contemporary up-to-date systematic review and meta-analysis of RCTs comparing RARC and ORC for BC. Our primary outcome was to compare the rates of 90-d perioperative events, including complications and hospital length of stay (LOS). The secondary outcomes included oncological endpoints and HRQoL.

## 2. Evidence acquisition

### *2.1. Search strategy*

The study protocol was registered on PROSPERO (CRD42022313481) prior to undertaking a systematic search of the literature using MEDLINE, Embase, Web of Science, and clinicaltrials.gov databases up to May 31, 2022. The full search strategy is provided in the Supplementary material. All results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

### *2.2. Study selection*

We included prospective RCTs comparing RARC and ORC for bladder cancer. Two investigators (P.K. and J.K.L.W.) independently performed the initial screening of all published manuscripts. Conference abstracts, review articles, editorials, comments, and letters to the editor were excluded.

### *2.3. Data extraction*

Data extraction was independently performed by two authors (P.K. and J.K.L.W.). Any disagreements were discussed with a third coauthor (J.D.K.) and resolved by consensus. Study characteristics including author, year, recruitment period, country, primary and secondary endpoints evaluated, patient demographics, type of urinary diversion, neoadjuvant chemotherapy, and pathological T stage were collected. Perioperative outcomes including blood loss, blood transfusions, operative time, LOS, and 90- and 30-d complications (defined using the Clavien-Dindo [CD] classification [16] and stratified into all, minor [CD $\leq$2], and major [CD $\geq$3]) were reviewed. Histopathological outcomes including lymph node (LN) yield and PSM rates were assessed as well. QoL outcomes included all domains of the various questionnaires used. Similar domains across different questionnaires were combined and represented as standardized mean differences, where appropriate.

### *2.4. Statistical analysis*

Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) were utilized for continuous variables. All median and IQR values were converted to means and SDs using the methodology described by Hozo et al [17]. The number of events as a proportion of sample size was collected for dichotomous variables. Statistical analyses were performed using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK). Funnel plots were used to assess the publication bias [18]. Pooled estimates were obtained using means and SDs for continuous variables, and event rates for dichotomous variables. The effect measure used for continuous variables was the mean difference (MD) when the measurement scales used by studies were similar and the standardized mean difference (SMD) when the measurement scales used were different. The effect measure used for dichotomous variables was the odds ratio (OR). The chi-square test was used to test for the extent of interstudy heterogeneity, with a $p$ value of 0.10 taken as significant heterogeneity [19]. The $I^2$ statistic was used to describe the proportion of interstudy variation caused by heterogeneity, with an $I^2$ value of 0–40% considered to represent negligible heterogeneity, 30–60% to represent moderate heterogeneity, 50–90% to represent substantial heterogeneity, and 75–100% to represent considerable heterogeneity [19]. For outcomes with moderate heterogeneity and higher, a random-effect model (by DerSimonian and Laird [20]) was used to obtain pooled estimates. Otherwise, a fixed-effect model (Mantel-Haenszel) was used for dichotomous variables and the inverse-variance model was used for continuous variables [19]. Sensitivity analyses of all outcomes were performed to examine the influence of each study on the pooled estimates.

### 2.5. Survival analysis

To compare survival outcomes across studies, published Kaplan-Meier (KM) plots from each trial were digitized using WebPlotDigitizer (Pacifica, CA, USA), and survival probabilities and follow-up times were extracted [21]. The number of individuals at risk at follow-up times was calculated using number-at-risk tables [22]. Pseudoindividual patient survival data were then reconstructed for each study using the methods by Guyot et al [23] and pooling of survival curves were done using the methods by Combescure et al [24] to arrive at summary survival curves for each trial with accurate censoring information. The meta-analyzed pseudoindividual patient data were then used to generate two overall pooled survival curves comparing ORC and RARC, one for overall survival (OS) and the other for progression-free survival (PFS). Additionally, Cox proportional hazard models were used to compare the survival outcomes, and the hazard ratio (HR) and its respective 95% confidence interval (CI) were reported.

### 2.6. Risk-of-bias assessment

Two authors (P.K. and T.R.) independently evaluated each study using the Cochrane Collaboration risk-of-bias (RoB2) assessment tool [25]. The risk of bias (RoB) graphic was created using the RoB2 tool (Cochrane Collaboration).

## 3. Evidence synthesis

### 3.1. Study characteristics

We identified 17 eligible publications, detailing 1024 participants (including 509 ORC and 515 RARC) from eight RCTs (Fig. 1, Table 1, and Supplementary Table 1) [6–15,26–32]. Four trials were undertaken in the USA, two in the UK, and one each in Germany and Italy. Perioperative, histopathological, QoL, and oncological outcomes were reported in all studies. Five and three studies performed extracorporeal (eRARC) and intracorporeal (iRARC) diversion in the RARC group, respectively. Most patients were male (80%), received an ileal conduit (73%), had muscle-invasive bladder cancer (57%) and did not receive neoadjuvant chemotherapy (67%). Four out of the eight RCTs included in the study reported the implementation of an enhanced recovery after surgery (ERAS) pathway [8,10–12].

### 3.2. Perioperative outcomes

#### 3.2.1. Length of stay

Subgroup analyses were performed for the meta-analysis on LOS. Studies were grouped according to country or region in which these were conducted (Fig. 2A). A pooled analysis from four studies conducted in the USA showed a longer LOS for ORC patients (MD 0.62 d, 95% CI 0.34–0.89, $p < 0.001$). The same conclusion was found through the pooled analysis from two studies conducted in the UK (MD 1.51 d, 95% CI 1.10–1.93, $p < 0.001$). The studies from two other EU countries showed a longer LOS for RARC patients instead (MD 0.90, 95% CI 0.61–1.20, $p < 0.001$). When grouped together, the overall pooled estimate from all countries showed that ORC patients had a significantly longer LOS (MD 0.21, 95% CI 0.03–0.39, $p = 0.02$). A sensitivity analysis revealed that the study by Parekh et al [29] influenced the pooled estimate, as removing the study from the meta-analysis revealed a nonsignificant difference between ORC and RARC in the USA. In terms of the UK trials, the study by Catto et al [10] that randomized 338 patients, found a difference between ORC and RARC, while Khan et al [8] with a smaller sample size of 40 patients did not find a difference. No publication bias was found for this outcome (Supplementary Fig. 1).

#### 3.2.2. Ninety-day complications

Eight studies contributed to the meta-analysis of 90-d overall complications (Fig. 2B). Pooled estimates showed no significant difference in 90-d overall complications between the ORC and RARC groups (OR 1.22, 95% CI 0.94–1.58, $p = 0.14$). Five studies were included in the meta-analysis for 90-d minor complications (Fig. 2C). Similarly, no significant difference was found between the two groups (OR 1.15, 95% CI 0.87–1.52, $p = 0.3$). The meta-analysis of 90-d major complications included eight studies (Fig. 2D). Again, no significant differences in major complications were found between the ORC and RARC groups (OR 1.08, 95% CI 0.79–1.48, $p = 0.6$). Likewise, no differences between the two groups were found for 30-d postoperative complications (Supplementary Fig. 2). Sensitivity analyses of 90-d complication outcomes revealed that no single study impacted the pooled estimates. No publication bias was found for all postoperative outcomes (Supplementary Fig. 3–8).

#### 3.2.3. Venous thromboembolic events

Six studies were included in the meta-analysis on venous thromboembolism (VTE; Fig. 3A). Pooled estimates showed a significantly higher number of VTE events in the ORC than in the RARC group (OR 1.84, 95% CI 1.02–3.31, $p = 0.04$). Sensitivity analyses revealed that the removal of the small studies by Khan et al [8], Maibom et al [11], and Nix et al [6] from the pooled estimates did not change this finding. There was no evidence of a publication bias (Supplementary Fig. 9).

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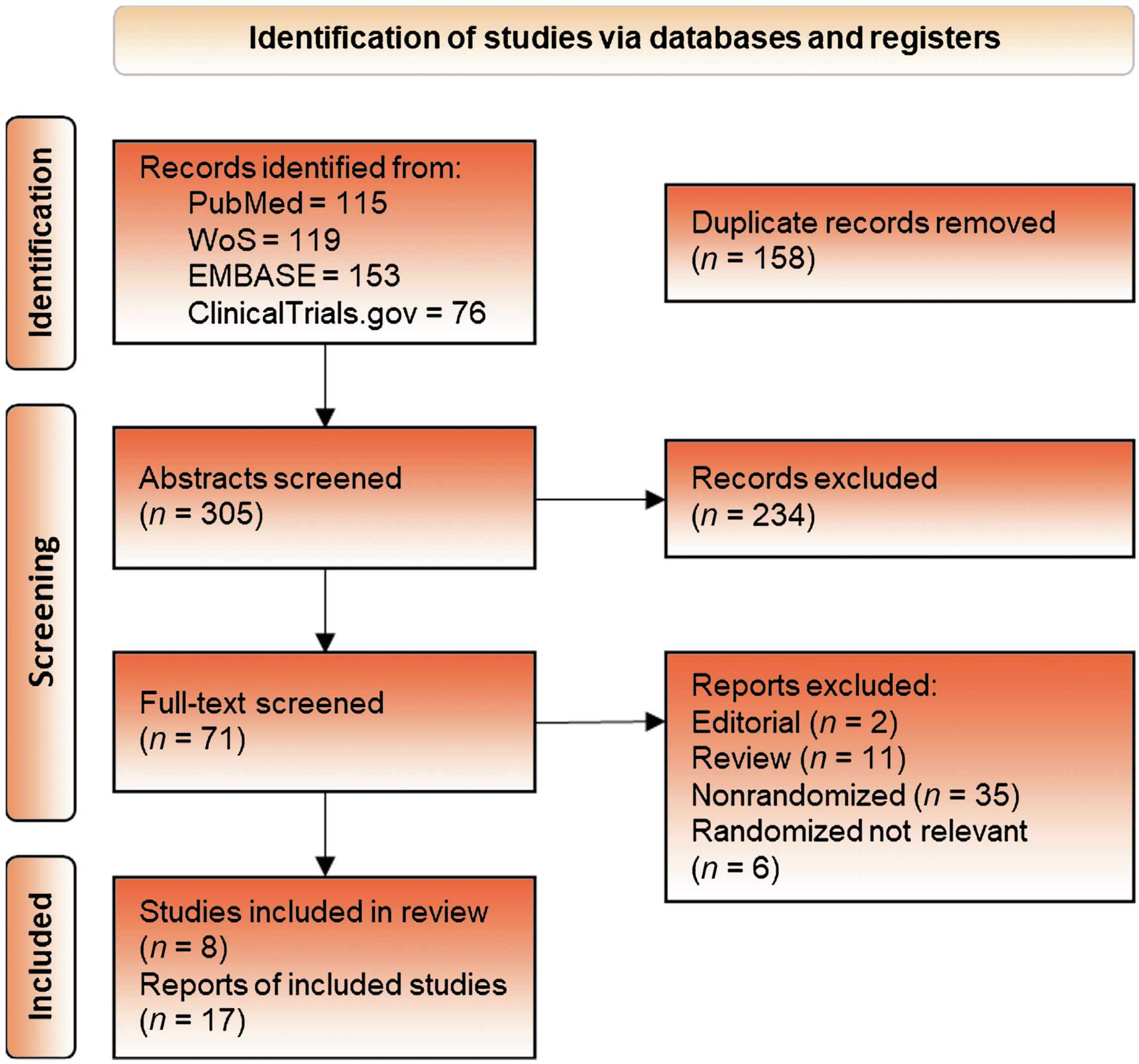


**Fig. 1 – PRISMA flowchart of studies included in the systematic review. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; WoS = Web of Science.**

#### 3.2.4. *Postoperative ileus and time to flatus*

Six studies were included in the meta-analysis on postoperative ileus (Fig. 3B). No significant difference in pooled estimates between RARC and ORC was identified (OR 1.07, 95% CI 0.72–1.57, $p$ = 0.8). Four studies were included in the meta-analysis on time to flatus (Fig. 3C), and again, no significant difference was found between RARC and ORC (MD –0.14, 95% CI –0.59 to 0.31, $p$ = 0.5). Although considerable heterogeneity existed, the sensitivity analysis did not change this result. A publication bias was found in time to flatus but not in postoperative ileus (Supplementary Fig. 10 and 11).

### 3.3. *Operative and pathological outcomes*

#### 3.3.1. *Blood loss and blood transfusion*

Eight trials were included in the meta-analysis for estimated blood loss (EBL; Fig. 4A). Pooled estimates showed that patients undergoing ORC had significantly higher EBL than those who had RARC (MD 322 ml, 95% CI 193–450, $p$ < 0.001). Supporting these findings, pooled estimates from the three studies that reported perioperative transfusion events showed that patients receiving ORC were transfused with more blood perioperatively (MD 0.53 units, 95% CI 0.34–0.73, $p$ < 0.001; Fig. 4B). Similarly, pooled estimates from five studies that reported perioperative transfusion rates showed that more patients in the ORC arm received a blood transfusion perioperatively (OR 2.35, 95% CI 1.65–3.36, $p$ < 0.001; Fig. 4C). Although considerable heterogeneity existed in the meta-analysis for EBL, the sensitivity analysis revealed that no single study impacted the pooled estimate. A Publication bias was not found in the blood transfusion outcomes but was found in the blood loss outcome based on funnel plots (Supplementary Fig. 12–14).

#### 3.3.2. *Operative time*

Eight studies were included in the meta-analysis for operative times (Fig. 4D). A significantly longer operative time was found in the RARC group (MD 76 min, 95% CI 39–112, $p$ < 0.001). Despite the presence of considerable heterogeneity, the sensitivity analysis found that no one study influ-

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**Table 1 – Studies included in this systematic review and meta-analysis.**

| Trial, ID and recruitment period | Date & Country | Primary outcome | Secondary outcomes | No. of pts | | Age Median (IQR) | | Male (n) | | BMI Median (IQR) | | Ileal conduit $ | | pTis- T1 | | pT2-T4 | | Neoadj. Ch. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ORC | RARC | ORC | RARC | ORC | RARC | ORC | RARC | ORC | RARC | ORC | RARC | ORC | RARC | ORC | RARC |
| **Extracorporeal reconstruction** | | | | | | | | | | | | | | | | | | | |
| Nix 2010[6] | 04/2008-01/ 2009 United States | Lymph node yield | Demographics, perioperative outcomes, pathology & narcotic use | 20 | 21 | 69.2 (51-80) ◇ | 67.4 (33-81)◇ | 17 | 14 | 28.4α | 27.5α | 14 | 14 | 5 | 6 | 15 | 15 | | |
| Parekh 2013[9], NCT01157676 | 07/2009-06/ 2011 United States | Oncologic efficacy & perioperative outcomes | HRQoL & functional recovery | 20 | 20 | 64.5 (59.8–72.3) | 69.5 (62.3–74) | 16 | 18 | 28.3 (26.1–32.3) | 27.6 (24.2–29.9) | 18 | 19 | 12 | 7 | 8 | 13 | 5 | 6 |
| Messer 2014[31], NCT01157676 | 07/2009-06/ 2011 United States | feasibility of randomising patients ORC or RARC | Oncological efficacy, perioperative outcomes, QoL | 20 | 20 | 64.5 (59.8–72.3) | 69.5 (62.3–74) | 16 | 18 | 28.3 (26.1–32.3) | 27.6 (24.2–29.9) | 18 | 19 | 12 | 7 | 8 | 13 | 5 | 6 |
| Bochner 2015[7], NCT01076387 | 03/2010-03/ 2013 United States | Overall 90-day CD grade 2–5 complications | Complications, blood loss, operative times, pathology, 3 & 6-months HRQoL & costs | 58 | 60 | 65 (58–69) | 66 (60-71) | 42 | 51 | 29.0 (26.3–33.7) | 27.9 (24.7–31.0) | 23* | 27 | 32 | 35 | 26 | 25 | 26 | 19 |
| Bochner 2018[27], NCT01076387 | 03/2010-03/ 2013 United States | Oncological outcomes | | 58 | 60 | 65 (58–69) | 66 (60-71) | 42 | 51 | 29.0 (26.3–33.7) | 27.9 (24.7–31.0) | 23* | 27 | 32 | 35 | 26 | 25 | 26 | 19 |
| *Khan 2016[8], CORAL, ISRCTN28499748 | 03/2009-07/ 2012 United Kingdom | 30 & 90-day complications | Perioperative, pathology and oncologic outcomes, & HRQoL | 20 | 20 | 68 (58–74) | 68 (65–74) | 18 | 17 | 27.0 (23.9–30.2) | 27.5 (24.0–30.8) | 17 | 18 | 14 | 11 | 6 | 9 | 3 | 2 |
| *Khan 2020[13], CORAL, ISRCTN28499748 | 03/2009-07/ 2012 United Kingdom | Recurrence, bladder cancer-specific and overall death | | 20 | 20 | 68 (58–74) | 68 (65–74) | 18 | 17 | 27.0 (23.9–30.2) | 27.5 (24.0–30.8) | 17 | 18 | 14 | 11 | 6 | 9 | 3 | 2 |
| Parekh 2018[29], RAZOR, NCT01157676 | 07/2011-11/ 2014 United States | 2-year Progression free survival | Blood loss, transfusion, PSM status, lymph nodes yield, operating time, LOS & 90-day complications. 3 & 6 months HRQoL | 152 | 150 | 67 (37–85) | 70 (43–90) | 128 | 126 | 28.2 (24.9–31.7)β | 27.8 (25–30.8)β | 122 | 113 * | 51 | 48 | 101 | 102 | 55 | 41 |
| Venkatramani 2020[14], RAZOR, NCT01157676 | 07/2011-11/ 2014 United States | 3-year oncological outcomes | | 152 | 150 | 67 (37–85) | 70 (43–90) | 128 | 126 | 28.2 (24.9–31.7) | 27.8 (25–30.8) | 122 | 113 * | 51 | 48 | 101 | 102 | 55 | 41 |
| **Intracorporeal reconstruction** | | | | | | | | | | | | | | | | | | | |
| *Catto 2022[10], iROC, NCT03049410 | 03/2017-03/ 2020 United Kingdom | DAOH-90 | Complications, HRQoL, disability, stamina, activity levels & survival | 156 | 161 | 69.2 (63.5-74.4) | 71.3 (65.1-74.9) | 122 | 128 | 27.0 (24.2–29.5) | 26.7 (24.4–29.9) | 140 | 142 | 70 | 71 | 68 | 72 | 53 | 54 |
| *Maibom 2022[11], BORARC, NCT03977831 | 06/2019-10/ 2020 Germany | Feasibility of double-blinding | LOS, peri-operative complications, blood loss, pain, readmission and opioid consumption | 25 | 25 | 67 (59-74) | 70 (63-74) | 20 | 18 | 27 (23-30) | 27 (23-29) | 25 | 25 | 6 | 9 | 19 | 16 | 10 | 9 |
| *Vejlgaard 2022[28], BORARC, NCT03977831 | 06/2019-10/ 2020 Germany | Patient-reported QoL | | 25 | 25 | 67 (59-74) | 70 (63-74) | 20 | 18 | 27 (23-30) | 27 (23-29) | 25 | 25 | 6 | 9 | 19 | 16 | 10 | 9 |
| *Mastroianni 2022[12], NCT03434132 | 01/2018-09/ 2020 Italy | Transfusion rate | 30-90 day outcomes, cost, functional, oncologic outcomes & HRQoL | 58 | 58 | 66 (58-71) | 64 (53-70) | 40 | 44 | 26 (24-29) | 26 (23-28) | 16 | 12 | 12 | 11 | 46 | 47 | 22 | 23 |

Abbreviations: ORC = Open radical Cystectomy; RARC = robot-assisted radical cystectomy; CD = Clavien Dindo; DAOH-90 = days alive and out of hospital in 90 days; Neoadj. Ch.= neoadjuvant chemotherapy; HRQOL = health related quality of life; LOS = length of stay; OS = overall survival; PFS = progression free survival; QoL = Quality of Life; IQR = Interquartile range.
$ Patients having Ileal conduit. All others had neobladder except *Bochner et al. for which 3 ORC patients had continent cutaneous diversion and Parekh et al. with 1 RARC patient had continent cutaneous diversion.
◇ reported mean (range), α reported mean, β reported median (range).

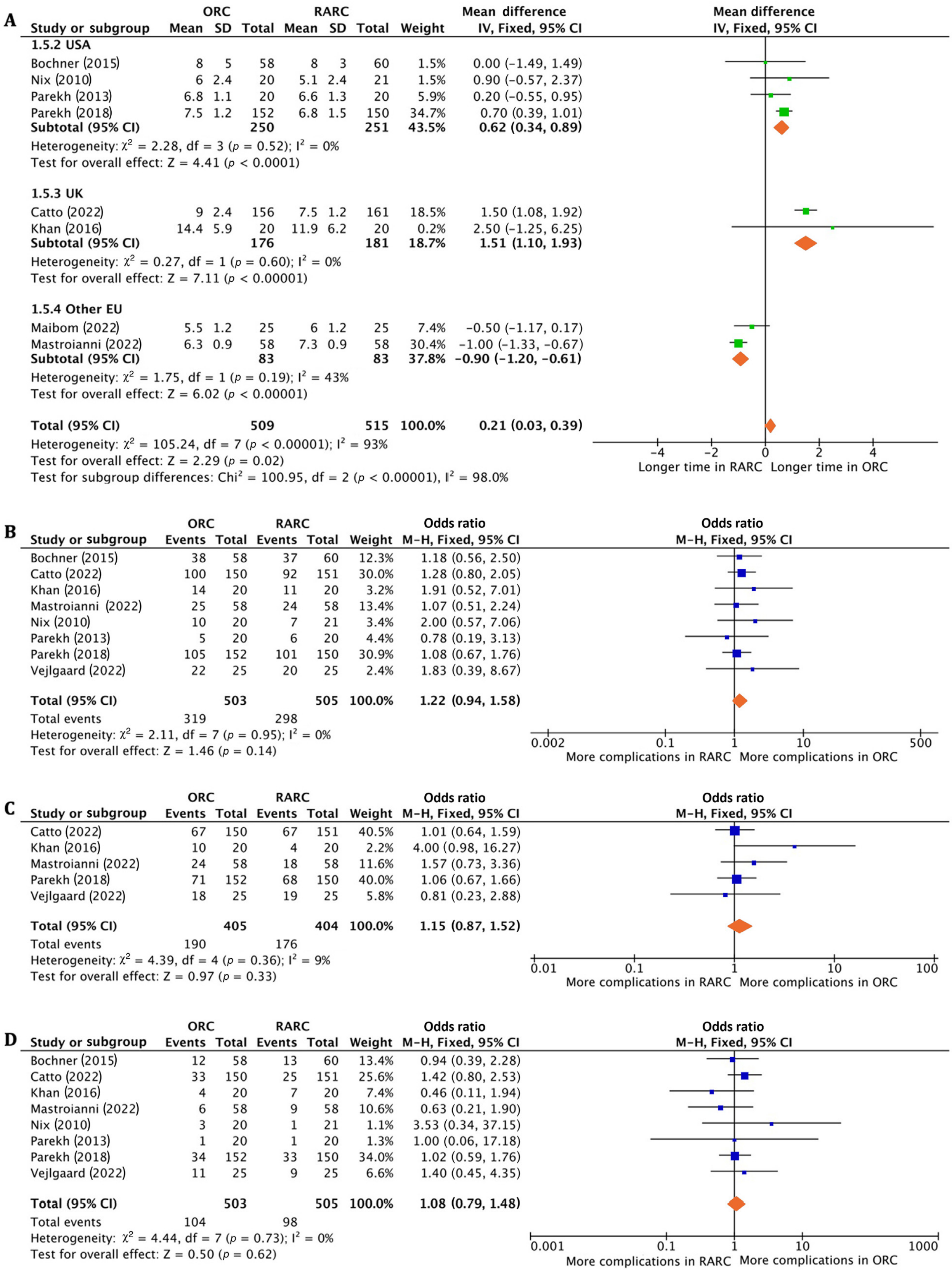


**Fig. 2 – Postoperative outcomes: (A) length of stay with subgroup analyses according to region, (B) 90-d overall complications, (C) 90-d minor complications (CD ≤2), and (D) 90-d major complications (CD ≥3). CD = Clavien-Dindo; CI = confidence interval; df = degree of freedom; IV = inverse variance; M-H = Mantel-Haenszel; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; SD = standard deviation.**

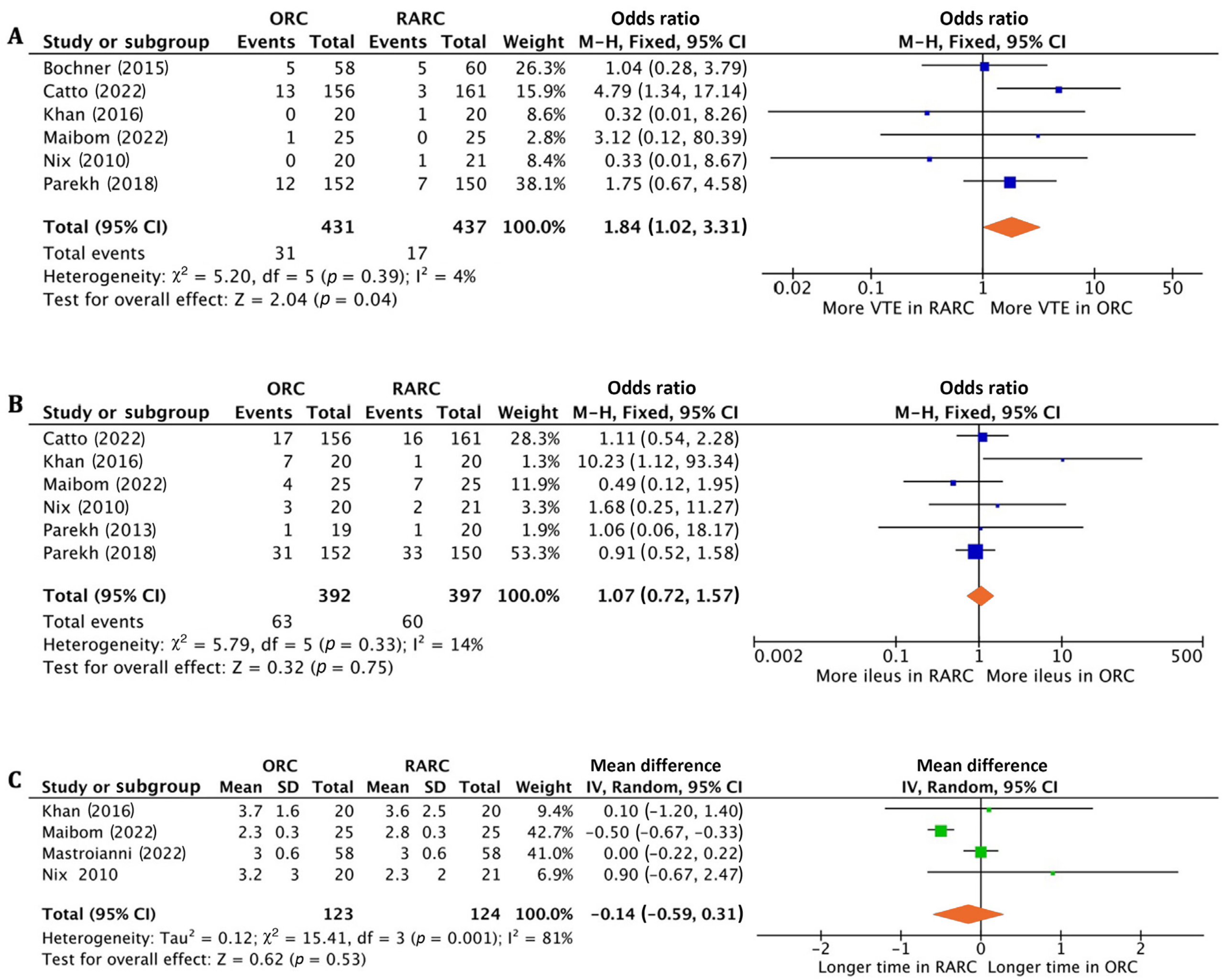


**Fig. 3 – Postoperative outcomes: (A) venous thromboembolic events, (B) postoperative ileus, and (C) time to flatus. CI = confidence interval; df = degree of freedom; IV = inverse variance; M-H = Mantel-Haenszel; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; SD = standard deviation; VTE = venous thromboembolism.**

enced the pooled estimate. Funnel plots demonstrated a publication bias for this outcome (Supplementary Fig. 15).

### 3.3.3. *Histopathological outcomes*

The meta-analysis on PSMs included eight studies (Fig. 4E). The pooled analysis did not show a significant difference in the number of patients with PSMs between the ORC and RARC groups (OR 0.95, 95% CI 0.54–1.67, $p$ = 0.9). Similarly, a pooled analysis from seven studies did not show a significant difference in the number of LNs yielded between the ORC and RARC groups (MD 1.07, 95% CI −1.73 to 3.86, $p$ = 0.5; Fig. 4F). Despite the presence of considerable heterogeneity, the sensitivity analysis revealed that no single study had influence on the pooled estimate. A publication bias was not found in the PSM outcome but was found in the LN yield outcome (Supplementary Fig. 16 and 17).

### 3.4. *Oncological outcomes*

Three studies contributed to the meta-analysis of OS and PFS [13,27,30]. The KM curves for OS and PFS are shown in Figures 5A and 5B, respectively. No significant differences were noted for either OS ($p$ = 0.9) or PFS ($p$ > 0.9) when comparing RARC and ORC over a median follow-up of 36 mo. The individual KM curves of PFS and OS for RARC and ORC are included in Supplementary Figure 18.

### 3.5. *QoL outcomes*

QoL outcomes were reported by all RCTs apart from one [6]. The method of collecting QoL data varied between studies. For example, Mastroianni et al [32] reported QoL data at 6 mo postoperatively, whereas all other studies reported QoL data at 3 mo postoperatively. Supplementary Table 2 summarizes the questionnaires, data collection time points, and overall QoL results of the studies. The European Organisation for research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients 30 Questions (QLQ-C30) and Functional Assessment of Cancer Therapy Vanderbilt Cystectomy Index (FACT-VCI) questionnaires were used by three [7,28,32] and two [29,31] studies, respectively, and hence were included in the QoL meta-analyses. QoL data from the two questionnaires across the five studies assess-

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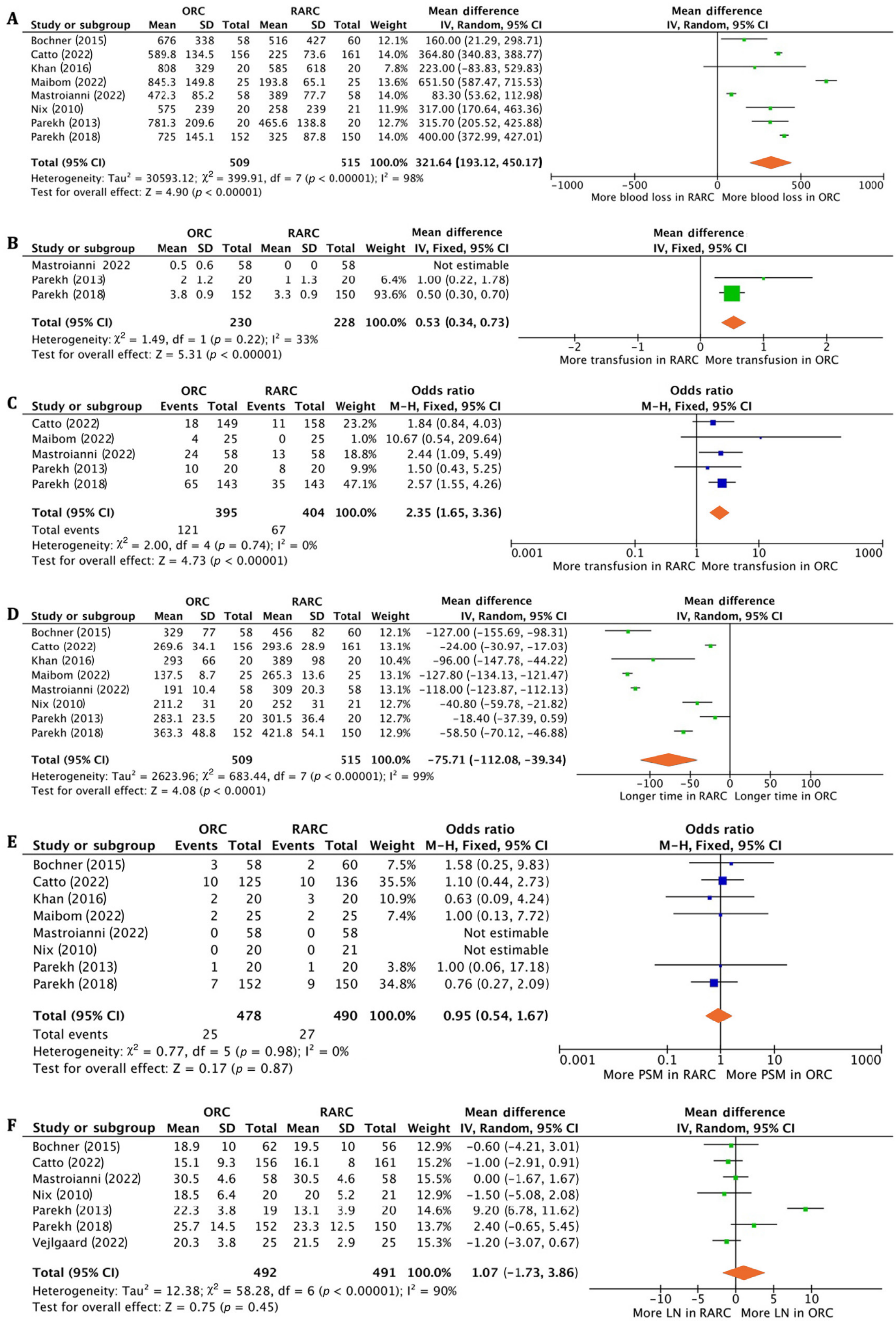


**Fig. 4 – Intraoperative outcomes: (A) Blood loss, (B) units of blood transfused perioperatively, (C) number of patients who required perioperative transfusions, (D) operative time, (E) positive surgical margin, and (F) lymph node yield. CI = confidence interval; df = degree of freedom; IV = inverse variance; LN = lymph node; M-H = Mantel-Haenszel; ORC = open radical cystectomy; PSM = positive surgical margin; RARC = robot-assisted radical cystectomy; SD = standard deviation.**

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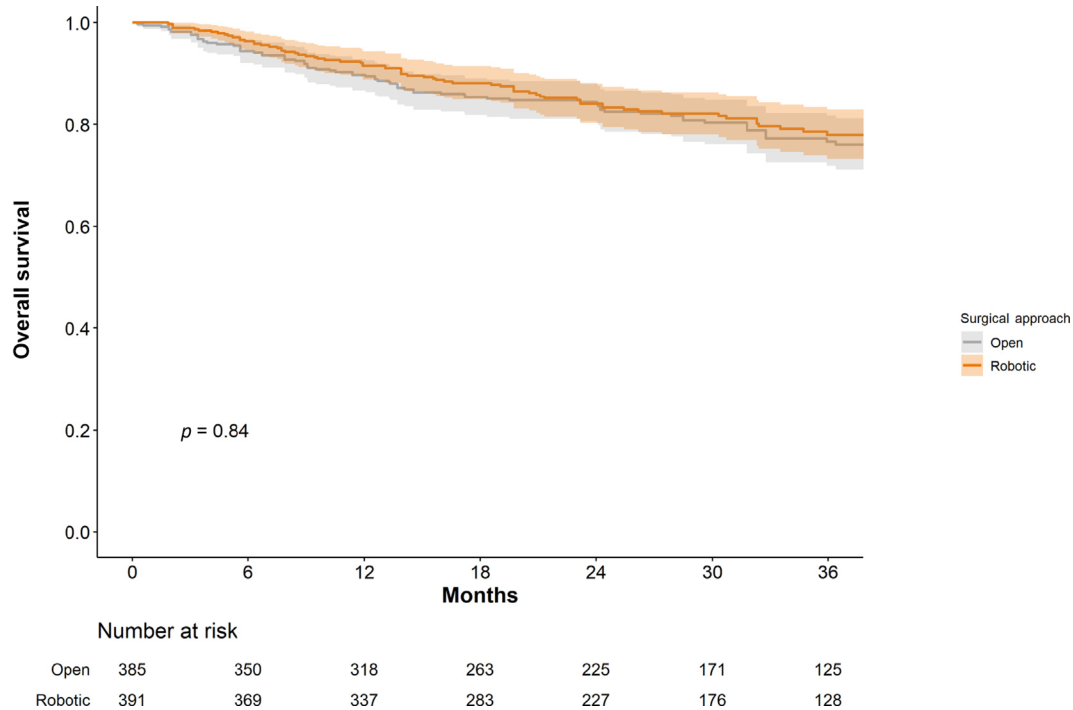



**Fig. 5a – Kaplan-Meier curves comparing A. Overall Survival (OS) and B. Progression-Free Survival (PFS).**

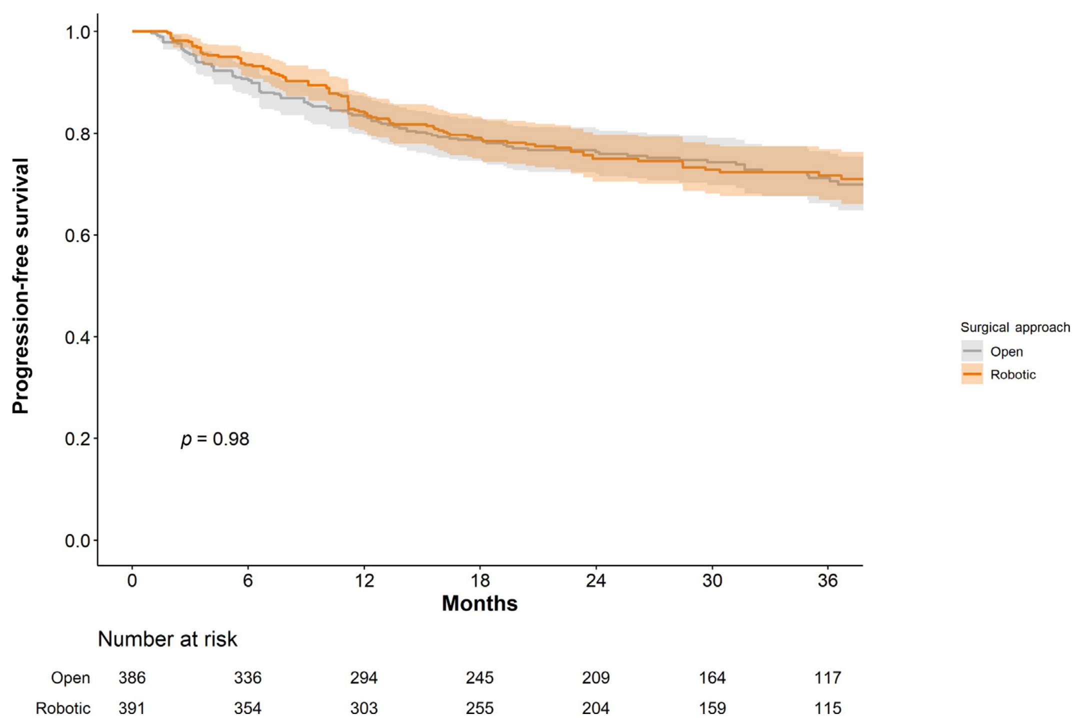


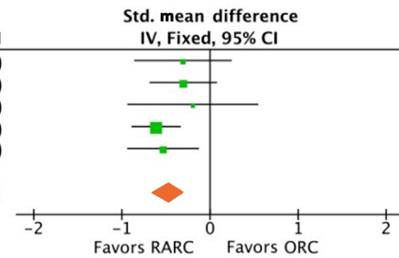

**Fig. 5b – Kaplan-Meier curves comparing A. Overall Survival (OS) and B. Progression-Free Survival (PFS).**

ing the same domains were combined (physical functioning and well-being, emotional functioning and well-being, and social functioning and social/family well-being). The role functioning and cognitive functioning domains from EORTC QLQ-C30, and the functional well-being domain from FACT-VCI were not combined, as there was an overlap in questions within the three domains. A significant difference favoring RARC was found in the physical functioning or well-being domain (SMD 0.47, 95% CI 0.29–0.65, $p < 0.001$; Fig. 6A) and the role functioning domain (MD

**A**

| Study or subgroup | ORC Mean | ORC SD | ORC Total | RARC Mean | RARC SD | RARC Total | Weight | Std. mean difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bochner (2015) | 87 | 14 | 30 | 91 | 11 | 22 | 10.6% | −0.31 (−0.86, 0.25) |
| Mastroianni (2022) | 76.6 | 23.5 | 54 | 83.3 | 20.2 | 52 | 22.2% | −0.30 (−0.69, 0.08) |
| Messer (2014) | 24.7 | 1.1 | 14 | 25 | 1.8 | 14 | 5.9% | −0.20 (−0.94, 0.55) |
| Parekh (2018) | 22.8 | 0.7 | 102 | 23.2 | 0.6 | 104 | 41.7% | −0.61 (−0.89, −0.33) |
| Vejlgaard (2022) | 84 | 21 | 48 | 93 | 11 | 48 | 19.6% | −0.53 (−0.94, −0.13) |
| **Total (95% CI)** | | | **248** | | | **240** | **100.0%** | **−0.47 [−0.65, −0.29]** |

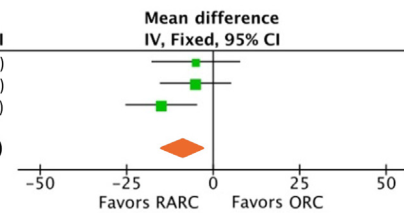
Heterogeneity: $\chi^2$ = 2.67, df = 4 ($p$ = 0.62); $I^2$ = 0%
Test for overall effect: Z = 5.11 ($p$ < 0.00001)




**B**

| Study or subgroup | ORC Mean | ORC SD | ORC Total | RARC Mean | RARC SD | RARC Total | Weight | Mean difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bochner (2015) | 76 | 25 | 30 | 81 | 22 | 22 | 24.5% | −5.00 (−17.83, 7.83) |
| Mastroianni (2022) | 75 | 30.3 | 54 | 80.1 | 23.6 | 52 | 37.9% | −5.10 (−15.42, 5.22) |
| Vejlgaard (2022) | 76 | 33 | 48 | 91 | 16 | 48 | 37.5% | −15.00 (−25.38, −4.62) |
| **Total (95% CI)** | | | **132** | | | **122** | **100.0%** | **−8.79 (−15.14, −2.43)** |

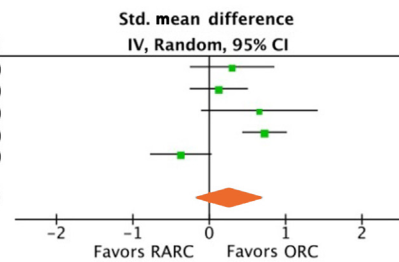
Heterogeneity: $\chi^2$ = 2.20, df = 2 ($p$ = 0.33); $I^2$ = 9%
Test for overall effect: Z = 2.71 ($p$ = 0.007)




**C**

| Study or subgroup | ORC Mean | ORC SD | ORC Total | RARC Mean | RARC SD | RARC Total | Weight | Std. mean difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bochner (2015) | 77 | 12 | 30 | 72 | 21 | 22 | 18.5% | 0.30 (−0.25, 0.85) |
| Mastroianni (2022) | 69.8 | 21.1 | 54 | 67.2 | 19.9 | 52 | 21.9% | 0.13 (−0.26, 0.51) |
| Messer (2014) | 133.5 | 7.9 | 14 | 127.7 | 9.2 | 14 | 14.7% | 0.66 (−0.11, 1.42) |
| Parekh (2018) | 125.2 | 3.4 | 94 | 122.8 | 3.2 | 97 | 23.4% | 0.72 (0.43, 1.02) |
| Vejlgaard (2022) | 77 | 23 | 48 | 84 | 13 | 48 | 21.5% | −0.37 (−0.78, 0.03) |
| **Total (95% CI)** | | | **240** | | | **233** | **100.0%** | **0.27 (−0.17, 0.71)** |

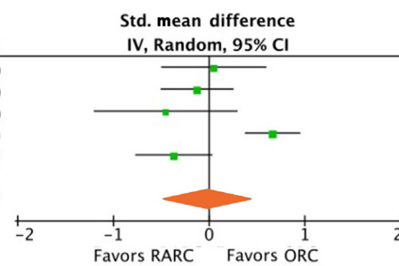
Heterogeneity: $Tau^2$ = 0.20; $\chi^2$ = 20.33, df = 4 ($p$ = 0.0004); $I^2$ = 80%
Test for overall effect: Z = 1.19 ($p$ = 0.23)




**D**

| Study or subgroup | ORC Mean | ORC SD | ORC Total | RARC Mean | RARC SD | RARC Total | Weight | Std. mean difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bochner (2015) | 82 | 23 | 30 | 81 | 15 | 22 | 18.7% | 0.05 (−0.50, 0.60) |
| Mastroianni (2022) | 75.2 | 26.5 | 54 | 78.2 | 20.5 | 52 | 21.6% | −0.13 (−0.51, 0.26) |
| Messer (2014) | 20 | 1.6 | 14 | 20.9 | 2.2 | 14 | 15.3% | −0.45 (−1.21, 0.30) |
| Parekh (2018) | 19.9 | 0.6 | 95 | 19.5 | 0.6 | 98 | 23.0% | 0.66 (0.37, 0.95) |
| Vejlgaard (2022) | 86 | 22 | 48 | 93 | 15 | 48 | 21.3% | −0.37 (−0.77, 0.03) |
| **Total (95% CI)** | | | **241** | | | **234** | **100.0%** | **−0.01 (−0.48, 0.45)** |

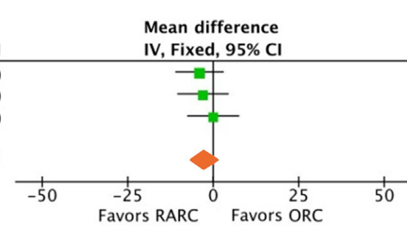
Heterogeneity: $Tau^2$ = 0.23; $\chi^2$ = 23.01, df = 4 ($p$ = 0.0001); $I^2$ = 83%
Test for overall effect: Z = 0.05 ($p$ = 0.96)




**E**

| Study or subgroup | ORC Mean | ORC SD | ORC Total | RARC Mean | RARC SD | RARC Total | Weight | Mean difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bochner (2015) | 89 | 14 | 30 | 93 | 12 | 22 | 36.3% | −4.00 (−11.09, 3.09) |
| Mastroianni (2022) | 88.3 | 22.8 | 54 | 91.3 | 16.3 | 52 | 32.2% | −3.00 (−10.52, 4.52) |
| Vejlgaard (2022) | 92 | 18 | 48 | 92 | 20 | 48 | 31.5% | 0.00 (−7.61, 7.61) |
| **Total (95% CI)** | | | **132** | | | **122** | **100.0%** | **−2.42 (−6.69, 1.85)** |

Heterogeneity: $\chi^2$ = 0.60, df = 2 ($p$ = 0.74); $I^2$ = 0%
Test for overall effect: Z = 1.11 ($p$ = 0.27)




**F**

| Study or subgroup | ORC Mean | ORC SD | ORC Total | RARC Mean | RARC SD | RARC Total | Weight | Std. mean difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bochner (2015) | 76 | 25 | 30 | 80 | 19 | 22 | 18.9% | −0.17 (−0.72, 0.38) |
| Mastroianni (2022) | 82.7 | 25.3 | 54 | 81.7 | 23.9 | 52 | 21.8% | 0.04 (−0.34, 0.42) |
| Messer (2014) | 23.5 | 0.3 | 14 | 22.3 | 1.4 | 14 | 14.7% | 1.15 (0.34, 1.96) |
| Parekh (2018) | 23.1 | 0.7 | 100 | 22.6 | 0.8 | 105 | 23.2% | 0.66 (0.38, 0.94) |
| Vejlgaard (2022) | 94 | 21 | 48 | 99 | 4.7 | 48 | 21.4% | −0.33 (−0.73, 0.08) |
| **Total (95% CI)** | | | **246** | | | **241** | **100.0%** | **0.23 (−0.25, 0.71)** |

Heterogeneity: $Tau^2$ = 0.24; $\chi^2$ = 24.27, df = 4 ($p$ < 0.0001); $I^2$ = 84%
Test for overall effect: Z = 0.93 ($p$ = 0.35)

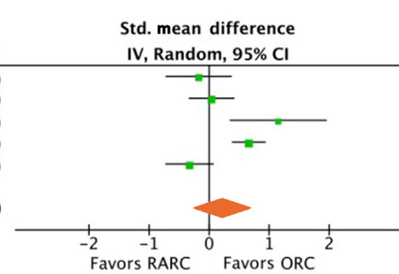



**Fig. 6 – Quality of life outcomes: (A) physical functioning or well-being, (B) role functioning, (C) global health status, (D) emotional functioning or well-being, (E) cognitive functioning, and (F) social functioning. CI = confidence interval; df = degree of freedom; IV = inverse variance; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; SD = standard deviation; Std. standard.**

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8.8, 95% CI 2.4–15.1, $p = 0.007$; Fig. 6B), accounting for similar baseline QoL for each domain ($p > 0.05$; Supplementary Fig. 19). No significant differences were found in other domains including global health status/QoL (SMD 0.27, 95% CI –0.17 to 0.71, $p = 0.2$; Fig. 6C), emotional functioning or well-being (SMD –0.01, 95% CI –0.48 to 0.45, $p > 0.9$; Fig. 6D), cognitive functioning (MD –2.42, 95% CI –6.69 to 1.85, $p = 0.3$; Fig. 6E), and social functioning (SMD 0.23, 95% CI –0.25 to 0.71, $p = 0.4$; Fig. 6F) between ORC and RARC postoperatively, accounting for similar baseline QoL (Supplementary Fig. 19). Although considerable heterogeneity existed in the meta-analyses for global health status, emotional functioning or well-being, and social functioning, sensitivity analyses excluding trials that used the FACT-VCI questionnaire did not change the pooled estimates from any domain (Supplementary Fig. 20). A publication bias was found in the global health status/QoL, emotional functioning or well-being, and social functioning or well-being domains (Supplementary Fig. 21).

### 3.6. Risk of bias

The RoB was assessed in all studies included. Apart from four studies that showed some concerns in the randomization process, all studies had a low RoB in all other domains (deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported result). This resulted in all studies having a low overall RoB. The RoB summary table is included in Supplementary Figure 22.

### 3.7. Discussion

We report the largest meta-analysis comparing ORC and RARC to date (including 1024 patients) to improve our understanding of recovery in the context of oncological and QoL outcomes following these surgeries. This meta-analysis demonstrates some new findings, such as a reduction in VTE events, better postoperative physical functioning and well-being, and role functioning after RARC. Additionally, we confirm previously reported findings of reduced LOS, blood loss (EBL), and transfusions in prior meta-analyses [4,5,33]. We also confirm no significant difference in perioperative complications, LN yields, PSM rates, overall HRQoL, and survival (both PFS and OS). It is important to note that the meta-analysis did not find any statistical differences in survival, which may corroborate with the findings of the RAZOR trial [29], which demonstrated the noninferiority of RARC to ORC in PFS.

Physical functioning and role functioning QoL domains scored higher for RARC than for ORC, with no significant difference in overall QoL postoperatively. There was no difference in the emotional, cognitive, and social functioning domains. This alludes to earlier recovery in the functional domains for patients undergoing RARC, but similar recovery in psychosocial domains to ORC. Modularized QoL scores such as the EORTC QLQ-C30 allow for these granular differences to be captured and would be a useful addition to any RCTs being undertaken in this field in the future [34].

Importantly, this meta-analysis is the first to report fewer VTE events with RARC when than with ORC. Our analysis included 868 patients from six different RCTs, and so the findings appear robust. Only one RCT [10] reported the use of extended thromboprophylaxis, with no other trial results or protocols mentioning the absence or presence of perioperative or extended thromboprophylaxis. Earlier mobilization is previously reported to be associated with reduced postoperative VTE events [35], and these findings are consistent with the earlier physical recovery described earlier in the manuscript. Given that VTE complications are reported in up to 8% of all patients undergoing RC [36], this reduction represents an important consideration for the decision between ORC and RARC.

The theoretical benefit of the robotic platform is more likely to be apparent during the early perioperative period. Both the large RCTs [10,29], our meta-analysis, and previous meta-analyses [4,5] concluded that RARC was associated with a shorter LOS than ORC, but no difference in complication rates. While it is plausible that there are truly no significant differences in traditional early recovery outcomes between RARC and ORC, there are some novel noteworthy markers of early recovery that we could not meta-analyze. For example, newer trials are looking at novel outcome measures such as wearable device–measured mobility [10], days alive, and out of hospital [10,28] to compare different approaches for RC.

There is a notable trend in recent trials of researchers focusing on new ways of measuring differences in recovery to detect any additional discernable differences over traditional metrics such as LOS and CD complications. For example, Parekh et al [29] utilized activities of daily living, hand grip strength, and the timed up and go walking test. Similarly, Catto et al [10] utilized the 30-s chair-to-stand test and objective step-count monitoring using wearable devices. While these novel metrics are not comparable across different trials, they represent potential new ways of measuring performance that may show differences in recovery patterns for RARC and ORC. These metrics could represent data points for future meta-analysis if future trials utilize them.

Our findings must be interpreted within the context of the study design. While we have performed an assessment of the publication bias as described by Sutton et al [18], this methodology may not be sufficient to detect all publication biases. This meta-analysis did not distinguish between the intracorporeal and extracorporeal approaches for urinary diversion in the RARC group. Restricting ourselves to either approach would have reduced the power of our analysis. However, any additional benefit of iRARC compared with eRARC may have been overlooked. The trend of more recent RCTs using the intracorporeal approach may be attributed to surgeons progressing in their learning curve in RC [37]. According to the data published by the International Radical Cystectomy Consortium (IRCC), iRARCs comprised 95% of all RARCs undertaken in 2018 among IRCC institutions [38]. While technically more challenging, iRARC may offer reduced EBL, less pain, better cosmesis, and reduced ileus rates [39]. A recent meta-analysis by Katayama et al [40], which compared iRARC and eRARC, concluded that patients undergoing iRARC was associated with superior perioperative outcomes, comparable complications, and similar onco-

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logical outcomes to eRARC. Moreover, our findings may include a lack of generalization given that trial patients and design may not reflect real-world evidence in addition to centers of excellence assessed in the current study. Only four of eight included studies mentioned the use of ERAS, a pathway that has been associated with reduced postoperative morbidity [41]. Even in studies that have implemented ERAS, there may be differences in the pathway at institutional level, which adds an element of heterogeneity that cannot be quantified in this study. Furthermore, there is considerable statistical heterogeneity in multiple outcomes of interest, as presented in the results. While the random-effect model and sensitivity analyses have been used to account for the heterogeneity, we cannot correct for all factors responsible for heterogeneity. This includes variations in surgical technique, postoperative protocols, institutional factors, and case-mix. Lastly, the QoL findings should be interpreted with caution as the unavailability of patient-level data limited meta-analyzing whether differences of postoperative QoL from baseline were significantly different. To overcome this, we conducted meta-analyses of preoperative QoL to ensure that there was no difference between RARC and ORC at baseline. Further long-term follow-up in large population-based studies will be critical to determine uptake of RARC and the purported benefits of RARC versus ORC.

## 4. Conclusions

In conclusion, RARC is associated with better perioperative outcomes, and improved physical functioning and role functioning domains, but similar overall QoL outcomes when compared with ORC. RARC might be more suitable in patients wishing to avoid blood transfusion, those wanting a shorter LOS, or those at a high risk of thromboembolic events. Cost effectiveness and health economic studies may be needed to evaluate which patient groups are most likely to benefit from these differences. RARC was associated with similar oncological outcomes when compared with ORC. Future trials would be helpful in addressing the comparison between iRARC and eRARC, and working out in which patients the differences are greatest.

***Author contributions:*** Pramit Khetrapal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: Khetrapal, Catto, Kelly.
*Acquisition of data*: Khetrapal, Wong, W.P. Tan, Rupasinghe.
*Analysis and interpretation of data*: Khetrapal, Wong, W.P. Tan, Rupasinghe.
*Drafting of the manuscript*: Khetrapal, Wong, W.P. Tan, Catto.
*Critical revision of the manuscript for important intellectual content*: W.S. Tan, Williams, Boorjian, Wijburg, Parekh, Wiklund, Vasdev, Khan, Guru.
*Statistical analysis*: Khetrapal, Wong, W.P. Tan.
*Obtaining funding*: None.
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*Supervision*: Catto, Kelly.
*Other*: None.

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***Data sharing:*** Deidentified data will be made available upon reasonable request.

## Peer Review Summary

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2023.04.004.

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